The Political Economy of Autism

Toby Rogers

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For R. & I.

Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Toby Rogers

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Abstract

Autism is a global epidemic. An estimated 1 in 40 children in Australia, 1 in 64 children in the U.K., and 1 in 36 children in the U.S. have an autism spectrum disorder (ASD). This is an enormous increase from the first known autism prevalence study in the U.S. in 1970, that established an autism prevalence rate of less than 1 per 10,000. Several studies have shown that changes in diagnostic criteria account for only a small fraction of the increased prevalence. Families of children on the spectrum face extraordinary additional expenses and decreased earnings as one parent often becomes a caregiver. Autism cost the U.S. $268 billion (1.5% of GDP) in 2015; if autism continues to increase at its current rate, autism will cost the U.S. over $1 trillion (3.6% of GDP) in 2025 (as a point of comparison, U.S. Defense Department spending is 3.1% of GDP). Over the last decade, several groups of leading epidemiologists, doctors, and public health experts have published consensus statements declaring that toxicants in the environment are contributing to the rising prevalence of neurodevelopmental disorders including autism. Beyond the consensus statements, a range of independent researchers have identified many additional factors that appear to increase autism risk. Given rising prevalence rates and the extraordinary impacts of ASD on individuals, families, and communities, what explains why public health authorities, thus far, have failed to ban or restrict toxicants that have been shown to increase autism risk? I argue that autism is not only a public health issue, it also represents a crisis of political economy. In this thesis I will show that: capitalism has transformed science and medicine from a focus on use values to a focus on exchange values; regulation is largely a reflection of political power not scientific evidence; and cultural and financial capture are blocking the sorts of regulatory responses that are necessary to stop the autism epidemic.

List of abbreviations and acronyms

AAP: American Academy of Pediatrics

ACIP: Advisory Committee on Immunization Practices (U.S.)

AMA: American Medical Association

ASD: autism spectrum disorders

ATSDR: Agency for Toxic Substances and Disease Registry (U.S.)

BBP: benzyl butyl phthalate

BPA: bisphenol A

CDC: Centers for Disease Control and Prevention (U.S.)

CI: 95% confidence interval

CMSRI: Children's Medical Safety Research Institute

COI: financial conflicts of interest

COID: Committee on Infectious Diseases (American Academy of Pediatrics)

CRO: contract research organisation

DBP: dibutyl phthalate

DEHP: diethylhexyl phthalate

DES: diethylstilbestrol

DIDP: diisodecyl phthalate

DINP: diisononyl phthalate

dl = decilitre = 10 millilitres = $1/100^{th}$ of a litre

DNOP: di-n-octyl phthalate

DTaP: diphtheria, tetanus, and acellular pertussis vaccine.

EMF: electromagnetic frequency

EPA: Environmental Protection Agency (U.S.)

FDA: Food and Drug Administration (U.S.)

FOIA: Freedom of Information Act (U.S.)

GACVS: Global Advisory Committee on Vaccine Safety

GAO: Government Accountability Office (U.S.)

GSK: GlaxoSmithKline

HBV: hepatitis B virus

Hep B: hepatitis B vaccine

HHS: Department of Health and Human Services (U.S.)

Hib: haemophilus influenzae type b vaccine

HPV: human papillomavirus

HR: hazard ratio

ICAN: Informed Consent Action Network

IOM: Institute of Medicine (renamed the National Academy of Medicine effective 1 July, 2015) (U.S.)

IPV: inactivated poliovirus vaccine

KOL: key opinion leader

MEHP: mono (2-ethylhexyl) phthalate

µg: microgram (one millionth of a gram)

MMR: measles, mumps, and rubella vaccine

MRL (ATSDR): minimal risk level

MRL (USDA): maximum residue limit or maximum residue level

NVAC: National Vaccine Advisory Committee

NCVIA: National Childhood Vaccine Injury Act of 1986

ng: nanogram (one billionth of a gram)

NIH: National Institutes of Health (U.S.)

NIMH: National Institute of Mental Health (U.S.)

NOAEL: no observed adverse effect level

NTP: National Toxicology Program (U.S.)

OR: odds ratio

PAHs: polycyclic aromatic hydrocarbons

PBDE: polybrominated diphenyl ether

PBO: piperonyl butoxide

PCB: polychlorinated biphenyl

PCV: pneumococcal conjugate vaccine

PFC: perfluorinated compound

PMA: professional medical association

POE-15: polyethoxylated tallowamine

POEA: polyoxyethyleneamine

PSR: pharmaceutical sales representatives

RFR: radiofrequency radiation

RR: relative risk

SSRI: selective serotonin reuptake inhibitor

TBB: 2-ethylhexyl-2,3,4,5-tetrabromobenzoate

TBPH: bis(2-ethylhexyl)-2,3,4,5-tetrabromophtalate

Tdap: tetanus, diphtheria, and acellular pertussis vaccine

TPP: triphenyl phosphate

UC: University of California

UN: United Nations

UNEP: United Nations Environment Programme

USDA: United States Department of Agriculture

VAERS: Vaccine Adverse Events Reporting System (U.S.)

VICP: Vaccine Injury Compensation Program (U.S.)

VSD: Vaccine Safety Datalink (U.S.)

WHO: World Health Organization

Styles

This thesis uses American Psychological Association (APA) referencing with a few changes that I will note here. When citing multiple authors in the text, APA recommends using alphabetical order but I list authors chronologically because, particularly in the scientific literature, each author is building on the work of earlier authors and I want to show that progression. APA uses the DOI abbreviation but I provide the full URL in references to make it easier to access sources. Secondary sources are noted with brackets instead of parenthesis and not included in the references at the end. I use Australian punctuation and spellings except for the names of U.S. institutions and direct quotes from authors writing in American English. All confidence intervals listed are 95%. I quote more than most — as a social scientist critiquing the biosciences I do not expect readers to just take my word for it; I think it is better to just present the sample size(s), odds/risk/hazard ratio(s), and confidence interval(s), when available, in the plain language of the original. I occasionally use first person pronouns; I do this intentionally because I believe that acknowledging perspective increases transparency, clarity, and readability.

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Glossary

allostatic load: ‘The sum total of stressors and burdens on the body’ (Herbert & Sage, 2013a).

astroturf: ‘2. *fig*. orig. *Politics*. Simulated or artificially created public or grass-roots support for a policy, product, movement, etc., generated by an organized campaign; cf. astroturfing *n.* 2. Frequently *attributive*, as Astroturf lobbying, Astroturf movement, etc.’ (OED).

bioaccumulation: ‘Progressive increase in the concentration of a chemical compound in an organism, organ, or tissue when the rate of uptake exceeds the rate of excretion or metabolism.... Bioaccumulation occurs within a trophic (food chain) level’ (Porta, 2014).

biomagnification: ‘Sequence of processes in an ecosystem by which higher concentrations (e.g., of a persistent toxic substance) are attained in organisms at higher levels in the food chain... Biomagnification occurs across trophic (food chain) levels’ (Porta, 2014).

black box warning: ‘A type of advisory notice printed (usually within a heavy black border) on the packaging of or insert accompanying certain prescription drugs, warning of potentially dangerous or fatal side effects. A black box warning is the strongest advisory issued by the American Food and Drug Administration (FDA) on medications. A similar type of warning is issued by the Australian Therapeutic Goods Administration (TGA)’ (OED).

case series: ‘A collection of subjects (usually, patients) with common characteristics used to describe some clinical, pathophysiological, or operational aspect of a disease, treatment, exposure, or diagnostic procedure’ (Porta, 2014).

carcinogen: ‘A physical, chemical, or biological agent that may induce or otherwise participate in the causation of cancer’ (Porta, 2014).

cohort study: ‘The analytic epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed — or exposed in different degrees — to a factor or factors hypothesized to influence the occurrence of a given outcome. A common feature of a cohort study is comparison of incidences in groups that differ in exposure levels’ (Porta, 2014).

confidence interval: ‘The conventional form of an interval estimate in frequentist statistics. If the underlying statistical model is correct and there is no bias, a confidence interval derived from a valid analysis will, over unlimited repetitions of the study, contain the true parameter with a frequency no less than its confidence level (often 95% is the stated level, but other levels are also used)’ (Porta, 2014).

contextual empiricism: An approach to the philosophy of science developed by Longino (1990) that treats ‘experience as the basis of knowledge claims in the sciences’ while also insisting on ‘the relevance of context’ including ‘the context of assumptions’ and ‘the social and cultural context’ surrounding any scientific inquiry.

de novo mutation: ‘A mutation that occurs in one member of a family as a result of a mutation in a germ cell of a parent or in a fertilized egg’ (King, Mulligan, & Stansfield, 2013).

endocrine disrupter: ‘A chemical compound or mixture of compounds that interferes with the normal functioning of the endocrine system and the physiological, developmental, and (especially) the reproductive processes regulated by it’ (OED).

genetics: ‘The study of genes and their roles in inheritance’ (Porta, 2014).

genomics: ‘The study of all of a person’s genes (the genome), including interactions of those genes with each other and with the person’s environment’ (Porta, 2014).

genotoxin: ‘A substance, setting, or process that is toxic or harmful to the genetic material’ (Porta, 2014).

hazard ratio: ‘A measure of how often a particular event happens in one group compared to how often it happens in another group, over time’ (National Cancer Institute, n.d.)

immunotoxin: ‘Any substance that produces an adverse or inappropriate change in the structure or function of the immune system’ (Office of Technology Assessment, 1991, p. 3).

incidence rate ratio (IRR): ‘The incidence rate in the exposed group divided by the incidence rate in the unexposed group’ (Porta, 2014).

Mertonian: ‘Of or relating to Robert K. Merton (1910–2003), American sociologist’ of science (YourDictionary, n.d.).

mutagen: ‘A microbiological, physical, or chemical agent that raises the frequency of mutations above the spontaneous rate. Any substance that can cause genetic mutations’ (Porta, 2014).

meta-analysis: ‘A statistical analysis of results from separate studies, examining sources of differences in results among studies, and leading to a quantitative summary of the results if the results are judged sufficiently similar or consistent to support such synthesis’ (Porta, 2014).

neurotoxin: ‘Any substance that is toxic to neurons or to the nervous system’ (OED).

odds ratio: ‘An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. OR=1 Exposure does not affect odds of outcome, OR>1 Exposure associated with higher odds of outcome, OR<1 Exposure associated with lower odds of outcome’ (Szumilas, 2010).

Pearson’s r: ‘Pearson’s product-moment correlation coefficient (usually denoted by r) is a measure of the degree to which a set of paired observations in a scatter diagram

approaches the situation in which every point falls exactly on a straight line. The possible range of values of r is from –1 (when there is a perfect negative correlation between the two observations) to +1 (when there is a perfect positive correlation)' (Szklo & Nieto, 2018).

positivism: 'The philosophy of Comte, holding that the highest or only form of knowledge is the description of sensory phenomena. Comte held that there were three stages of human belief: the theological, the metaphysical, and finally the positive, so-called because it confined itself to what is positively given, avoiding all speculation' (Blackburn, 2016).

poststructuralism: A '...critique of structuralism, especially as used in critical textual analysis, which rejects structuralist claims to objectivity and comprehensiveness, typically emphasizing instead the instability and plurality of meaning...' (OED).

randomised controlled trials (RCT): 'A clinical-epidemiological experiment in which subjects are randomly allocated into groups, usually called test and control groups, to receive or not to receive a preventive or a therapeutic procedure or intervention. The results are assessed by comparison of rates of disease, death, recovery, or other appropriate outcome in the study groups' (Porta, 2014).

reproductive toxin: 'Any substance that produces adverse effects on sexual function and fertility in adults as well as developmental toxicity in offspring' (United Nations, 2011).

risk ratio: 'The ratio of two risks, usually of exposed and not exposed' (Porta, 2014).

systematic review: 'The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardized methods for selecting and assessing articles' (Porta, 2014).

teratogen: 'A substance that produces abnormalities in the embryo or fetus by disturbing maternal homeostasis or acting directly on the fetus in utero' (Porta, 2014).

toxic: ‘Poison or poisonous. Any agent capable of producing a deleterious response in a biological system’ (Green, n.d.).

toxicant: ‘A poison that is made by humans or that is put into the environment by human activities’ (National Cancer Institute, n.d.).

toxin: ‘A toxic substance produced by biological systems such as plants, animals, fungi, and bacteria’ (Green, n.d.).

Part I:

Background and context

Chapter 1

History, prevalence, cost, and theories of causation of ASD

1.0 Introduction

In July of 2015, my then partner's son was diagnosed as being on the autism spectrum. Growing up my mom had been a special education teacher who specialised in working with non-verbal children, so I had a passing familiarity with autism. But I had never studied it in depth. At first, I was in denial and thought that this must have been a misdiagnosis. But over the course of several weeks of talking with my partner and others I came to understand that this diagnosis was likely correct.

In addition to the wave of different emotions that arise following the diagnosis of a loved one there were troubling signs that this might be part of a larger trend. Newspapers seemed to report higher autism prevalence numbers every few years. High school friends who had become teachers reported rising numbers of students on the spectrum in their classrooms. Friends in my peer group often had children on the spectrum. As a graduate student instructor at the University of California, Berkeley, I often wrote letters of recommendation for my students. One student who had been placed with Teach for America, reported three to four students on the autism spectrum in every one of her classes in a middle school in Southern California. She was not a special education teacher, these were regular education classes and that was the norm at her school. But these were all just isolated reports, I had never seen anyone put together the larger picture of what was happening with autism on the macro level.

One Saturday, I decided to spend eight hours researching autism. I reasoned that political economy has a set of tools for helping to understand the world and perhaps those tools could be applied to this situation as well. I was curious as to whether anyone had done cost estimates on the impact of autism spectrum disorders (ASD) on families and governments. Furthermore, I knew that there was a standard narrative about autism in the popular media that has four or five pillars — "it is likely genetic", "it is not an epidemic", "rising prevalence numbers are the result of better diagnosis", "we do not know exactly what causes it", but "we know for sure that vaccines are not involved". With access to one of the best libraries in the world and electronic access to almost all current scientific and medical journals, I simply wanted to find the study or studies that supported each of the pillars of the standard narrative. I wanted to make sure that someone (public health officials) had it figured out and that we were in good hands so that I could return to my thesis on Adam Smith.

I quickly discovered two very good estimates, one from the London School of Economics and one from the University of California, Davis, that showed that costs associated with autism are massive and pose an existential threat to budgets in the U.K. and the U.S. respectively (I will provide more details on those studies below). And then to my astonishment, I discovered that each of the pillars of the standard narrative is, at best, incomplete, and in many cases, demonstrably untrue. One day of reading, turned into two, turned into three, turned into six weeks of reading about autism twelve hours a day seven days a week. I have been researching autism ever since and this thesis is the story of what I have discovered.

Researching autism, one quickly discovers that every facet of the autism debate is fiercely contested. The differing views do not merely represent differences of opinion but rather completely different ontologies and epistemologies for understanding the world. In this thesis I will endeavour to present the range of views on each facet of the debate. But as I will show in the theoretical framework in chapter 2, I think contextual empiricism is the best way to approach this material. So within a very noisy debate, I think some data and some arguments are more valid than others and I will devote the bulk of the narrative to lines of inquiry that I think are more promising, while showing why I think they are more promising.

In this chapter I will provide a history of autism (1.1); define autism spectrum disorders (1.2); examine autism prevalence in the U.S. (1.3), Australia (1.4), and worldwide (1.5); examine the fiscal implications of ASD (1.6); discuss problems with the genetic explanations for autism (1.7); explain why rising autism rates are not explained by diagnostic expansion and substitution (1.8); review environmental factors associated with autism (1.9); explore issues of correlation and causation (1.10); compare how the U.S. government has responded to environmental factors associated with autism versus other products shown to cause harm (1.11); state my research question (1.12); explain the boundaries of my thesis (1.13); and then provide a summary of my argument (1.14).

1.1 A brief history of autism

Spikins (2017) argues that autism is genetic, that some ‘autism genes’ date back to ‘our shared ape heritage’ and that other autism genes are over 100,000 years old. Furthermore she argues that cave paintings in southern France are so detailed that they

could only have been made by people with autistic traits and that autism is likely responsible for much of human evolution since then (Spikins, 2017). Donvan and Zucker (2016a) point to stories like the Wild Boy of Avignon discovered in 1799 as possible early cases of autism; they argue that the first case in the United States was discovered by noted doctor and social reformer Samuel Howe in 1846. These sorts of narratives are influential in shaping perceptions of autism but they are not necessarily helpful in responding to the autism epidemic. While there may have been isolated ASD cases in the historical record, these accounts likely overstate the historical prevalence of ASD while minimising or ignoring large scale studies from reputable researchers (that I will discuss below) that show that prevalence rates started to grow dramatically in the 20th century, particularly since the early 1970s.

Swiss psychiatrist Eugen Bleuler first coined the term autism in 1910 'to describe the social withdrawal and detachment from reality often seen in children with schizophrenia' (Zeldovich, 2018). A Russian neurologist named Grunya Sukhareva[1] provides the first documented medical record of a cluster of cases that resemble our present day understanding of autism (Wolff, 1996; Manouilenko & Bejerot, 2015). 'In 1921, Sukhareva founded a therapeutic school for children with psychiatric problems at the Psychoneurological Department for Children in Moscow' (Manouilenko and Bejerot, 2015). In 1925 in Russian and then in 1926 in German, Sukhareva published a case series of six boys with a new disorder that closely matches the present day definition of an ASD as contained in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)* (Wolff, 1996; Manouilenko & Bejerot, 2015). The article would have

[1] Груня Ефимовна Сухарева, is transliterated as Ssucharewa by Wolff (1996, 2004). Manouilenko and Bejerot (2015) argue that Ssucharewa is a misspelling by the original German publisher and that the proper transliteration is Sukhareva. Shorter and Wachtel (2013) also find the transliterations Sucharewa and Soukhareva.

been noteworthy — *a Soviet, Jewish, woman, neurologist discovers a cluster of cases of a novel psychiatric condition in children*; yet it went largely unnoticed, or perhaps simply uncredited, until rediscovered in 1996 by British psychiatrist Sula Wolff.

Most histories of autism begin with Austrian-American physician, Leo Kanner. In 1935, Miriam Partridge brought her three and a half year old son David Speck in to Dr. Kanner for an examination (Olmsted & Blaxill, 2010, p. 171). He presented an unusual set of symptoms: lack of affective contact, delayed language development, a rigid insistence on sameness, a resistance to any change in routine, and an apparent preference for playing alone (Olmsted & Blaxill, 2010, p. 171). Soon Kanner started seeing other children with a similar set of symptoms and he wrote that he was seeing a 'unique and as yet unreported condition' (Olmsted & Blaxill, 2010, pp. 172–174). By 1943, Kanner had seen eleven children who seemed to fit the same pattern and he published 'Autistic Disturbances of Affective Contact' in the journal *The Nervous Child* which became the first published case series on autism in the English language (Olmsted & Blaxill, 2010).

A continent away, Austrian paediatrician Hans Asperger, who had no previous contact with Kanner, began noticing children in his practice with a severe lack of affective contact (Olmsted & Blaxill, 2010, p. 193). In 1944, Asperger published 'Autistic Psychopathy in Childhood' to document this case series of four children who seemed to represent a new and novel psychiatric condition (Olmsted & Blaxill, 2010, p. 193). Today, Asperger is generally associated with higher functioning cases of autism — where the person has speech but may lack other social skills. Recent scholarship (Donvan & Zucker, 2016b; Sheffer, 2018) has revealed that this was not a coincidence.

During the Nazi occupation of Austria, Asperger participated in a euthanasia program that killed the more severely disabled children in Vienna; the higher functioning cases that he documented were from the children who were spared execution based on the belief that they could still serve as soldiers for the Reich (Donvan & Zucker, 2016b, pp. 327–341; Sheffer, 2018).

By 1957, Kanner had seen 120 cases of autism in his practice (Olmstead & Blaxill, 2010). By training and practice he was inclined more toward psychobiology than psychoanalysis but in an article in 1957, he offered up this speculation as to the causes of autism, 'The emotional frigidity in the typical autistic family suggests a dynamic experiential factor in the genesis of the disorder of the child' (Olmstead and Blaxill, 2010, p. 204). This theory of the case is now completely discredited but it was dominant for decades.

In 1967, another Austrian-American, Bruno Bettelheim, made headlines for his theories on autism (Pollack, 1997). A survivor of the Dachau and Buchenwald concentration camps, Bettelheim emigrated to the U.S. in 1939 and became a professor of psychology at the University of Chicago in spite of the fact that his educational background was primarily in art history (Pollack, 1997). Bettelheim, amplified Kanner's theory that 'refrigerator mothers' were to blame for their autistic children; then he took the concept one step further to argue that the cause of autism was the *homicidal urges* of mothers towards their children (Olmsted & Blaxill, 2010, pp. 212–213). Bettelheim was prolific and media savvy: he published articles in *Scientific American* and *Ladies Home Journal;* he appeared on NBC's *Today Show* and *The Dick Cavett Show* to talk about his work;

and he received glowing reviews and endorsements by the *New Yorker*, *Time Magazine*, *The Atlantic*, and *The New Republic* (Olmsted & Blaxill, 2010).

In 1956, a Navy psychologist in San Diego, Bernard Rimland and his wife Gloria, had their first child, a son named Mark; early on Mark displayed signs of autism and was soon formally diagnosed (Olmsted & Blaxill, 2010, p. 202). Rimland began a correspondence with Kanner (Olmsted & Blaxill, 2010, p. 202). Rimland did not think that poor parenting was to blame and he began treating Mark with vitamin supplements, dietary changes, and other interventions and he argued that they led to improvements in Mark's behaviour (Olmsted & Blaxill, 2010). Rimland soon dedicated his life to researching the biological factors that might be involved with autism and in 1964 he published, *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior* that explored the physiological factors that might be involved with autism (Olmsted & Blaxill, 2010). Rimland's approach is now called the biomedical model and it is based on the idea that autism is caused by a child's metabolic and immune processes and susceptibility to toxicants (Olmsted & Blaxill, 2010).

Rimland and Bettelheim battled each other throughout their lives: Rimland built a powerful base of parents of autistic children, through founding the National Society for Autistic Children (now the Autism Society of America with 50,000 members and 200 chapters); but Bettelheim, for a time, was more effective at shaping conventional wisdom about autism because of his more aggressive self promotion and the receptive welcome he received from mainstream media (Olmsted & Blaxill, 2010). At the time, autism was still considered a rare disorder affecting a very small number of children. Solomon (2012) writes that the director of the National Institute of Mental Health,

Thomas Insel, ‘recounted a time during the 1970s when an autistic child was admitted to Boston Children’s Hospital; the chief of service called the residents together to observe him, reasoning that they might never see an autistic child again’ (p. 261).

Sometime between 1987–1990, autism prevalence rates began to increase sharply in the U.S. and other industrialised countries (McDonald & Paul, 2010). (I will discuss the history of prevalence estimates below.) Clearly there had not suddenly been an explosion in bad parenting and the psychoanalytic theories of Kanner and Bettelheim quickly fell out of favour. The Human Genome Project launched in 1990 and soon autism was socially reconstructed as a *genetic condition*. One can imagine that the genetic explanation must have had a certain emotional appeal — if autism is genetic, and the U.S. government is on the case, perhaps soon even rare genetic disorders like autism would be treatable. The extraordinary claims coming out of the Human Genome Project fed those hopes. However, the genetic explanation for autism has always been problematic because, as is often repeated by critical voices in the autism debate, ‘there is no such thing as a genetic epidemic’ (Kirby, 2005; see variations on this argument from Newschaffer in Barclay, 2005, and Hertz-Picciotto in Cone, 2009). So even as public health authorities promoted a genetic narrative that fit existing research programs, the Centers for Disease Control and Prevention’s (CDC) own sharply rising prevalence numbers showed that this could not possibly be the whole story.

Concurrent with genetic explanations for autism, officials at the CDC also promote the notion that rising autism rates are the result of ‘diagnostic expansion’ and ‘diagnostic substitution’. The idea is that the sharp increases in prevalence rates do not reflect a real underlying change in the number of children with the disorder. Rather, children with

milder conditions, that in previous years would have been considered just misbehavior, are now being classified as autistic (‘diagnostic expansion’) and children who were formerly classified with other disorders (e.g. mental retardation) are now being classified as autistic (‘diagnostic substitution’). As I will show below, this theory of the case has been tested by large scale epidemiological studies and shown to only explain a small fraction of the increased prevalence rates; and yet this narrative persists.

In the past few years, autism appears to be going through yet another discursive shift. Stephen Silberman, author of *NeuroTribes: The Legacy of Autism and the Future of Neurodiversity* (2015), claims that autism has always been with us, is not an epidemic, does not need to be solved, and represents yet another form of difference that should be celebrated like homosexuality or left-handedness. The book is popular in both the medical community and certain segments of the autism community. In 2015, *NeuroTribes* was awarded the Samuel Johnson Prize, a British honour for the best non-fiction writing in the English language. In spite of the acclaim for the book, Silberman’s argument is not supported by the empirical data that shows sharply rising prevalence rates that are only partly explained by increased awareness.

1.2 Present day definitions of autism

As yet there are no biomarkers for autism so diagnosis is made based on observation of behaviors. The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (American Psychiatric Association, 2013) provides the definitions and the billing codes that are used by health insurers and government when paying for mental health care

services in the United States. Autism spectrum disorders are defined in the *DSM-5* according to the following criteria:

A. Persistent deficits in social communication and social interaction across multiple contexts.
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following...
    1. Stereotyped or repetitive motor movements, use of objects, or speech.
    2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior.
    3. Highly restricted, fixated interests that are abnormal in intensity or focus.
    4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (American Psychiatric Association, 2013).

The definition also states that ‘symptoms must be present in the early developmental period’, that ‘symptoms must cause clinically significant impairment’, and that one should make sure to rule out other possible explanations such as ‘intellectual developmental disorder or global developmental delay’ (American Psychiatric Association, 2013).

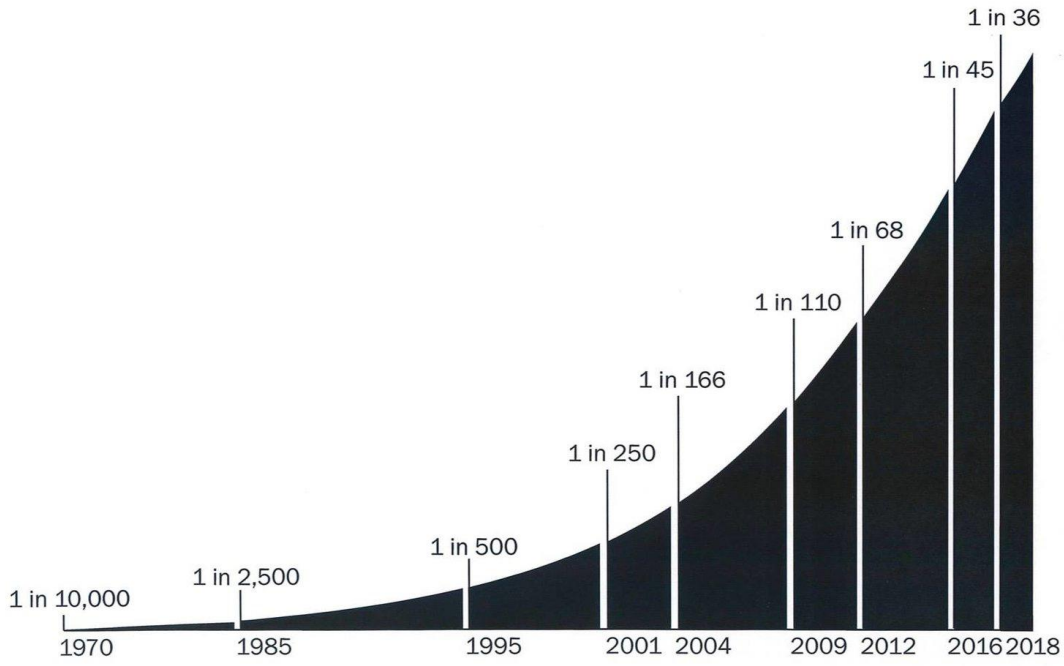
Ozonoff et al. (2018) explain that ASD is usually characterised in one of two ways: ‘an early onset pattern, in which children demonstrate social-communication delays early in

life, and a regressive pattern, in which children develop typically for some period and then experience a substantial decline in or loss of previously developed skills' (p. 788). Early onset ('from birth') was assumed to be the dominant mode of presentation but more recent scholarship suggests that regression may be 'more the rule than the exception' (see Ozonoff et al., 2018, p. 788, for a review of the recent literature). A third pattern of onset is described in some studies as well, 'that of developmental stagnation or plateau [Shumway et al., 2011], that is characterized by intact early skills that fail to progress or transform into more advanced developmental achievements' (Ozonoff et al., 2018, p. 788).

1.3 Autism prevalence in the U.S.

One in 36 American children has been identified with ASD according to estimates from the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network (Zablotsky, Black, & Blumberg, 2017). This is a 27,000% increase from the first autism prevalence estimate in the U.S. that established an autism prevalence rate of less than one per 10,000 people in the population (Treffert, 1970). ASD is almost 5 times more common among boys than among girls (Baio, 2014). Buescher, Cidav, Knapp, and Mandell (2014) estimate that more than 3.5 million Americans live with an autism spectrum disorder.

Figure 1.1: Increase in Autism Prevalence in the U.S. 1970 to 2017



Source: Handley (2018).

1.4 Autism prevalence in Australia

Three studies show that autism prevalence rates appear to be increasing in Australia. MacDermott et. al. (2007) reported a prevalence estimate of 1 in 160 (0.6%) children with ASD in Australia. In a prospective surveillance study, Barbaro and Dissanayake (2010) reported that 1 in 119 (0.8%) to 1 in 233 (0.4%) Victorian two-year-olds met criteria for ASD. Randall et al. (2016) estimated that 1 in 40 (2.5%) of all Australian children age four to five have an autism spectrum disorder. The different prevalence estimates may reflect different study designs. However, these three studies were conducted over an eight year period and given the rate of increase that we are seeing in other countries it is also possible that the different estimates may all be correct and simply reflect the increased prevalence over time.

1.5 Autism prevalence worldwide

The CDC (2018) reports that studies in Asia, Europe, and North America show that 1–2% of the global population have an autism spectrum disorder. Prevalence rates vary widely by country. Hinkka-Yli-Salomäki et al. (2014) estimate 1 in 189 (0.53%) in Finland; Ouellette-Kuntz (2010) estimate 1 in 94 (1.06%) in Canada; Baron-Cohen et al. (2009) estimate 1 in 64 (1.6%) in the U.K.; and Kim (2011) estimates 1 in 38 (2.6%) children with an autism spectrum disorder in South Korea.

1.6 Fiscal implications

Cidav, Marcus, and Mandell (2012) found that ‘mothers of children with ASD earned, $20,479 annual on average’; that was ‘35% ($7,189) less than the mothers of children with another health limitation and 56% ($14,755) less than the mothers of children with no health limitations’ (p. 617).

A metastudy by researchers at the University of Pennsylvania and the London School of Economics found that in the U.S. on average, ‘the cost of supporting an individual with an ASD and intellectual disability during his or her lifespan was $2.4 million... The cost of supporting an individual with an ASD without intellectual disability was $1.4 million’ (Buescher, Cidav, Knapp, & Mandell, 2014, p. 721). Knapp (2014), on behalf of the study team, wrote that ‘autism is the most costly medical condition in the UK’; ASD ‘costs the UK more than heart disease, cancer, and stroke combined’; and ‘it costs the

country at least £32 billion per year in treatment, lost earnings, and care and support for children and adults with autism'.

Leigh and Du (2015) estimate that autism cost the U.S. $268 billion (1.5% of GDP) in 2015 in 'direct medical, direct non-medical, and productivity costs'. They project that autism will cost the U.S. $461 billion annually by 2025; but that estimate assumes an autism prevalence rate of 1.1%; if autism continues to increase at its current rate, *ceteris paribus*, autism will cost the U.S. over $1 trillion per year (3.6% of GDP) by 2025 (Leigh & Du, 2015). To put these numbers in perspective, U.S. defense spending in 2016 was 3.1% of GDP (World Bank, n.d.).

The estimated 70 million people worldwide with autism understates the true impact because caregivers are impacted as well. As a point of reference, there are currently 65 million refugees worldwide from war, famine, and persecution (Edwards, 2016). Given current trends, it seems reasonable to conclude that autism could easily reach two per cent of global population by 2025 (as shown above, the U.S., South Korea, and Australia are already at close to three per cent autism prevalence rates). In the face of this crisis, governments have responded by providing medical, psychological, and educational support services — which are vital and necessary. But no government has yet engaged in lawmaking or regulation to try to ban or restrict toxic chemicals that might be associated with autism.

1.7 Problems with the genetic explanations for autism

Studies of twins and autism beginning with Folstein and Rutter (1977) suggested a strong genetic component to autism. But nearly all of the early twin studies suffered from small sample size and flaws in study design. With twins it is extremely difficult to isolate the effect of genes versus environment.

Francis Collins (2006), Director, National Institutes of Health, wrote, ‘Genes alone do not tell the whole story. Recent increases in chronic disease like diabetes, childhood asthma, obesity or autism cannot be due to major shifts in the human gene pool as those changes take much more time to occur’. And yet, genetic research continues to receive the bulk of federal funding in connection with autism (Wright, 2012; Interagency Autism Coordinating Committee [IACC], 2012, p. 16; IACC, 2017, p. 59).

The State of California contracted with 16 of the best geneticists in the U.S. and gave them total access to all birth records in the state. The study that resulted is Hallmayer et al. (2011) which is the most comprehensive study of twins and autism to date. They found that genetic heritability explains at most 38% of ASD cases; in two places they explain that this is likely an overestimate (Hallmayer et al., 2011). So at least 62% of ASD cases are caused by something other than genes.

1.8 Are rising autism rates the result of diagnostic expansion and substitution?

Many people have looked at the skyrocketing prevalence rates and wondered if perhaps they merely reflect increased awareness or changes in diagnostic criteria (e.g. did the

change from the *DSM-III* to the *DSM-IV* to the *DSM-5* result in vastly higher estimates?). Others wondered whether the higher rates in states like California and New Jersey reflected families moving to those states to take advantage of better autism support services. But the evidence suggests that diagnostic changes only explain a relatively small proportion of the overall increase in prevalence.

In 1999, the California Department of Developmental Services produced a report showing that autism increased in the state by 273% over the period 1987 to 1998 (Byrd et. al, 2002, p. 2). In response, the California legislature contracted with the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute at the University of California, Davis to investigate whether this increase was real or the result of a change in diagnostic criteria or people moving to the state to take advantage of better social services (Byrd et al., 2002). The principal investigator was paediatric epidemiologist Robert S. Byrd at UC Davis and he led a team of investigators at UC Davis and UCLA (Byrd et al., 2002). Among the major findings of the study, the investigators concluded that, 'The observed increase in autism cases cannot be explained by a loosening in the criteria used to make the diagnosis' and 'children served by the State's Regional Centers are largely native born and there has been no major migration of children into California that would explain the increase in autism' (Byrd et al., 2002, p. 5).

Hertz-Picciotto and Delwiche (2009), also at UC Davis, conducted a study to determine the extent to which 'changes in diagnostic criteria, the inclusion of milder cases of autism, and an earlier age at diagnosis' might have contributed to the 600% to 700% increase in autism cases in California over the period 1990 to 2006 (p. 89). They found that changes in diagnostic criteria explained 120%, the inclusion of milder cases

explains 56%, and earlier age at diagnosis explains 12% of the increase — for a total of 188% (Hertz-Picciotto and Delwiche, 2009, p. 89).[2] But remember, Hertz-Picciotto and Delwiche (2009) are trying to identify the factors responsible for a 600% to 700% increase in autism over that 16 year time period. So these three factors (diagnostic criteria, milder cases, and earlier age) combined explain just 26.9% (188/700) to 31.3% (188/600) of the total increase in autism over that time period. In a subsequent interview about the study with *Scientific American*, Hertz-Picciotto explained that these three factors 'do not get us close' to the 600% to 700% increase in autism over that time period and she urged the scientific community to take a closer look at environmental factors (Cone, 2009, para. 13).

Autism was first included in the *DSM-III* that was published in 1980. The *DSM-IV* that came out in 1994 added Asperger's Disorder but it was separate from autism (Autism Society, n.d.). The *DSM-5* that came out in 2013 merged autism, Asperger's, and pervasive developmental disorders under the umbrella diagnosis 'autism spectrum disorders' (Autism Society, n.d.). There are sometimes also smaller changes in definition between the different editions. A number of studies have looked at whether changes in definitions of autism might account for the rising prevalence numbers. Croen, Grether, Hoogstrate, and Selvin (2002) concluded that the increase in autism prevalence in California from 1987–1994 may have been the result of changes in diagnostic criteria. Blaxill, Baskin, Spitzer (2003) identified several problems in the Croen et al. (2002) analysis. Croen and Grether (2003) then reversed course and agreed

[2] There appears to be a typo in the Hertz-Picciotto and Delwiche (2009) article published in *Epidemiology*. On page 89, the earlier age at diagnosis is listed as explaining a 24% increase in autism prevalence even though in two separate places earlier in the article (p. 84 and p. 88) earlier age at diagnosis is listed as explaining a 12% increase. The author manuscript available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113600/ shows a 12% increase attributable to earlier age at diagnosis (p. 8) so that is the figure that I used. I have written to *Epidemiology* to request clarification or a correction.

with Blaxill et al. (2003) that ‘diagnostic substitution does not appear to account for the increased trend in autism prevalence’.

Barton, Robins, Jashar, Brennan, and Fein (2013) and Mazefsky, McPartland, Gastgeb, and Minshew (2013) concluded that the more precise definition of autism in the *DSM-5* will result in fewer numbers of children diagnosed with autism. Maenner et al. (2014) conducted a retrospective analysis of 6,577 children who had been diagnosed with autism according to the *DSM-IV-TR* [text revision between editions] and found that the *DSM-5* definition would lead to an 11.5% decrease in the number of children diagnosed with autism.

There are also questions about how the slightly different definition used by the Individuals with Disabilities Educational Act might impact prevalence estimates. Although the IDEA was last updated in 2004, it is remarkably consistent with the *DSM-5* (Harker & Stone, 2014). The American Psychiatric Association (that publishes the *DSM*) also works in concert with the World Health Organization and designed the *DSM-5* to be consistent with the forthcoming *International Classification of Disease, 11th edition* (ICD-11) (Regier, Kuhl, & Kupfer, 2013).

1.9.0 Introduction to environmental factors associated with autism

There is a growing body of evidence that suggests that the autism epidemic is being driven by toxicants in the environment. There are four overlapping groups of environmental factors associated with autism that one can study — known (widely agreed upon) environmental triggers (1.9.1), consensus statements about environmental

factors linked with neurodevelopmental disabilities including but not limited to autism (1.9.2), individual studies of particular toxicants (1.9.3); and studies initiated via activist initiated participatory science (1.9.4). There are strengths and weaknesses associated with each group of studies that I will explain below.

1.9.1. Known environmental causes of autism

There are four known and widely agreed upon environmental causes of autism — 'thalidomide, misoprostol, valproic acid, and first-trimester rubella [also known as German measles] infection' (Landrigan, Lambertini, & Birnbaum, 2012). While these factors provide 'proof of the principle' that autism can be caused by environmental triggers (Landrigan et al., 2012), thalidomide and misoprostol have been withdrawn from the market, valproic acid is contraindicated for pregnant women, and rubella infections are now rare because of widespread vaccination — so these factors cannot explain the sharp rise in autism rates starting in the late 1980s.

Furthermore, Olmsted and Blaxill (2010) provide an important caveat about the relationship between rubella infection during pregnancy and autism. They explain that congenital rubella syndrome (CRS, the condition that sometimes produces autism and other harms in fetuses) was first identified in the 1950s and the standard treatment for pregnant women who contracted rubella was injection with gamma globulin (Olmsted & Blaxill, 2010). The preservative used in gamma globulin was thimerosal which is 49.6% ethylmercury, a known neurotoxin (Grandjean & Landrigan, 2014). Olmsted and Blaxill (2010) argue that a toxicant plus a virus is sometimes more dangerous than either of those factors by themselves; they point to a study by Lock, Gatling, Mauzy,

and Wells [1961] that showed that 16% of pregnancies with rubella infection had abnormal outcomes, 6% of pregnancies with gamma globulin treatment by itself in the absence of rubella infection had abnormal outcomes, and 25% of pregnancies characterised by rubella infection plus gamma globulin treatment had abnormal outcomes. Recent studies of CRS in Brazil [Lanzieri et al., 2004] and Oman [Al-Awaidy et al., 2006] did not report any cases of autism which lends further support to the theory that autism cases linked to rubella infection in the U.S. in the 1960s may have been driven by some additional factor (Olmsted & Blaxill, 2010, p. 223).

1.9.2 Consensus Statements

Over the last decade, several consensus statements have been published by groups of leading epidemiologists and public health experts who have concluded that neurodevelopmental disabilities (NDD) including autism are caused by toxicants in the environment. The consensus statements tend to list well known toxicants and they do not break out the causes of autism separately from other NDDs. The consensus statements are important because they tell us that autism and other NDDs are potentially preventable through stricter regulation of toxicants.

In 2008, the Collaborative on Health and the Environment's Learning and Developmental Disabilities Initiative published a 'Scientific Consensus Statement on Environmental Agents Associated with Neurodevelopmental Disorders' (Gilbert, 2008). It was signed by 57 scientists, researchers, and health professionals including some of the biggest names in environmental epidemiology. The statement focused on 11 'high confidence conclusions' ('alcohol, lead, mercury, PCBs, PBDEs, manganese, arsenic,

solvents, PAHs, pesticides, and tobacco smoke') and three 'emerging concerns' ('endocrine disruptors, fluoride, and food additives') (Gilbert, 2008).

In 2010, the Mount Sinai Children's Environmental Health Center in partnership with Autism Speaks organised a workshop on 'Environmental Causes of Autism and Learning Disabilities' that brought together researchers from around the world (Landrigan et al., 2012). A similar meeting organised by Mount Sinai Hospital in 1964 was pivotal in establishing the link between asbestos and cancer (Michaels, 2008a, p. 29). The 2010 workshop 'generated a list of 10 chemicals and mixtures widely distributed in the environment that are already suspected of causing developmental neurotoxicity' including 'lead, methylmercury, polychlorinated biphenyls, organophosphate pesticides, organochlorine pesticides, endocrine disruptors, automotive exhaust, polycyclic aromatic hydrocarbons, brominated flame retardants, and perfluorinated compounds' (Landrigan et al., 2012, p. A259).

In 2016, a group of 47 of the top epidemiologists, doctors, and public health experts in the U.S. came together under the banner of 'Project TENDR: Targeting Environmental Neuro-Development Risks' and published a consensus statement that toxic chemicals in the environment contribute to neurodevelopmental disorders including autism (Bennett et al., 2016). The consensus statement focused on six 'prime examples of neurodevelopmentally toxic chemicals' including 'organophosphate pesticides, PBDE flame retardants, combustion related air pollutants, lead, mercury, and PCBs' (p. 118–119). Arthur Lavin (2015), a member of Project TENDR wrote, 'if we reduce the exposure from the top neuro-toxic chemicals by as little as 20%, the country could experience drops in the chances of our children developing autism, ADHD, and/or

learning disabilities by 15–40%'. The conflict of interest statement at the end of the statement lists the John Merck Fund as a sponsor of Project TENDR. Given the ongoing debate over a possible association between vaccines and autism (that will be discussed below), the fact that Merck & Company is a large vaccine producer, and the abundant evidence on the funding effect (that will be discussed in chapter 5) it is problematic that this group accepted funds derived from the Merck family fortune.

On the one hand, these consensus statements are an important step forward in addressing rising levels of neurodevelopmental disorders including autism. On the other hand, it is striking how politically safe the consensus statements are in their lists of environmental triggers. The dangers of lead have been well-established for fifty years, the dangers of mercury have been known for 100 years, organophosphates were developed as chemical weapons in World War II, problems with organochlorine pesticides like DDT have been known since before Rachel Carson wrote *Silent Spring*, and the manufacture of PCBs was banned in the U.S. in 1979. With a few exceptions, the uses of many of these chemicals have been flat or declining in the U.S. (Nevison, 2014). While there could be low-dose, non-linear, cumulative, or synergistic effects or biomagnification as these toxicants move up the food chain, as a first step (consistent with Hill, 1965) it would make sense to explore toxicants that are increasing in use in line with the increases in autism prevalence. So again, even though these consensus statements help to establish that toxicants cause autism, they do not necessarily explain why autism rates started to increase sharply in the late 1980s.

1.9.3.0 Individual studies of individual toxicants

Next there are specific studies that look at individual toxicants and associated risks of developing autism in those exposed to that toxicant. These studies are important because they suggest where one might apply regulatory efforts to prevent autism. In this section I will review individual studies on six possible autism triggers: mercury from coal fired power plants and other industrial sources (1.9.3.1); vehicle emissions (particularly diesel trucks) (1.9.3.2); endocrine disruptors including phthalates, BPA, and flame retardants (1.9.3.3); Roundup (1.9.3.4); pesticides (1.9.3.5); and selective serotonin reuptake inhibitors (1.9.3.6).

1.9.3.1 Mercury from coal fired power plants and other industrial sources

Palmer, Blanchard, Stein, Mandell, and Miller (2006) used ‘data from the Texas Education Department and the United States Environmental Protection Agency’ to ‘examine the association between environmentally released mercury, special education, and autism rates in Texas’. They found that ‘on average, for each 1,000 pounds [453 kilo] of environmentally released mercury, there was a 43% increase in the rate of special education services and a 61% increase in the rate of autism’ (Palmer et al., 2006). Palmer, Blanchard, and Wood conducted a second study in (2009) to refine their initial analysis. They found that for every ten miles (16 kilometers) further a family lives from an industrial mercury source, a child’s risk of autism goes down 2% and for every ten miles further a family lives from a coal fired power plant the autism risk declines 1.4% (Palmer et al., 2009).

Windham, Zhang, Gunier, Croen, and Grether (2006) examined autism and air pollution in the San Francisco Bay Area. Their analysis focused on nineteen compounds with known developmental, neurologic, or endocrine-disrupting toxicity (Windham et al., 2006). They found statistically significant increased risks of autism for those exposed to higher levels of several hazardous air pollutants including methylene chloride, trichloroethylene, vinyl chloride, cadmium, mercury, and nickel (Windham et al., 2006). Specifically with reference to mercury, they found nearly double the autism risk in the areas with the highest concentrations of airborne mercury pollution (adjusted odds ratio = 1.92; confidence interval: 1.36, 2.71) (Windham et al., 2006, p. 1441). All statistical terms used in this thesis are defined in the glossary.

1.9.3.2 Vehicle emissions (particularly diesel trucks)

In 2002, the U.S. Environmental Protection Agency (EPA) and the University of Michigan Air Quality Laboratory (UMAQL) conducted a pilot program ‘to investigate mercury emissions from motor vehicles’. The subsequent report, Hoyer, Baldauf1, Scarbro, Barres, and Keeler (2004) found that vehicle emissions contain mercury and that diesel trucks emitted much higher levels of mercury than cars — emissions for ‘vapor-phase mercury plus particulate mercury for light-duty gasoline vehicles ranged from 0.31 to 1.4 nanograms per mile [1.6 km] while diesel vehicles ranged from 6.3 to 11.0 ng/mi’ (Hoyer et al., 2004).

Volk, Hertz-Picciotto, Delwiche, Lurmann, and McConnell (2011) found that children living within 1,000 feet (300 meters) from a freeway at birth had nearly a two-fold increase in autism risk (OR = 1.86; CI: 1.04, 3.45). The link held up even after

researchers controlled for other factors that may influence development, such as parental education, maternal age, and exposure to tobacco smoke (Volk et al., 2011). A similar correlation did not appear in connection with living within 1,000 feet of a road (Volk et al. 2011). The authors speculated that the higher risk of autism as a result of living near a freeway could be a result of diesel emissions from trucks which are found more often on freeways (Volk et al., 2011). Volk, Lurmann, Penfold, Hertz-Picciotto, and McConnell (2013) found that 'exposure to traffic-related air pollution, nitrogen dioxide, [particulate matter] $PM_{2.5}$, and PM_{10} during pregnancy and during the first year of life was associated with autism' (p. 71).

1.9.3.3 Endocrine disruptors: Phthalates, BPA, and flame retardants

Endocrine disruptors are chemicals that interfere with the hormone (endocrine) system in mammals. Consensus statements from Gilbert (2008), Landrigan, Lambertini, and Birnbaum (2012), and Bennett et al. (2016) expressed concern and called for more research regarding possible links between endocrine disrupting chemicals and adverse neurodevelopmental outcomes including autism in children. Endocrine disruptors are abundant in our environment and in our bodies. Common endocrine disruptors include phthalates which 'are a group of chemicals used to soften and increase the flexibility of plastic and vinyl' (ToxTown, n.d.); bisphenol A (BPA) which is a chemical used to harden plastics and is often found in food and beverage packaging; and polybrominated diphenyl ethers (PBDEs) which are sold as flame retardants and found in furniture, clothing, and plastics used in electronics (CDC, 2009). It is important to point out that phthalates, BPA, and flame retardants are not the only endocrine disruptors — just the most well known examples (but there is concern about this entire class of chemicals).

Furthermore, endocrine disruption is not the only mechanism of action associated with phthalates, BPA, and flame retardants. There are also concerns about their toxic effects on other systems in the body including the brain, central nervous system, and reproductive system (so endocrine disruption is just one way of thinking about the dangers of these chemicals).

Sjodin et al. (2004) show that PBDE (flame retardant) concentrations in human tissues have been increasing over the last few decades. Lang et al. (2008) using data from the U.S. National Health and Nutrition Examination Survey 2003–2004 found that 92% of participants had detectable levels of BPA. Woodruff, Zota, and Schwartz (2011) in a study of 268 pregnant women in the U.S. found that 99–100% had detectable levels of 'polychlorinated biphenyls, organochlorine pesticides, PFCs, phenols, PBDEs, phthalates, polycyclic aromatic hydrocarbons, and perchlorate' (p. 878).

Larsson, Weiss, Janson, Sundell, and Bornehag (2009), in a study (initially designed to look at allergies) of 4,779 children between ages 6 to 8 in Sweden found that vinyl flooring in the parents' bedroom was associated with an increased risk of ASD by 140% (OR = 2.4; CI: 1.31, 4.40). Engel et al. (2010) as part of the Mount Sinai Children's Environmental Health Study compared measurements of third trimester phthalate metabolites (in the urine of pregnant women) with later cognitive and behavioral development when those children were between 4 and 9 years old. Low molecular weight phthalate metabolites were associated with a range of subsequent behavioral problems in children including aggression, attention, conduct, and depression (Engel et al., 2010, p. 568). Messer (2010) notes that multiple animal and human studies have found that PBDE interferes with the thyroid and theorises a possible link between

PDBE exposure and autism. Testa et al. (2012) in a study in Italy of 48 children with ASD and a control group of 45 neurotypical controls found a statistically significant association between ASD and two metabolites of the phthalate DEHP in urine samples. Stein, Schluter, Streer, and Ming (2013) found that many children with ASD seemed to have a defect that limited their ability to detoxify DEHP (p. 2677). Degroote, Hunting, Sébire, and Takser (2014) in animal experiments found that prenatal exposure to even low doses of phthalates and flame retardants produced autistic-like traits in offspring. Ejaredar, Nyanza, Eycke, and Dewey (2015) in a systematic review of 11 studies found that 'prenatal exposure to phthalates is associated with adverse cognitive and behavioral outcomes in children, including lower IQ, and problems with attention, hyperactivity, and poorer social communication' (p. 51). Stein, Schluter, Steer, Guo, and Ming (2015) in a study of 46 children with ASD and 52 neurotypical controls, found that children with ASD had three times more BPA metabolites in their urine than the children in the control group. Kardas et al. (2016) in blood samples of 48 children with ASD as compared with 41 neurotypical controls found elevated levels of three endocrine disruptors (two phthalates — MEHP and DEHP, as well as BPA) in the children with ASD. The political economy of the regulation of phthalates, BPA, and flame retardants is the subject of chapter 6.

1.9.3.4 Roundup (glyphosate+ adjuvants)

In 1974, Monsanto began selling Roundup to farmers. Roundup is a combination of the chemical glyphosate plus various adjuvants. Monsanto's patent expired in 2000 but glyphosate-based herbicides have become the most widely used herbicides in the United States agricultural sector; 'since the late 1970s the volume of glyphosate-based

herbicides applied has increased approximately 100-fold' and now 240 million pounds (~108.8 million kilograms) are applied to U.S. crops every year (Myers et al., 2016).

Swanson, Leu, Abrahamson, and Wallet (2014) found highly significant correlations between glyphosate applications and a wide range of chronic health conditions including autism (Pearson's r = 0.989). There are many reasons to take this study with a grain of salt. The authors are not academics, the *Journal of Organic Systems* that it was published in is not well regarded, and *anything* that experienced a sharp increase during the past three decades is likely to be highly correlated with autism even if there is no plausible causal connection (e.g. single parent families or video game sales).

Monsanto has long claimed that Roundup is safe because it interferes with the shikimate pathway (that plants use for biosynthesis) and animals do not have a shikimate pathway. But Samsel and Seneff (2013a, 2013b) point out that gut bacteria have a shikimate pathway and the majority of children with autism also suffer from gastrointestinal issues. Scientists are finding that gut bacteria plays an important role in mental health (Dietert, 2016). While autism was once considered exclusively a neuropsychiatric disorder, increasingly doctors and research scientists are coming to understand it as affecting a range of systems including the gut, central nervous system, and the immune system.

1.9.3.5 Pesticides

Roberts et al. (2007) for the California Department of Public Health found that maternal residence during pregnancy within 500 meters of a field sprayed with the organochlorine pesticides endosulfan and dicofol increased incidence of autism by

600%. In 2010, the EPA reached an agreement with manufacturers to phase out all endosulfan uses within two years. Dicofol is still used on cotton, apples, and citrus. Many other organochlorine pesticides are still in use — particularly in developing countries (Jayaraj, Megha, & Sreedev, 2016).

Project TENDR (Bennett et al., 2016) lists five studies that show an association between organophosphate pesticides and developmental disabilities [Rauh et al., 2006; Eskenazi et al., 2007; Marks et al., 2010; Fortenberry et al., 2014, and Furlong et al., 2014]. Shelton et. al. (2014) found that living within 1.25 km of fields sprayed with organophosphates at any point during pregnancy was associated with a 60% increased risk for ASD (aOR = 1.6; CI: 1.02, 2.51); there was a 99% increased risk for ASD if organophosphate pesticides were applied during the third trimester (aOR = 1.99; CI: 1.11, 3.56). Living within 1.75 km of a field sprayed with chlorpyrifos was associated with a 78% increased risk for ASD (aOR = 1.78; CI: 1.05, 3.02); there was a 163% increased risk if the chlorpyrifos pesticide is applied during second trimester (aOR = 2.63; CI: 1.28, 5.41) (Shelton et. al., 2014). Furthermore, ‘each 100-lb (45.4 kg) increase in the amount of chlorpyrifos applied over the course of pregnancy (within 1.5 km of the home) was associated with a 14% higher prevalence of ASD (aOR = 1.14; CI: 1.0, 1.32)’ (Shelton et. al., 2014). Ten million pounds [4,535,923 kilo] of chlorpyrifos pesticides are applied to U.S. crops every year (EPA, 2002). Pregnant women who lived within 1.5 km of a field sprayed with pyrethroids during the third trimester faced an 87% increased risk of having a child with autism (aOR = 1.87; CI: 1.02, 3.43). Proximity to fields sprayed with carbamates was associated with a 148% increased risk for developmental disabilities (aOR = 2.48; CI: 1.04, 5.91) and a 37% increased risk for ASD (aOR = 1.37; CI: 0.66, 2.84) — although the ASD risk was not statistically

significant. Shelton, Hertz-Picciotto, and Pessah (2012) explore the potential mechanisms of action by which pesticides may lead to autism.

Indoor use of pesticides to kill fleas and ticks on pets has also been found to increase the risk of autism. Keil, Daniels, and Hertz-Picciotto (2014) compared 262 neurotypical children with 407 children with ASD and found that women who were pregnant who applied imidacloprid, a common flea and tick treatment, to their pets had a two-fold higher risk of having children with autism than those who did not use imidacloprid (p. 1). Imidacloprid is part of a class of chemicals called neonicotinoids that interfere with the central nervous system in insects leading to paralysis and death (Keil et al., 2014). Schmidt et al. (2017) looked at the association between folic acid intake during pregnancy, which is thought to protect against developmental harms from certain toxicants, and pesticide exposure (including indoor exposures from flea and tick treatments for pets). Low folic acid intake (<800 μg) was associated with a 20% increased risk for autism (OR = 1.2; CI: 0.7, 2.2), but that result was not statistically significant. Exposure to any indoor pesticide was associated with a 70% increased risk for autism (OR = 1.7; CI: 1.1, 2.8), and the combination of low folic acid and any indoor pesticide exposure was associated with a 150% increased risk of autism (OR = 2.5; CI: 1.3, 4.7) (Schmidt et al., 2017, p. 097007-1). Low folic acid and regular pregnancy exposure (≥6 months) to pet pesticides increased the risk of autism by 290% (OR = 3.9; CI: 1.4, 11.5); low folic acid and regular pregnancy exposure (≥6 months) to outdoor sprays and foggers increased autism risk by 310% (OR = 4.1; CI: 1.7, 10.1) (Schmidt et al., 2017, p. 097007-1). The political economy of the regulation of herbicides and pesticides is the topic of chapter 7.

1.9.3.6 Selective serotonin reuptake inhibitors and other antidepressants

Selective serotonin reuptake inhibitors (SSRIs) are designed to cross the blood brain barrier and they cross the placental barrier at a high rate (Hendrick et al., 2003; Rampono et al., 2009). Eight studies have found a statistically significant association between selective serotonin reuptake inhibitor (SSRI) use in mothers and subsequent autism in their children (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011; Eriksson, Westerlund, Anderlid, Gillberg, & Fernell, 2012; Rai et al., 2013; Sørensen et al., 2013; Gidaya et al., 2014; Harrington, Lee, Crum, Zimmerman, & Hertz-Picciotto, 2014; El Marroun et al., 2014; Boukhris, Sheehy, Mottron, & Bérard, 2016). Two other studies found an association but some of their results were not statistically significant (Hviid, Melbye, & Pasternak, 2013; Clements et al., 2015). Taking each of these studies in turn:

Croen et al. (2011) 'found a two-fold increased risk of ASD associated with treatment with SSRIs by the mother during the year before delivery (adjusted odds ratio = 2.2; CI: 1.2, 4.3)' (p. 1104). They also found a more than three-fold increased risk of ASD with treatment with SSRIs during the first trimester (aOR = 3.8; CI: 1.8, 7.8) (Croen et al., 2011, p. 1104). 'No increase in risk was found for mothers with a history of mental health treatment in the absence of prenatal exposure to SSRIs' (Croen et al., 2011, p. 1104).

Eriksson et al. (2012) compared the family histories of 208 children with autism against 119,183 controls (the entire birth cohort in Sweden during the years 2002–2006). They found that mothers of children with autism were 4.4 times more likely to have taken

SSRIs during pregnancy than controls (OR = 4.4; CI: 2.5, 8.0) (Eriksson et al., 2012, p. 1645).

Rai et al. (2013) in a study of 4,429 cases of ASD and 43,277 controls found that maternal antidepressant (both SSRIs and tricyclic antidepressant) use during pregnancy more than tripled the risk of having a child with autism (aOR = 3.34; CI: 1.50, 7.47). The increased risk was entirely associated with children on the spectrum *without* an intellectual disability (n = 2601) and there was no observed association between maternal antidepressant use and rates of autism *with* an intellectual disability (n = 1828) (Rai et al., 2013). They estimated that if their calculations are correct, 'antidepressant use during pregnancy explained 0.6% of the cases of autism spectrum disorder' in their sample (Rai et al., 2013, p. 1).

Sørensen et al. (2013) found that children exposed prenatally to any antidepressant (which included SSRIs, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants) had a 50% increased risk of autism (adjusted hazard ratio = 1.5; CI: 1.2, 1.9). But then Sørensen et al. (2013) decided to restrict the analysis only to women with a diagnosis of affective disorder (which eliminated 80.1% of the sample) and then further discounted the hazard ratio if unexposed siblings also had an ASD diagnosis which moved the hazard ratio to 1.1 (CI: 0.5, 2.3) and below the level of statistical significance.

Gidaya et al. (2014) found any SSRI exposure during pregnancy doubled the risk of having a child with autism (aOR = 2.0; CI: 1.6, 2.6); exposure to SSRIs during the third trimester tripled autism risk (aOR = 3.1; CI: 2.1, 4.5). Harrington et al. (2014) found

that SSRI use during pregnancy nearly triples the risk of developing autism if the fetus is male (aOR = 2.92; CI: 1.07, 7.93); the strongest association occurred with first-trimester exposure (aOR = 3.22; CI: 1.17, 8.84). El Marroun et al. (2014) in a study of 376 children prenatally exposed to maternal depression, 69 children prenatally exposed to SSRIs, and 5,531 controls found that SSRI exposure nearly doubled the risk for autistic traits as compared with mothers who experienced depression but were not treated with SSRIs (β = 0.17; CI: 0.1, 0.24). In linear regression models, 'the beta coefficient, β, is the degree of change in the outcome variable for every 1-unit of change in the predictor variable' (Lani, n.d.). Boukhris et al. (2016) in a study of all 'singleton full-term infants born alive [in Québec] between January 1, 1998 and December 31, 2009' (*n* = 145,456) found that exposure to SSRIs during the second and/or third trimester more than doubled the risk of autism (aHR = 2.17; CI: 1.20, 3.93).

Two other studies had mixed results. Hviid, Melbey, and Pasternak (2013) in 'a cohort study of all singleton live births in Denmark from 1996 through 2005' found an association between SSRI use during pregnancy and autism but it was not statistically significant (adjusted rate ratio = 1.20; CI: 0.90, 1.61). However, SSRI use 2 years to 6 months before pregnancy showed a statistically significant increased risk of autism (aRR = 1.46; CI: 1.17, 1.81) (Hviid, Melbey, & Pasternak, 2013). Clements et al. (2015) compared 1,377 children diagnosed with ASD matched 1:3 with neurotypical controls. In gathering the history of the parents and children in the study they found that caesarean section delivery increased autism risk 28% (aOR = 1.28; CI: 1.11, 1.47) (Clements et al., 2015). They also found a statistically significant association between antidepressant use and autism if the exposure occurred during prepregnancy ('anytime before the last menstrual period', read: ever), preconception ('3 months before

conception'), the first trimester, or second trimester — adjusting for 'gender, race, birth year, insurance type, maternal age, and median income' (Clements et al., 2015, p. 728). But then they built a second model that controlled for past history of maternal depression claiming that they wanted to 'address the possibility of confounding by indication' (Clements et al., 2015). As described above, Croen et al. (2011) did not find an association between maternal depression in the absence of antidepressant use and autism so it is not clear that confounding by indication is actually a problem in this case. Clements et al. (2015) seem to assume that maternal depression itself can cause autism but they make no effort to suggest a mechanism of action nor do they provide empirical evidence to support this assumption. Their second model showed a statistically significant association between antidepressant use and autism if the exposure occurred during prepregnancy (aOR = 1.62; CI: 1.17–2.23) and an elevated but not statistically significant risk if antidepressant exposure occurred during preconception and pregnancy (Clements et al., 2015). One of the co-authors of Clements et al. (2015) reported ties to each of the five largest antidepressant manufacturers in the world and two other co-authors also reported financial conflicts of interest. I will show in chapter 5 that the funding effect consistently distorts research outcomes. The political economy of the regulation of SSRIs is the subject of chapter 8.

1.9.4 Activist initiated participatory science

Next, there are studies produced as a result of 'Activist-Initiated Participatory Science' (Moore, 2006). In the wake of rising autism prevalence, parents' groups have often funded their own research into possible environmental triggers associated with autism. It would be easy to dismiss these studies because they are often underfunded and

undersized, usually conducted by outsiders and those on the fringe of the scientific community, and published in obscure journals if at all. But to dismiss these studies out of hand would be to misunderstand the political economy of science and medicine in general (which I will discuss more fully in chapter 5) and autism in particular.

Activist-Initiated Participatory Science has a long history going back to the social movements of the 1960s and 1970s that were alarmed by the role of scientists in the chemical and weapons industries (Moore, 2006, p. 301). Scientists were both targets of and sometimes participants in these activist social movements (Moore, 2006, p. 301). Activist-Initiated Participatory Science has often been a key feature of anti-toxics/anti-pollution campaigns [Brown, 1992; Bullard, 1994; Lichterman, 1996; and Allen, 2003] and health-related social movement groups [Morello-Frosch, 2006] (Moore, 2006, p. 305). Many of these studies could also be considered examples of 'popular epidemiology' which is defined as 'the process by which laypersons gather scientific data and other information, and also direct and marshal the knowledge of other experts in order to understand the epidemiology of a disease' (Brown, [1992], p. 269, in Moore, 2006, p. 305). In this section I will review studies on EMF/RFR (1.9.4.1), acetaminophen (1.9.4.2), and vaccines (1.9.4.3).

1.9.4.1 EMF/RFR

Herbert and Sage (2013a, 2013b) argue that electromagnetic frequency and radiofrequency exposures (EMF/RFR) may be associated with autism. In 1993, only 6% of American adults owned a cell phone; in 2018 that number was 95% (Hertsgaard & Dowie, 2018). Exposure to EMF/RFR comes from cell phones, microwave towers that

now dot the landscape, and wireless routers that have become standard appliances in homes and offices (Herbert & Sage, 2013b, pp. 222–223). Herbert and Sage (2013a) show that there are ‘a series of parallels between the pathophysiological and genotoxic impacts of EMF/RFR and the pathophysiological underpinnings of’ ASD including ‘DNA damage; immune and blood-brain barrier disruption; cellular and oxidative stress; [altered] calcium channel [signaling]; disturbed circadian rhythms; hormone dysregulation; and degraded cognition, sleep, autonomic regulation and brainwave activity’ (p. 200). They argue that increased EMF/RFR exposure contributes to total ‘allostatic load — the sum total of stressors and burdens on the body’ and that even small increases in allostatic load can produce significant impacts on health (Herbert & Sage, 2013a). Further, they cite, Juutilainen, Kumlin, and Naarala [2006] who show that EMF/RFR can increase the harms caused by other toxicants ‘when both exposures occur together’ (Herbert & Sage, 2013a, p. 193). An excellent political economy of the lack of regulation of EMF/RFR is provided by Hertsgaard and Dowie (2018).

1.9.4.2 Acetaminophen (Tylenol, Panadol, Paracetamol)

Acetaminophen (sold under the brand names Tylenol, Panadol, Paracetamol) is used by up to 65% of pregnant women in the U.S. (Werler, Mitchell, Hernandez-Diaz, & Honein, 2005). Acetaminophen is one of three analgesics derived from aniline dye (which initially was derived from benzene, a component of coal tar); the other two, acetanilide and phenacetin, were withdrawn from the market because of their toxicity (Bertolini et al., [2006], in Schultz & Gould, 2016). Torres (2003) first proposed that antipyretics (drugs used to reduce fevers) during pregnancy might cause neurodevelopmental disorders such as ASD. This theory was later developed by Schultz (2008, 2010, 2016),

a successful dentist who returned to university and got a Ph.D. in public health epidemiology after his son regressed into autism. The temporal association between acetaminophen and autism is intriguing. For decades, aspirin was the dominant pain reliever and antipyretic in the U.S. However, in 1980, aspirin was found to cause Reye's Syndrome in some children so doctors recommended that parents use acetaminophen instead (Bauer & Kriebel, 2013). Sales of acetaminophen in the U.S. increased from $400 million in 1982 to $2.6 billion in 2008 (Bauer & Kriebel, 2013). A systematic review by Bauer, Kriebel, Herbert, Bornehag, and Swan (2018) identified nine studies conducted since 2013 that show an association between acetaminophen use and adverse neurodevelopmental outcomes. Two of those studies looked at the association between Tylenol during pregnancy and ASD in offspring. Avella-Garcia et al. (2016) found that males exposed to acetaminophen for all three trimesters have significantly elevated risk of autism ($\beta = 1.91$; CI: 0.44, 3.38). Liew, Ritz, Virk, and Olsen (2016) found that persistent exposure to acetaminophen in utero (>20 weeks) increased the risk of autism with hyperkinetic disorder (ADHD) by 77% (HR = 1.77; CI: 1.24, 2.53). Bauer and Kriebel (2013) and Frisch and Simonsen (2015) found an association between male circumcision and autism and that raises the question as to whether acetaminophen sometimes administered before and/or after the procedure may be the trigger. Clearly more research is needed. However, it is very difficult to rule out confounding factors; in the case of acetaminophen and pregnancy the confounding factor could be the underlying illness or inflammation and with acetaminophen and circumcision the confounding factors could pain/trauma associated with the procedure itself or vaccines administered around the same time.

1.9.4.3 Vaccines

The CDC, Food and Drug Administration (FDA), National Institutes of Health (NIH), American Medical Association, and the American Academy of Pediatrics all argue that vaccines do not cause autism. They point to more than 20 scientific studies that have concluded that there does not appear to be an association between vaccines and autism (Fombonne & Chakrabarti, 2001; Madsen et al., 2002; Mäkelä, Nuorti, & Peltola, 2002; Pichichero, Cernichiari, Lopreiato, & Treanor, 2002; Hviid, Stellfeld, Wohlfahrt, & Melbye, 2003; Madsen et al., 2003; Nelson & Bauman, 2003; Stehr-Green, Tull, Stellfeld, Mortenson, & Simpson, 2003; Verstraeten et al., 2003; Wilson, Mills, Ross, McGowan, & Jadad, 2003; Andrews et al., 2004; Heron & Golding, 2004; Smeeth et al., 2004; Honda, Shimizu, & Rutter, 2005; Fombonne et al., 2006; Miles & Takahashi, 2007; Thompson et al., 2007; Baird et al., 2008; Hornig et al. 2008; Schechter & Grether, 2008; and Tozzi et al., 2009). Critics contend that there are problems of study design and conflict of interest with each of these studies (Handley, n.d.). Furthermore, they point out that even though randomised double blind controlled trials are the gold standard of biomedicine, *none* of these studies has a proper control group of unvaccinated children.

The case to answer in connection with vaccines and autism is surprisingly straightforward. Vaccines often contain toxic ingredients. The U.S. vaccine schedule increased sharply starting in 1987 which coincides with the inflection point in the autism epidemic. The vaccine schedule now starts earlier which puts it in key developmental windows. There are at least 10,000 parental eyewitnesses who claim that vaccines caused autism in their children. There are 83 instances where the vaccine court

awarded compensation to families whose children developed autism following vaccination. The flu shot during pregnancy appears to increase the risk of autism, several studies have shown an elevated risk of autism associated with the hepatitis B vaccine, and there are concerns about the safety of other vaccines. Five studies funded by parents' groups or interested doctors comparing the health outcomes between vaccinated and unvaccinated children show that unvaccinated children have fewer chronic illnesses including autism. Three CDC researchers appear to have violated accepted scientific practices or committed outright fraud in connection with key vaccine safety studies. I will briefly cover each of these points below.

Vaccines often contain a number of additives including ethylmercury, aluminum hydroxide, aluminum phosphate, and neomycin and streptomycin (antibiotics). Thimerosal is still in three different brands of multidose flu vaccines (Fluvirin, Flulaval, Fluzone), one meningococcal vaccine, and three tetanus-diphtheria vaccines (Thomas & Margulis, 2016, p. 14). Thimerosal is 49.6% ethylmercury which is a known neurotoxin (Grandjean & Landrigan, 2014). Aluminium is a known neurotoxin (Finberg et al., 1986; Joshi, 1990; Wisniewski, Moretz, Sturman, Wen, & Shek, 1990; Bishop, Morley, Day, & Lucas, 1997; Petrik, Wong, Tabata, Garry, & Shaw, 2007; Tomljenovic & Shaw, 2011a; and Shaw et al., 2014). Even as it was phasing thimerosal out of some vaccines, the U.S. Advisory Committee on Immunization Practices (ACIP) added to the schedule as much as 25 µg of thimerosal and 625 µg of aluminium for pregnant women (which exposes the fetus to these metals during a vulnerable developmental window) along with up to 50 µg of thimerosal and 1,000 additional µg of aluminium for children in the first two years of life (Miller, 2016b). Furthermore, some people are allergic to neomycin and streptomycin. Using in vitro experiments, Haley (2005) showed that the

synergistic effect of thimerosal, plus aluminum, plus neomycin, plus testosterone is one hundred times more toxic than thimerosal alone — which he argues might explain why autism rates are so much higher in boys than in girls.

The vaccine schedule in most developed countries increased dramatically in the last 65 years. In the 1950s, children in the U.S. received seven vaccinations before age six. In 1983, the U.S. vaccination schedule mandated ten vaccinations. From 1983 to 2013, the number of recommended vaccinations more than tripled to thirty-six and the U.S. now gives more doses of more vaccines at earlier ages than any other country in the world (Miller & Goldman, 2011). If vaccines work as advertised, they should reduce infant mortality. But Miller and Goldman (2011) found the opposite — in developed countries the more vaccines on the schedule the higher the infant mortality rate ($r = 0.992$, $p = 0.0009$). That does not establish a causal connection with autism per se. But critics argue that the total allostatic load on children (from the ingredients listed above and from other environmental factors described in this chapter) may have increased in the last three decades.

A growing body of literature from toxicologists and environmental epidemiologists shows that there are ‘windows of vulnerability’ (Miodovnik, 2011) where the human body is uniquely susceptible to toxicants. Critics point out that not only has the vaccine schedule tripled, but it has also moved earlier — starting now in pregnancy — so the bulk of the vaccine schedule is administered when the human body is uniquely vulnerable to toxic insults. Johanson (1980) and Adinolfi (1985) showed that the blood-brain barrier is not fully developed in infants. Zheng (2001) writes, ‘chemical exposure at a young age may have profound neurotoxic consequences’. During early development

the blood-brain barrier is porous to allow blood-borne nutrients to reach the growing brain; ‘however, this relative openness of the barriers in early life renders the brain highly susceptible to insults from exposure to toxic substances’ (Zheng, 2001, p. 7). Grandjean and Landrigan (2014) write that ‘in utero and during infancy and early childhood... chemicals can cause permanent brain injury at low levels of exposure that would have little or no adverse effect in an adult’ (p. 330). The FDA takes no account of these windows of vulnerability and allows safety studies conducted with healthy adults to be the basis for licensing vaccines that are added to the schedule for pregnant women, neonates, and infants.

In 1986 the U.S. Congress passed the National Childhood Vaccine Injury Act (NCVIA) that provided legal liability protection to vaccine makers. It set up a separate vaccine court under the United States Court of Federal Claims to administer compensation to people injured by vaccines. As autism rates grew in the United States, 5,600 families filed suit arguing that vaccines caused autism in their children. These claims were eventually consolidated in what was called the Omnibus Autism Proceedings. Another 3,000 families who wished to file suit were denied standing because they did not file the required paperwork within four years of the injury as required by the national Vaccine Injury Compensation Program (VICP). In the U.K., 1,500 families filed suit alleging a connection between vaccines and autism in their children. By 2012 all of these claims had been denied by the courts. Of course, not all class action lawsuits have merit. But these cases highlight an unusual and uncomfortable conflict at the heart of the autism epidemic — the overwhelming majority of doctors say there is no association between vaccines and autism, but many parents of children on the spectrum say that they saw with their own eyes that vaccines caused their children to regress.

Holland, Conte, Krakow, and Colin (2011) discovered 83 instances where the Vaccine Injury Compensation Program in the U.S. awarded compensation to families of children who developed autism as a result of vaccines. Holland et al. (2011) point out that the table of injuries that can be compensated by the VICP includes encephalopathy and the VICP's definition of encephalopathy is very similar to the *DSM-IV* definition of autism (p. 495). In a cruel twist of administrative law, sometimes the Special Masters of the Vaccine Court are willing to grant compensation for vaccine injuries that produce symptoms characteristic of autism so long as the petitioners describe these symptoms as 'autism-like' (rather than autism per se) and/or include other co-morbid conditions (Holland et al., 2011). The 83 cases establish that there is some connection between vaccines and autism, it is just not clear how large the connection may be because the necessary research to solve that question has never been done (i.e. the CDC has never funded a study with an unvaccinated control group).

Because there are many vaccines on the schedule, many combined vaccines (MMR, DTaP), and many vaccines given at a single 'well-baby' visit it is difficult to measure the safety in the population of any one vaccine. Clinical trials as part of the licensure process should provide assurances that each individual vaccine is safe but as I will show in chapter 9, the licensure process at the FDA is often too short, studies are too small, the contents of placebos are not regulated, and the population in the clinical trials is usually healthier and older than the target population. But the effect of the flu shot during pregnancy and the hepatitis B vaccine given on the first day of life can be studied in isolation because they are not necessarily given with other vaccines. Zerbo et al. (2017) in a cohort study using in-house data from Kaiser Permanente (private health

maintenance organisation) of 196,929 children, of whom 3,103 had autism spectrum disorder, found that maternal vaccination with the flu shot during the first trimester was associated with a 20% increased risk of autism (Zerbo et al. 2017, p. 1). They later applied a Bonferroni adjust to make the association disappear but I explain in chapter 9 why this statistical manoeuvre rests on a weak theoretical foundation. Gallagher and Goodman (2008) using data from the National Health and Nutrition Examination Survey 1999–2000 found that boys who received all three doses of the hepatitis B vaccine (*n* = 46) were 8.63 times more likely (CI: 3.24, 22.98) to have a developmental disability including autism than boys who did not receive all three doses (*n* = 7). Gallagher and Goodman (2010) using data from the National Health Interview Survey 1997-2002 found that boys 'who received the first dose of hepatitis B vaccine during the first month of life had 3-fold greater odds for autism diagnosis (n = 30 with autism diagnosis and 7,044 without autism diagnosis; OR = 3.002; CI: 1.109, 8.126)' as compared with 'boys either vaccinated later or not at all' (p. 1669). The Gallagher and Goodman (2008, 2010) studies are unusual because they are among the few in the vaccine safety literature that do not have a financial conflict of interest.

There are no safety studies that prove the safety of the entire vaccines schedule. Defenders of the current vaccine schedule argue that since vaccines are so obviously beneficial it would be unethical to deny this life saving medical intervention to those assigned to a control group. But this assumes away the question ('are vaccines safe and effective?'). In the absence of double blind randomised control trials (RCTs) from established public health agencies, parents' groups and interested doctors have funded their own research comparing the health outcomes between vaccinated and unvaccinated populations. Studies conducted by the Dutch Association of Critical

Diseases (NVKP) in 2004, Generation Rescue in 2007, Dr. Paul Thomas in 2016, and (two studies led by) Anthony Mawson in 2017 (funded by Generation Rescue and the Children's Medical Safety Research Institute) found that autism rates were significantly lower in the unvaccinated population. All of these studies would be subject to the funding effect (that will be discussed in chapter 5) but the mainstream scientific community has no studies to counter them because the CDC has never funded a study with an unvaccinated control group.

On three separate occasions, officials acting on behalf of the CDC appear to have engaged in manipulation of data and/or outright fraud in connection with vaccine safety studies. Using the Freedom of Information Act, e-mails were turned over that showed that Verstraeten et al. (2003) intentionally manipulated the data to cover up a statistically significant association between thimerosal and autism (Kirby, 2005). Poul Thorsen was the data manager on Madsen et al. (2002, 2003) and he was indicted by a federal grand jury and charged with '13 counts of wire fraud and 9 counts of money laundering' in April 2011 (Crosby, 2011). More recently, CDC research scientist William Thompson confessed (in recorded phone conversations, in documents turned over to Congress, and in a statement issued by his attorney) that DeStefano, Bhasin, Thompson, Yeargin-Allsopp, and Boyle (2004) intentionally omitted data that showed a statistically significant association between administration of the MMR vaccine before age 3 and autism in African American boys (Ferris, 2015). The political economy of the regulation of vaccines is the topic of chapter 9.

1.9.5.0 Additional risk factors

Finally there are a couple of risk factors that do not fit neatly into the categories described above — the age of parents at conception and diabetes in pregnant women.

1.9.5.1 Age of the parents at conception

Durkin et al. (2008) found that if the father is over 40 years old at the time of conception, the risk of autism increases by 40% (OR = 1.4; CI: 1.1, 1.8). If the mother is over 35 at conception, the risk of autism increases by 30% (OR = 1.3; CI: 1.1, 1.6). Having both a father over 40 and a mother over 35 at conception increases the risk threefold that the child will develop autism (OR = 3.1; CI: 2.0, 4.7). Four other studies found a statistically significant association between maternal age and autism (Croen, Grether, & Selvin, 2002; Glasson, 2002; Bhasin & Schendel, 2007) and four additional studies found a statistically significant relationship between advanced paternal age after controlling for maternal age (Glasson, 2002; Lauritsen, Pedersen, & Mortensen, 2005; Reichman & Teitler, 2006; Croen, Najjar, Fireman, & Grether, 2007). One study found neither parent's age to be predictive of autism spectrum outcomes (Larsson et. al., 2005).

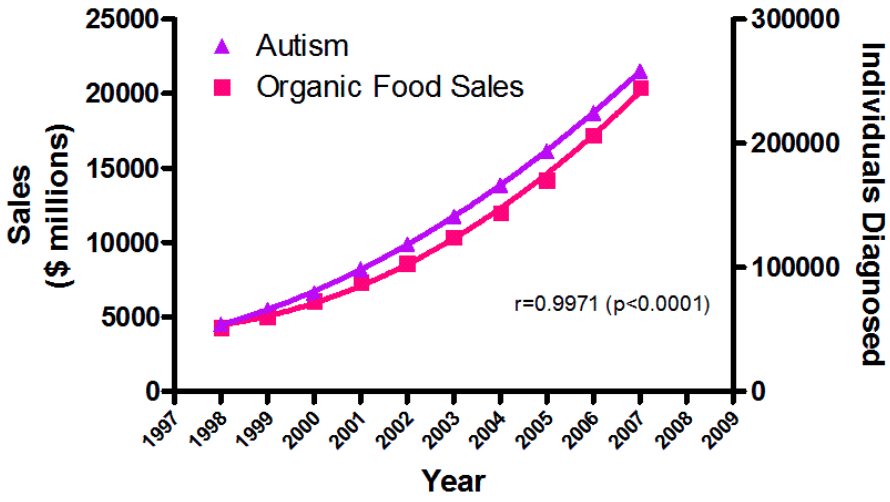
1.9.5.2 Diabetes

Li et al. (2016) in a cohort study of 2,734 children found that 'mothers with obesity and pregestational diabetes (hazard ratio = 3.91; CI: 1.76, 8.68) and those with obesity and gestational diabetes (HR = 3.04; CI: 1.21, 7.63) had a significantly higher risk of offspring ASD' (p. 1). It is common to blame 'lifestyle factors' (diet, lack of exercise)

for these adverse health outcomes, however, there is growing evidence that endocrine disrupting chemicals (pesticides, plastics) may be contributing to both obesity and diabetes (Gore et al., 2015). So even the association between obesity plus diabetes and autism may be a story of environmental triggers.

1.10 Correlation is not causation

Figure 1.2: Rise in U.S. Autism Rates and Rise in Organic Food Sales 1998 to 2007.



Source: Doctorow (2013).

After presenting all of the above data, there is still the issue that correlation does not equal causation. In a debate about vaccine safety, tech writer Cory Doctorow (2013) cited the above chart on the correlation between the rise of autism and the rise of organic food sales to point out the perils of confusing correlation and causation (and it was soon picked up by a range of science blogs). As any statistician will point out, correlation is only the start of the conversation, one also needs to establish the causal

mechanism(s) that may be driving the effect on the dependent variable. But in all of the cases described above, the causal pathway seems plausible.

What is interesting about the autism and organic food chart is that there may be causation here too — it is just that people usually get the arrow of time wrong. Organic foods sales are not likely causing the rise in autism. But it seems possible that fears over the rise of autism (and possible links between autism and pesticides) may be driving people to buy organic food.

Furthermore, public policy decisions are often made on the basis of weaker correlations than those described in this chapter. A reduction in prison recidivism by 10% is probably enough to keep a counseling program funded even though it may have had nothing to do with the outcome. Given the stakes, it would be odd to completely dismiss correlation in each of the examples listed above, especially given that there is a plausible physiological explanation that goes along with each factor. In the midst of this epidemic, the phrase ‘correlation is not causation’ has become an agnotological device that diverts attention from possible environmental factors.

Epidemiologists point out that one study is never determinative. Rather one should take the preponderance of all of the studies on a particular topic in order to establish causation. But the possible environmental triggers listed in this chapter are made by some of the largest and most politically powerful firms in the world. As I will show in this thesis, these firms are able to shape the public research agenda to *prevent* many studies from ever being funded in the first place. In the event that a large number of studies somehow are conducted over time, for example in the case of asbestos, lead, or

tobacco, even if the preponderance of evidence points to a likely causal association, that does not necessarily lead to increased regulation, victims' compensation, or cleanup.

1.11 A different standard?

Products are often pulled from the market that have smaller effect sizes than those listed above. Vioxx (Rofecoxib) was pulled from the market in 2004 (Rubin, 2004). It increased heart attack risk from 0.1 to 0.4 (Bombardier et. al, 2000). But the results were statistically significant only for those patients who already had a history of myocardial infarction or other existing heart problem (Bombardier et. al, 2000). In 2002, NIH stopped the trial of hormone replacement therapy in connection with the Women's Health Initiative (WHI) because of finding: breast cancer 26% increase, colorectal cancer 37% *decrease*, heart attack & cardiac death 29% increase, hip fracture 34% *decrease*, pulmonary embolism 113% increase, stroke 41% increase (Writing Group for the Women's Health Initiative Investigators, 2002). All of these are below the 200% increase often required to establish causation in tort cases (Cranor, 2016, p. 228). Zicam Cold Remedy was pulled from the market in 2009 because 130 people complained of loss of sense of smell over the course of a decade (Harris, 2009). But a loss of sense of smell is also an effect of the common cold; there was no evidence that it was a statistically significant effect of Zicam (Harris, 2009). In these cases, various parties (corporations, the FDA, and NIH) made decisions based on an abundance of caution to protect public health.

Much of the data shown above, linking environmental insults to autism, have bigger effects sizes than what is usually necessary to establish legal liability and trigger a recall.

And yet, with these environmental triggers that may be linked to autism, the CDC, FDA, EPA, and NIH have *not* shown the same abundance of caution in protecting the health of children. These asymmetrical responses by public health officials appear to be a result of political power, not good science.

1.12 Research question

Autism is an epidemic and a pandemic by any reasonable definition of those words. The inflection point in rising autism prevalence rates is around 1987 (McDonald & Paul, 2010). It is worldwide and it seems to affect every income group, race, and ethnicity but prevalence rates are particularly high in liberal capitalist developed countries. It appears to be driven by environmental sources. Yet it is happening even as many sources of pollution (e.g. smog, DDT, smoking, etc.) are going down in many developed countries. There are a finite number of factors with sufficient global scale during that time period that could be responsible.

Solving the riddle of autism would seem to require figuring out patterns, understanding correlations, identifying risk, and using massive amounts of data to select likely targets for regulatory action. In an earlier era, that might have been beyond the capacity of government agencies. But in the age of terrorism, governments in the U.S., the U.K., and Australia are actually extremely good at using big data to figure out patterns, correlations, risk, and likely targets. It is just that most of those resources are devoted to (military) defense rather than public health. The point is, solving a problem this complex is no longer beyond the *technical capacity* of government. It appears to be a problem of *political will*, not institutional ability.

What is strange about autism is that none of the government institutions in a position to respond to the epidemic seem to have a sense of urgency in finding the cause. This is a crisis that demands a massive coordinated policy response. And yet, thus far, there is no policy response aimed at autism prevention at all. So my research question is: given rising prevalence rates and the extraordinary impacts of ASD on individuals, families, and communities, what explains why public health authorities, thus far, have failed to ban or restrict toxicants that have been shown to increase autism risk? The evidence presented over the next nine chapters will make the case that one possible reason why public health authorities have failed to ban or restrict toxicants that have been shown to increase autism risk is because of extraordinary levels of cultural and financial capture of almost all levels of science, medicine, and government.

1.13 What the thesis does not cover

I focus entirely on the political economy of research in connection with autism causation and prevention. I do not focus on education, treatment, or services for those who already have autism; nor do I focus on the psychological, sociological, or anthropological experience of autism for individuals, families, or communities — as those topics are already covered well by others.

1.14 Conclusion

In this chapter I showed that the history of autism is contested and winding; provided definitions of autism; documented rising autism prevalence in the U.S., Australia, and

worldwide; showed that the fiscal implications are already dire and projected to get worse; explained the problems with genetic theories of causation; showed that neither diagnostic expansion and substitution nor changing definitions of autism entirely account for the sharp rise in prevalence; explored environmental factors associated with autism; discussed issues of correlation and causation; compared the lack of response to possible environmental triggers with the more aggressive U.S. federal response to other products with lower relative risks; stated my research question; and also explained what facets of the debate will not be covered. In the next chapter I will discuss the theoretical framework that I use to approach this material.

Chapter 2

Theoretical framework

2.0 Introduction

Interpretation is what gives meaning to empirical evidence. Interpretation is a subjective process so it is important to be clear about how one approaches the data. My aim in this chapter is to explain the theoretical lenses I use to understand the evidence in connection with autism. My epistemology is informed by the contextual empiricism of Helen Longino (2.1). This thesis is a work of synthesis with some important differences from the usual approaches of systematic review and meta-analysis (2.2). My methodology is informed by both descriptive epidemiology and political epidemiology (2.3). I use Steven Lukes' study of power (2.4) to understand how power shapes science and medicine. I conclude this section with a discussion on the social construction of disability (2.5).

2.1 Contextual Empiricism

By most accounts positivism is dead. Ever since Kuhn (1962) there has been a growing recognition that science is social. But it is not entirely clear what replaces positivism. While poststructuralism has become dominant in the social sciences, it does not offer a solid foundation for making science-based policy decisions. At the end of the day, scientists, doctors, policy makers, and citizens are either going to take some action or not (and not taking an action is itself a form of action). And so society needs some sort of basis, however imperfect, for weighing conflicting evidence. American philosopher

of science Helen Longino's (1990) solution to this problem is 'contextual empiricism' that attempts to blend the best elements of the empiricist approach with the best insights from its critics. She writes, 'It is empiricist in treating experience as the basis of knowledge claims in the sciences. It is contextual in its insistence on the relevance of context — both the context of assumptions that supports reasoning and the social and cultural context that supports scientific inquiry — to the construction of knowledge' (Longino, 1990, p. 219). She concludes, 'A consequence of embracing the social character of knowledge is the abandonment of the ideals of certainty and of the permanence of knowledge. Since no epistemological theory has been able to guarantee the attainment of those ideals, this seems a minor loss' (Longino, 1990, p. 232).

There are aspects of contextual empiricism that make me uncomfortable. It feels like a straddling of two different epistemologies, trying to have it both ways, a hybrid that will do justice to neither contextualism nor empiricism. And yet the notion that a system of thought should be just one thing is itself a socially constructed value judgment. One can make the case that the both/and nature of contextual empiricism is a strength that overcomes Cartesian and other dualisms and allows room for paradox, dissonance, and an on-going unfolding of knowing.

Following Longino, in this thesis I will closely examine the available data from a wide range of scientific studies as well as the social context in which this knowledge is produced. Consistent with contextual empiricism I believe that within the range of what is 'known' now, there are relatively better and worse choices available to policymakers. But also following Levins and Lewontin (1985) and Longino, I hold all conclusions as

permanently tentative because they are subject to change as new data and context become available.

Longino (1990) argues that objectivity is ‘a matter of degree’ (p. 76). She proposes a method for increasing objectivity even while recognising that this is a socially embedded idea. She writes:

> Scientific communities will be objective to the degree that they satisfy four criteria necessary for achieving the transformative dimension of critical discourse: (1) there must be recognized avenues for the criticism of evidence, of methods, and of assumptions and reasoning; (2) there must exist shared standards critics can invoke; (3) the community as a whole must be responsive to such criticism; (4) intellectual authority must be shared equally among qualified practitioners (Longino, 1990, p. 76).

Longino (2001) argues that these discursive methods are not ‘offered as a criterion of truth, but a criterion distinguishing legitimate from illegitimate consensus’ (p. 131). Longino (2001) also renames her theory critical contextual empiricism (CCE) to reflect the critical nature of the approach.

Solomon and Richardson (2005) point out that there is not a lot of empirical evidence that the methods of CCE, if properly followed, necessarily produce more reliable scientific outputs. The history of science suggests that closed systems also produce scientific breakthroughs (Solomon & Richardson, 2005). So while CCE is ‘intuitively

reasonable' it is normative and marries epistemology to liberal democratic politics (M. Solomon & Richardson, 2005, p. 216). But one might reply, how does one measure 'good science'? If there can be no God's eye perspective on one's findings (because one is always part of the world one is studying) then the process of reaching consensus necessarily leads one back to the sort of methodological process of criticism and debate that CCE recommends. In order for science to be legitimate it must go through some sort of political process and so urging science to apply an open and dialogical process seems healthy for both science and society.

2.2.1 A brief note on the epistemology of alternative sources

In addition to journal articles in peer reviewed publications I sometimes use first person accounts from families, investigative reports from muckraking journalists, internal government documents obtained by parents using the U.S. Freedom of Information Act (FOIA), the accounts of whistleblowers, and documents turned over via discovery in legal proceedings. In an ideal world, one would only rely on peer reviewed studies from academics who have no conflict of interest published in academic journals with no conflict of interest. But that ideal world does not exist in the study of toxicants. Academia has been slow to study this crisis so the pool of academic studies is somewhat limited (with the exception of the UC Davis MIND Institute and a handful of other environmental epidemiologists whom I rely on). As I will show throughout this thesis, public health authorities have often acted in ways that are counterproductive, so the pool of useful government public health studies is limited as well. If one wants to study the impact of toxicants, alternative sources can provide essential new data and insights.

But it is not just necessity; epistemologically, I think these sources are more reliable than they are often given credit for. First person accounts are an integral part of legal proceedings (Broun et al., 2014) and our construction of understanding in everyday life (Longino, 2001, p. 2; McMyler, 2011). Poststructuralism in the social sciences has affirmed the importance of first person perspectives and flattened prior epistemological hierarchies (I am not saying that one needs to become a poststructuralist, only that first person perspectives are valued in many spheres). Muckraking journalism has been an essential part of uncovering information that is vital to public health for over a century. FOIA requests, the accounts of whistleblowers, and documents turned over via discovery can provide an unvarnished look inside an institution at a time when no one thinks anyone is watching. Furthermore, I will show in chapter 5 that peer review and publication in academic journals do not necessarily protect against bias nor ensure quality to the extent that many believe.

2.3 Synthesis

This thesis is a work of synthesis. I weave together data and insights from political economy, political science, sociology, history, epidemiology, and toxicology to build a case to answer in connection with possible environmental triggers of autism. As a methodology, synthesis is often overshadowed by its more popular quantitative and qualitative cousins (particularly in the U.S.). I believe that synthesis is the proper method for answering my research question because autism sits at the nexus of these different fields of knowledge.

Over the past forty years research synthesis has become increasingly sophisticated (Cooper & Hedges, 2009). Traditional methods of synthesis include systematic reviews and meta-analysis. While I use both systematic reviews and meta-analysis in the thesis, neither approach is exactly the right fit for my research question. That is because the bulk of the research in connection with autism is characterised by financial conflicts of interest. In chapter 5, I show that the funding effect consistently distorts research outcomes. Combining conflicted studies with unconflicted studies in a systematic review or meta-analysis (as is standard practice at the CDC, EPA, FDA, and NIH) combines biased studies with unbiased studies leaving the ultimate findings muddled and meaningless. Industry knows this and so it contracts with science-for-hire firms to produce favourable studies that it can use to stymie the regulatory process (Michaels, 2008a). If I were to exclude all studies with a financial conflict of interest (which would be warranted), then in many cases I would be excluding the majority of the research on a particular environmental trigger.

Instead, I draw upon the ideas of ‘thick description’ (Geertz, 1973; Gibson-Graham, 2014) in reviewing the relevant literature. With each of the toxicants listed as a possible environmental trigger for autism I ask what is the relevant data, who are the interested parties, what is the regulatory history, what are the financial conflicts of interest, and how have financial conflicts of interest come to bear on the process? Thick description is rarely used and not well regarded in political economy because it is seen as side-stepping some of the hard choices and critical debates in theory and practice that are the coin of the realm in the field. But in this case, I believe thick description is the proper approach. As I showed in chapter 1, the gap between what public health officials say about autism and what is actually on the page of scientific journals is enormous. By

zooming in on both the empirical data and its social context I can analyse and question consensus in ways that will hopefully produce a new and more multifaceted understanding of autism.

2.4 Descriptive epidemiology and political epidemiology

Consistent with the thick description described above, my thesis is informed by both descriptive epidemiology and political epidemiology. The CDC's (2012) *Principles of Epidemiology* describes descriptive epidemiology as follows:

> Clusters or outbreaks of disease frequently are investigated initially with descriptive epidemiology. The descriptive approach involves the study of disease incidence and distribution by time, place, and person. It includes the calculation of rates and identification of parts of the population at higher risk than others. Occasionally, when the association between exposure and disease is quite strong, the investigation may stop when descriptive epidemiology is complete and control measures may be implemented immediately. John Snow's 1854 investigation of cholera is an example (p. 1–17).

I write more about John Snow and the 1854 London cholera outbreak in the next chapter. While is it common to think of labs and test tubes as tools for responding to an epidemic, descriptive epidemiology shows that maps, patterns, logic, and reason can be powerful tools as well. The Boston University School of Public Health (n.d.) notes that

even though descriptive epidemiology began with the study of infectious diseases, now it is also used to study chronic diseases (‘Hypothesis Formulation’, para. 1).

Some descriptive epidemiology has already been done in connection with autism (most notably Croen, Grether, & Selvin, 2002). But given the size of the epidemic, it is remarkable how little descriptive epidemiology is available. Furthermore, the few studies that are conducted are often circumscribed in their approach. Perhaps the lack of descriptive epidemiology stems from the fact that any comprehensive overview of autism must include a discussion about vaccines and including a variable about vaccines in the current political climate is seen by many as a career-limiting decision (Martin, 2018). So for example, Croen, Grether, and Selvin (2002) do not include a variable for vaccination status even though that information might be relevant and would be easy to collect — the lead author works for Kaiser Permanente (a fully enclosed health maintenance organisation) so that data is readily available in-house.

What is striking about the autism epidemic is how universal it is in developed countries and how it does *not* fit traditional patterns of an epidemic. It is increasing rapidly in all developed countries (where there is good data on autism prevalence), autism is diagnosed at similar rates across all income groups (with slightly higher rates in higher income families that may be because of greater access to diagnostic services); and there does not appear to be a distinction between urban, suburban, and rural areas. This is unusual. Higher income groups usually have better health outcomes and poor people have higher rates of diabetes, heart disease, and all sorts of other chronic health problems. Urban areas and rural areas have different exposures to pesticides and pollution. And a wide range of variables in different countries including weather, diet,

pollution, and healthcare systems usually produces different health outcomes. But not with autism.

But there is an additional step to my work in that I am examining the interaction between the patterns in the autism epidemic and the political factors that may have contributed to these patterns. So my methodology is also informed by political epidemiology (Muntaner et al., 2010, 2011). Pega, Kawachi, Rasanathan, and Lundberg (2013) define political epidemiology as 'the study of the impact of welfare regimes, political institutions, and specific policies on health and health equity' (p. 1). My unique contribution is that I examine the relationship between regulatory capture and autism. My methodology looks at the three descriptive epidemiology factors (time, place, and person), as well as the sorts of factors discussed in political epidemiology (toxicants, law, and regulatory institutions).

To be clear, this thesis is a work of political economy not epidemiology. But issues of politics, economics, and health intersect. The field of political epidemiology draws from a wide range of sources including the health sciences and the social and behavioural sciences (Pega et al., 2013) — so a contribution from a political economist is not necessarily outside the norm. Furthermore, even if it were outside the norm for a political economist to participate in these debates, the evidence I present in this thesis suggests that the level of cultural and regulatory capture is so extensive in science and medicine that an outsider perspective on the autism epidemic would be warranted.

Navarro (2008) notes that there is a large literature on the 'social and cultural determinants of health', but relatively little research on the 'political determinants of

health' (p. 354). He offers at least three reasons why this might be so. First, 'the public-health field is dominated by professionals trained in medicine and biology rather than in the social sciences. Epidemiologists and statisticians tend to dominate the field of public-health research. To them, politics seems to be very shaky and risky ground, something to be avoided' (Navarro, 2008, p. 354). Second, most public health research is funded by government and government is 'unlikely to fund any type of research that may please some political forces but displease others that have a voice in the funding of research institutions' (Navarro, 2008, p. 354). This is not just hypothetical, Navarro (2008) notes that even in democratic societies, when research is displeasing to the establishment, the response is often the 'discontinuation of one's research funding' (p. 354). Third, Navarro (2008) observes that international bodies like the World Health Organization tend to avoid discussing the political determinants of health because they are trying to reach consensus and do not want to 'antagonize' powerful members. So Navarro (2008) highlights 'the need to undertake studies on politics and health' (p. 354). The traditional Marxian/progressive response to such a call usually focuses on more equal distribution of power and resources, reductions in poverty, and expanded access to (existing capitalist) healthcare. My approach is somewhat different in that I argue that capitalist healthcare itself is part of the problem and that more access would not necessarily improve the situation. Instead one must grapple with the problem of political capture and how it distorts scientific research, medicine, law, and policy in ways that are catastrophic for the health of the public.

2.5 Sociology of Power

Understanding theories of power is important for the study of any disease or complex health condition because power shapes what is studied, what is not studied, and how matters are studied. Science and society are intertwined in epidemics and the response to an epidemic is a reflection of power operating on many dimensions. What follows in this section comes from Steven Lukes' seminal (1974) study *Power: A radical view*.

Lukes' (1974) first dimension of power considers the work of Dahl (1961), Polsby (1963), Wolfinger (1971), and others who developed what is known as the pluralist approach. Lukes (1974) summarising the pluralist view of power writes that it 'involves a focus on *behaviour* in the making of *decisions* on *issues* over which there is an observable *conflict* of (subjective) *interests*, seen as express policy preferences, revealed by political participation' (italics in the original, Lukes, 1974, p. 15). In the pluralists' view, individuals come together to form groups to maximise their interests. Groups compete with each other for power and influence. While it would appear that corporations would dominate that process given their financial superiority, pluralists like Polsby argue that other groups (such as unions, civil rights activists, and environmentalists) can offset corporate power through numerical advantage (turning out more people to vote, lobby, or protest). Like classical economics, pluralism is an equilibrium model that posits that, over time, advantages tend to balance out and that resources from the political process tend to be divided equitably throughout society.

Lukes' (1974) second dimension of power considers the work of Bachrach and Baratz (1970) who argue that real power is also about the ability to control the agenda and the

ability to keep issues off the table. In a critique and elaboration on the pluralists' view, they write: 'to the extent that a person or groups — consciously or unconsciously — create or reinforce barriers to the public airing of policy conflicts, that person or group has power' (Bachrach & Baratz, 1970, p. 8).

So for example, the U.S. Congress almost never debates royalty rates for oil exploration because oil companies have enough political power that they can keep that issue off the agenda. As Schattschneider (1960) wrote, 'Some issues are organised into politics while others are organised out'. Lukes (1974) writes that the second dimension of power 'allows for consideration of the ways in which decisions are prevented from being taken on potential issues over which there is an observable conflict of (subjective) interests...' (p. 20). Wagner's (1995, 1997) work on 'the science charade in toxic risk regulation', Proctor's (1996, 2008) work on 'agnotology', McGoey's (2007) research 'on the will to ignorance in bureaucracy', and the considerable literature on 'undone science' (Gross, 2007; Hess, 2007, 2009; Frickel at al. 2010; Frickel 2014; and Wilyman, 2015) are all interesting applications of and elaborations upon how topics are organized out of science and medicine.

But then Lukes goes one step further in developing what he calls a three-dimensional view of power. Echoing Gramsci's (1971) views on the construction of hegemony and Fanon's (1963) views on internal colonisation, Lukes (1974) argues that power also influences the interests, preferences, and ideation of disadvantaged groups. Power may or may not involve observable conflicts. Power is also about latent conflicts where there is 'a contradiction between the interests of those exercising power and the *real interests* of those they exclude' (Lukes, 1974). Perhaps most controversially, Lukes argues that

those who are excluded from power ‘may not express or even be conscious of their interests’, but, ‘the identification of those interests always rests on empirically supportable and refutable hypotheses’ (Lukes, 1974, pp. 24–25). Michael Reich (1991) in *Toxic politics: Responding to chemical disasters* applies Lukes’ three-dimensional view of power to three cases of toxic contamination (see chapter 4).

Benton (1981), Clegg (1989), and Hay (2002) all take issue with *Power: A radical view* for slightly different reasons. Benton (1981) contends that Lukes’ third dimension of power suffers from the ‘paradox of emancipation’ — one cannot simultaneously support self-emancipation while also arguing that people are unaware of their real interests as a result of the distorting influence of power (p. 162). Clegg (1989) is troubled by the ‘moral relativism’ of Lukes’ third dimension of power. He notes that by Lukes’ own admission, what one’s real interests are ‘will differ according to whether one is a liberal, a reformist, or a radical’ (Clegg, 1989, p. 87). If that is the case then real interests are both a priori and beyond analytical critique (Clegg, 1989, p. 87). Hay (2002) argues that Lukes’ distinction between perceived and real interests is normative and nonfalsifiable in spite of Lukes’ claims that real interests are empirically knowable (p. 181). He also worries that the paternalism inherent in Lukes’ distinction between perceived and real interests may create a ‘paternalist license for tyranny’ (Hay, 2002, p. 182).

None of these critiques appears insurmountable. The problem of ‘false consciousness’ that runs through all of these critiques is a recurring debate within Marxism. But many streams of Marxism have come to accept the need for a vanguard to act as a catalyst for the transformation of consciousness (to shift awareness from perceived to real interests). The enduring success of cigarettes, soft drinks, and trans fats suggests that there clearly

is a distinction between preferences and real interests even if those are difficult to quantify. Furthermore, I think one should welcome normative discussion of interests. That does not render the theory invalid, nor does it necessarily lead to tyranny; robust normative debates are also constitutive of healthy thriving democratic communities.

Lukes' (1974) three dimensional view of power has enormous implications for the study of autism. Autism at first appears to fit the pluralist view of power — a battle between competing groups over resources. But autism also fits the second dimension of power as autism prevention has, thus far, been kept completely off the political agenda. And power also shapes the way that families and autism groups conceive of what is possible politically in the midst of this crisis — focusing for example on insurance reform rather than banning of certain toxic chemicals.

2.5 Social construction of disability

When I present my research on the political economy of autism I often get critical questions on the social construction of disability so I want to briefly explain my approach to that debate.

Wendell (1996) argues that there are two distinct but interrelated aspects to the social construction of disability. First, there are the social, economic, and political conditions which create illness and injuries and impair physical functioning. These include things like war, crime, domestic violence; lack of access to water, food, shelter, or quality health care; working conditions, toxicants in the environment, stress, and poverty. Second, there are the social and cultural factors that determine standards of normality

and how people are included or excluded from full participation in society. These are issues of access; expectations around work and family; rights; and policy issues in connection with the way cities, corporations, buildings, institutions, and laws are set up.

My thesis focuses almost entirely on Wendell's first aspect of the social construction of disability — the social, economic, and political conditions which create illness and injuries and impair physical functioning. I believe that this aspect is under-examined and under-theorised at the moment. These are political economy factors and it seems to me that this is where I can add the most value to the discussion.

There is lots of very good work being done in anthropology, sociology, and cultural studies around Wendell's second aspect of the social construction of disability (see, e.g., Maclean, 2013).

Over the last twenty years, as poststructuralism has become mainstream in the social sciences, many people such as Donna Haraway (1991) argue that disability is *entirely* constructed in the second sense described here. The notion is that there is no disability but for our construction of it socially. In this view, disability is entirely constituted by our actions and beliefs around it.

I disagree with Haraway's (1991) view and I think that Wendell (1996) is correct when she argues that there is a material reality to disabilities such as autism, that this material reality is often caused by our political and economic institutions, and that this material reality is made more or less disabling by psychological and cultural factors and how we set up our society.

If one believes that disability is entirely constituted by our discourses around it, one will likely be displeased by my work (but that is a decision from first principles, so no amount of evidence from me is going to change that view). By the same token if one believes, as I do, that disability is constructed through these two sets of factors (the material and the social), then one sees the poststructural-only approach as an impediment to vitally need political and environmental reforms. It seems to me that the material and poststructural approaches could be complimentary (as a society we should stop the factors that lead to additional physical limitations and do everything we can to create conditions for complete access and accommodation for those with such limitations). But that is not how most people see it, most people see these two different approaches as incommensurable. Furthermore, the poststructural approach is dominant in the social sciences right now so I am swimming against the tide in this thesis.

2.6 Conclusion

In a post-positivist world it is difficult to know how to proceed in weighing evidence so the best one can do is to use contextual empiricism — assemble the most unbiased evidence one can and examine it in its context, knowing that all conclusions are tentative and subject to change. In studying toxicants, one often has to rely on alternative sources and the epistemological validity of these sources is often stronger than one might imagine. My thesis is a work of synthesis but rather than systematic review or meta-analysis I tend to engage in thick description to study how financial conflicts of interest may have shaped research findings. My research is influenced by descriptive epidemiology and political epidemiology while breaking somewhat with the

traditional Marxian literature on the political determinants of health. My research will also be an examination of power and will look at how various interest groups compete for influence, how powerful interests shape the issue agenda through keeping certain issues off the table, and how power shapes the ideation and preferences of the powerful and the powerless. Finally, there are strong disagreements about the social construction of disability; I tend to agree with Wendell (1996) that disability is socially constructed through political economy factors and sociological factors and this thesis will focus on the political economy factors associated with autism. In the next chapter I will explore the histories of science and medicine to better understand the factors that shape the path of scientific research.

Chapter 3

What can the histories of science and medicine teach us about governments' failure to engage in autism prevention?

3.0 Introduction

In chapter 1, I showed that we have a fairly good understanding of the 'time, place, and person' (to use the language of descriptive epidemiology) associated with autism. In 1925, Sukhareva published the first case series of a disorder that today we would call autism based on her work with children in Moscow. In 1943, Kanner published the first case series in the English language based on his practice in Baltimore, and Asperger soon followed with a case series from Vienna. But autism was still a relatively rare condition for several decades. Then in the late 1980s, autism rates started to skyrocket in the U.S. and other developed countries and they have continued to rise ever since (McDonald & Paul, 2010). Autism appears in all industrialised countries (with some important variation) and cuts across all income groups, ethnicities, regions, and is much higher in males than in females.

This is exactly the sort of crisis that a century of progressive reforms were designed to address. Industrialised countries have a range of public health agencies for the purposes of addressing epidemics, regulating toxic substances, and advancing a range of health objectives in the population. In the U.S., the Department of Health and Human Services (that includes the National Institutes of Health, the Centers for Disease Control and Prevention, the National Center on Birth Defects and Developmental Disabilities, and the Agency for Toxic Substances and Disease Registry), the Environmental Protection

Agency, the Food and Drug Administration, the Department of Agriculture, plus state public health agencies, and a network of hospitals and research universities are seemingly well situated to address an epidemic like this. But it has been thirty years since the start of the autism epidemic and the response from the U.S. government has not matched the scale of the crisis. Resources devoted to autism research are still minimal, most government agencies do not even use the word 'epidemic', no biomarkers have been identified, and most of the research money is directed towards proving genetic causation even though 'there is no such thing as a genetic epidemic' (Kirby, 2005, p. xiii) and the Director of the NIH acknowledges that 'genes alone do not tell the whole story' (Collins, 2006). In spite of a wealth of information about known environmental risk factors there is almost no public discussion about autism prevention. The AIDS epidemic in the U.S. peaked in 1995, just 14 years after the first published case series on the disorder (Osmond, 2003) in response to a range of preventative measures and pharmaceutical interventions. Autism is still on square one even though it has been 90 years since the first case series and 30 years since the start of the epidemic. Science, medicine, and government in the U.S. appear stuck in paradigms and approaches that are not working and yet they seem unable to shift gears toward more promising avenues of inquiry. What explains the failure, thus far, of established public health agencies in the U.S. to respond effectively to this epidemic?

Histories of science and medicine can help us to understand how and why the government response to the autism epidemic has been inadequate thus far. What I will show in this chapter is that this is not the first time that medicine in general and public health agencies in particular have failed in response to a crisis. Historically, science and medicine have been characterised by long periods of failed practices, missed

opportunities, and resistance to new methods driven by financial, religious, and cultural interests. I start with a discussion of Kuhn's seminal 1962 book, *The Structure of Scientific Revolutions* (3.1). I argue that Kuhn developed an idealised model that is not as helpful as it might appear because he left out important external factors. Then I look at the history of medicine using the work of Wootton (2006) who argues that science and medicine are shaped by power in ways that often delay, by decades or even centuries, important advances (3.2). Next I examine the political economy of the 1854 London cholera epidemic and the work of John Snow because it represents an important breakthrough that might offer important lessons for the autism epidemic (3.2.1). I conclude by reviewing the more recent history of science and medicine in the U.S. using the work of Mirowski (2011) who argues that the Bayh Dole Act of 1980 ushered in an era of privatised science that has been very profitable for some elite actors but has hindered scientific development overall (3.3).

3.1 Thomas Kuhn: How science changes its mind

Thomas Kuhn's (1962) book, *The Structure of Scientific Revolutions,* was a watershed moment in the study of the history of science. Kuhn argues that in the early stages of the development of a science, there are a range of competing theories and approaches (p. 15). Eventually the discipline coalesces around various 'paradigms' which Kuhn (1962) defines as 'universally recognized scientific achievements that for a time provide model problems and solutions to a community of practitioners' (p. x). He goes on to note that paradigms share 'two essential characteristics': 'their achievement was sufficiently unprecedented to attract an enduring group of adherents away from competing modes of scientific activity. Simultaneously, it was sufficiently open-ended to leave all sorts of

problems for the defined group of practitioners to resolve' (Kuhn, 1962, p. 10). What follows is a period of 'normal science' where scientists articulate, prove, and apply facets of the theory already supplied by the paradigm (Kuhn, 1962, p. 24). Kuhn (1962) refers to these as 'mopping up operations' (p. 24) but they are vitally important and can go on for decades. Eventually however, new discoveries create anomalies that cannot be explained satisfactorily by existing paradigms. This leads to new conflicts and competition between different theories and eventually the adoption of a new paradigm with greater explanatory power (Kuhn, 1962, p. 75).

Sociologist Steve Fuller (1995, 2000, 2004, 2005) is critical of Kuhn's failure to address the external influences that can distort the scientific process.[3] Indeed, Kuhn (1962) admits, 'except in occasional brief asides, I have said nothing about the role of technological advance or of external social, economic, and intellectual conditions in the development of the sciences' (p. xi). Kuhn was aware of the extraordinary power of outside influences and yet he made a conscious choice not to explore them. Fuller (2000, p. 37) argues that 'paradigms should be seen, not as the ideal form of scientific inquiry, but rather an arrested social movement in which the natural spread of knowledge is captured by a community that gains relative advantage by forcing other communities to rely on its expertise'.

As I showed in chapter 1, the aetiology of autism has already gone through at least five paradigm shifts since 1925 (bad parenting, biomedical, genetics, diagnostic expansion and substitution, and neurodiversity). The transition from Kanner (bad parenting) to Rimland (biomedical) fits the model supplied by Kuhn. But since then, the process of

[3] I am grateful to Costa (forthcoming) for drawing my attention to Fuller's work.

scientific discovery in connection with autism has not followed Kuhn's model. Since the 1980s autism research has been characterised by dead ends, misdirection, and a willful indifference to promising leads. The genetic theory coincided with an existing multibillion-dollar research program. Thus far, $2 billion has been spent on genetic research and no 'autism gene' has yet been found that might explain the current epidemic and the entire genetic theory of the case has come into question. Diagnostic expansion and substitution appears to be an ad hoc response to public anger over rising prevalence rates — the empirical basis was always weak at best. Autism as natural neurodiversity does not have an empirical basis either. So the three most recent paradigm shifts did not offer a better fit for the data nor greater explanatory power and were driven by something other than scientific reason. It seems that autism should be on the verge of yet another paradigm shift (or a reversion to Rimland) because existing theories are not able to explain the anomalies of rising prevalence rates and eyewitness accounts of autistic regression. And yet, the self correcting scientific process described by Kuhn has not (yet?) happened.

3.2 History of Western Medicine: How doctors change their minds

David Wootton in *Bad Medicine: Doctors Doing Harm Since Hippocrates* (2006) shows that the history of medicine is very different from the history of the physical sciences presented by Kuhn. Wootton (2006) begins with a critique of Galenic medicine that was based on the idea that an excess or deficiency of any of four bodily humours ('blood', 'phlegm', 'yellow bile', and 'black bile') was responsible for disease. Four forms of treatment were then recommended: emetics, purgatives, bloodletting, and cautery (Wootton, 2006, p. 31). More recent scholarship has revealed that the only gains

from going to see a doctor who practiced this form of medicine were from the placebo effect and in many cases the standard treatments actually decreased one's odds of survival (Wootton, 2006, p. 8). While many histories of medicine focus on Galenic medicine, Collyer (2010) points out that for most of human history (certainly up until the 19th century) there was no dominant paradigm in medicine, instead there were lots of different competing ideas, methods, and types of practitioners.

Wootton (2006) then works through several additional historical examples and shows that issues of power and prestige often get in the way of scientific advancement. The telescope and microscope were invented in the early seventeenth century (Van Helden, Dupre, & Van Gent, 2011). The telescope launched a revolution in astronomy. It appeared that there would soon be revolution at the microscopic level too as Malpighi, Hooke, Swammerdam, Grew, and Leeuwenhoek all published the results of their microscopic investigations in the 1660s and 1670s (Wootton, 2006, pp. 110–111). Everything was in place to discover the germ theory of disease (Winslow, [1943], in Wootton, 2006). But by 1690, work in microscopy had largely stopped and the next generation did not pick up where the great early microscopists left off (Wootton, 2006, pp. 110–111). It was not until the 1830s that microscopy resumed its central role in science and medicine (Wootton, 2006, p. 110).

English natural philosopher and chemist Joseph Priestley first synthesised nitrous oxide in 1775 (Wootton, 2006, p. 95). The anesthetic effects of nitrous oxide were soon apparent as it was used as a 'fairground amusement' (Wootton, 2006, p. 21) and as a recreational drug at 'laughing gas parties' among British elites (Zuck, Ellis, & Dronsfield, 2012). But nitrous oxide was not used as an anesthetic in a medical setting

until 1846, and it was a dentist, Horace Wells, not a doctor who first used it to relieve the pain of surgery (Wootton, 2006, pp. 21–22).

The cure for scurvy was known for centuries before it was implemented as policy in the British navy — the Dutch knew about the critical role of dietary citrus by the late 1500s (Stephen & Utecht, 2001); Captain James Lancaster carried lemon juice on his ship sailing to the East Indies in 1601 (Wootton, 2006, p. 161); and the Dutch and English East India Companies used it too in the early seventeenth century as did the Portuguese, the Spanish, and the first American colonists (Wootton, 2006, p. 161).

> Yet this treatment [lemons] made no sense to doctors with a university education, who were convinced that this disease, like every other, must be cause by bad air or an imbalance of the humours, and it was under their influence (there can be no other explanation) that ships stopped carrying lemons. (Wootton, 2006, p. 161).

It was not until 1795, that daily rations in the British navy included lemon juice on the advice of Gilbert Blane, the physician to the West Indies Fleet (Wootton, 2006, p. 165). In the interim, nearly 100,000 sailors died of scurvy (Wootton, 2006, 161).

Penicillin was discovered in 1871 by Sir John Burdon-Sanderson who ‘reported that moulds of the *Penicillium* group would prevent the development of bacteria in the broth exposed to air. In 1872, Lister confirmed that *Penicillium glaucum* would kill off bacteria in a liquid culture’ (Wootton, 2006, p. 247). But it was not until 1940 when the

first penicillin-based antibiotic was developed by Howard Florey and Ernst Chain (Wootton, 2006, p. 245).

What explains the delay between early discoveries and widespread implementation of effective therapies? Wootton (2006) writes that up until the 1820s, Galenic medicine was akin to religion and not subject to practical testing (p. 144). He argues:

> The primary obstacle to progress, was not practical (Leeuwenhoek's microscopes worked well), nor theoretical (the germ theory of putrefaction was not difficult to formulate), but psychological and cultural. It lay in doctors' sense of themselves, their awareness of their own traditions, their habit of conferring authority upon an established canon and upon established therapies (Wootton, 2006, p. 286).

Often the early innovators who first discovered the revolutionary insight were driven to financial ruin, death, or insanity by the resistance of their colleagues. Horace Wells, the first practitioner of painless dentistry 'was driven to suicide by the hostility of the medical profession' (Wootton, 2006, p. 22). Alexander Gordon who discovered the cause of puerperal fever in 1795 and published his findings was driven from his practice and died at 46 (Wootton, 2006, p. 212). So too, Ignaz Semmelweis who dramatically reduced incidence of puerperal fever in a hospital in Vienna (by requiring doctors to wash their hands with chloride of lime), was shunned by his colleagues and died in an insane asylum in 1865 (Wootton, 2006, p. 217). In every one of these instances, the doctors were shunned by their colleagues because these medical breakthroughs also revealed the primitive state of existing practices.

So how did scientists finally figure out the germ theory of disease and subsequent treatments? Wootton (2006) argues that the creation of teaching hospitals in the middle of the 19th century led medicine to start counting in earnest for the first time. To the extent that they measured their results, they found that all of their therapies were completely ineffective (Wootton, 2006). '"Therapeutic nihilism", the belief that most conventional medical therapies did not work, became the norm amongst sophisticated (particularly Parisian) doctors in the 1840s as a result of a new interest in statistics' (Wootton, 2006, p. 141).

One of the most interesting uses of counting occurred during the 1854 London cholera outbreak and it led to a turning point in the history of medicine. A pioneering local doctor named John Snow, took it upon himself, without pay, to try to figure out the cause of the outbreak. 'Snow and an associate set out to visit every house in which there had been a cholera fatality and establish which company supplied its water' (Wootton, pp. 202–203). Snow recorded the cholera cases and fatalities on a decidedly low tech device — a map of the neighborhood. Through looking at patterns and anomalies in the data displayed on the map, Snow and a local minister named Henry Whitehead were able to establish the source of the outbreak. The lessons from the 1854 London cholera outbreak are potentially important to the study of autism so I discuss them in detail in section 3.2.1 below.

Later, British surgeon, Joseph Lister, broke with tradition when he applied Louis Pasteur's research in microbiology by testing various methods for chemically killing microorganisms prior to and during surgery (Wootton, 2006). In the process, Lister

developed the first antiseptics and the first antiseptic surgery — thus dramatically lowering the fatality rate in his practice (Wootton, 2006).

Wootton (2006) writes:

> Individuals and institutions are naturally conservative and risk averse. Unless circumstances are very unfavourable, they prefer the known to the unknown, continuity to change. Major change requires a crisis of the sort that hospitals were undergoing in the 1860s: adaptation comes late, not early. Even then change is likely to be easier to bring about in low-status institutions than in high-status institutions, on the periphery than in the centre. Listerism triumphed first in Glasgow, then in Edinburgh, it established itself quickly in Scotland, but slowly in England (p. 259).

Elite institutions are often the last to adopt the new methods because they are the ones who profit most (in terms of both prestige and financial benefit) from established practices.

What is strange about *Bad Medicine* is that it concludes with the invention of antibiotics and the first randomised controlled trials (RCTs) in the late 1940s. Wootton's view is that for most of its history, medicine did not make sufficient use of statistics. But first with the work of Lister and later with RCTs, medicine finally became a proper science. But then how does one explain the medical failures that have continued even after the adoption of RCTs in 1947?

Starting in 1957 (ten years after the first RCTs), 14 pharmaceutical companies marketed thalidomide in 46 countries under 37 different trade names (Gøtzche, 2013). An estimated ten thousand babies were born with birth defects (including phocomelia, the malformation of limbs) and only fifty percent of them survived (Strickson, 2014). But it still took *four years* to pull it from the market. A single regulator, Frances Oldham Kelsey, prevented its approval in the U.S. (Mintz, 1962). Regulators, medical associations, and the pharmaceutical industry all failed to catch their own error. Instead, a small number of individual medical professionals (Widukind Lenz in Germany and Sister Sparrow and William McBride in Australia) eventually connected the dots and figured out that the babies born with phocomelia were the result of thalidomide (Stephens & Brynner, 2001; Daemmrich, 2002; Swan, 2018).

The current situation with selective serotonin reuptake inhibitors (SSRIs), which came onto the market in 1987, forty years after the first RCTs, is similarly troubling. More than ten percent of the population are on these drugs in the United States and yet they are toxic, increase suicide risk for many, and do not outperform a placebo for everyone except the very most depressed people (Angell, 2011). As I showed in chapter 1, if taken during pregnancy, SSRIs increase the risk of autism. Yet 6.5% of all women enrolled in private health insurance and 8.1% of women on public health insurance in the U.S. use these drugs during pregnancy (Dawson et al., 2016).

RCTs are not the panacea that Wootton would have us believe. RCTs are an important method but the outcome of that method depends on the sociopolitical context in which this research takes place. As I will show in chapter 5, corporate interests have figured

out how to manipulate the RCT process to serve their profit interests. More layers of analysis are needed in order to understand the history of medicine in our current era.

3.2.1 The Political Economy of the 1854 and 1866 London Cholera Epidemics

Wootton (2006) observes that the 1854 London Cholera Epidemic is one of the most pivotal moments in the history of medicine. A closer examination of the details of the outbreak and how it was stopped provides an interesting model of how paradigms shift in medicine.

Cholera was brought to London in 1831 as a result of empire. Cholera does not naturally live in London, the bacteria thrives in warmer climates like India (Johnson, 2006, p. 33). The British colonisation of India resulted in British soldiers and merchants bringing the bacteria back home with them (Johnson, 2006, pp. 33–34).

Miasma theory, the belief that disease was caused by bad smells, was popular in that era (Johnson, 2006). So health authorities, led by Edwin Chadwick, worked to build a sewer system to carry the bad smells out of town (Johnson, 2006). The problem is that the sewage was then directed into the Thames River — which was where private water companies drew the drinking water that they sold back to the residents (Johnson, 2006, pp. 33–34). Johnson (2006) comments, ‘The first defining act of a modern centralized public-health authority was to [accidentally] poison an entire urban population’ (p. 120).

When a cholera outbreak hit London in 1854, a respected anaesthesiologist, John Snow, set out to determine the cause. Snow’s initial theory of the case was that cholera was

transmitted through contaminated water and that some private water companies supplying the region would have higher fatality rates than others (Johnson, 2006). Wootton (2006) reports that Snow was likely most influenced by John Frank Newton's *The Return to Nature: A Defence of the Vegetable Regime* [1811] that claimed that London drinking water was polluted with 'septic matter' (p. 198). So Snow set out to map the Soho neighborhood, identifying illnesses and fatalities and the water company supplying each house (Johnson, 2006, pp. 105–106). Snow's focus on corporate misconduct seems unusual for a doctor of that era. Indeed, one of the things that separated Snow from his contemporaries is that Snow was from a working class background and displayed remarkable class consciousness (Johnson, 2006, p. 148).

Snow did not rely on clinical lab work and he never saw the cholera bacteria (Johnson, 2006, p. 99). Instead he relied on the simple technology of a map that enabled him to pinpoint the source of the outbreak. Snow worked in partnership with a local Anglican minister, Henry Whitehead, who had no formal medical training (Johnson, 2006).

> ...Whitehead's investigations in 1855 were ultimately as decisive as Snow's in solving the Broad Street mystery. His 'conversion experience' reading Snow's monograph set him off in search of the index case, eventually leading him to baby Lewis. The discovery of baby Lewis led to York's excavation of the pump, which confirmed a direct connection between the pump and the cesspool at 40 Broad (Johnson, 2006, p. 199).

Once the Broad Street pump was identified as the source of the water connected with most of the fatalities, it was just a matter of removing the pump handle, and the cholera

deaths stopped within a week (Johnson, 2006, p. 160). Newspapers ignored the removal of the pump handle and credited a change in the weather (based on the miasma theory) as ending the epidemic (Johnson, 2006, p. 160).

Throughout the crisis, the medical establishment was an impediment to solving the problem (Johnson, 2006). Indeed, even once Snow and Whitehead had definitely proved the source of the outbreak, public health authorities remained unconvinced (Johnson, 2006). Reviewing Snow's report on the cholera outbreak, Benjamin Hall, who led the Board of Health Committee tasked with investigating the outbreak, concluded:

> After careful inquiry, we see no reason to adopt this belief. We do not find it established that the water was contaminated in the manner alleged; nor is there before us any sufficient evidence to show, whether inhabitants of the district, drinking from that well, suffered in proportion more than other inhabitants of the district who drank from other sources (Johnson, 2006, p. 183).

In 1866, a cholera epidemic broke out in East London (Johnson, 2006, p. 209). Snow had died in 1858, but William Farr, the registrar-general of London, had worked with Snow and Whitehead on the 1854 cholera investigation (Johnson, 2006). Farr brought in Whitehead and together they pursued Snow's original theory, that one of the water companies supplying the region might be to blame (Johnson, 2006, p. 210). Indeed, they discovered that 93% of the fatalities were customers of the East London Water Company (Johnson, 2006, p. 211). Further investigation revealed that a key section of the sewer line had not been completed and so sewage was overflowing into the reservoir

used by the East London Water Company (Johnson, 2006, p. 211). The 1866 epidemic confirmed Snow's initial theory of the case; miasma theory was official dead; and London has not had a cholera outbreak since (Johnson, 2006, p. 214).

Imagine, for a moment, if the lessons of the 1854 and 1866 cholera epidemics were applied to the autism epidemic. One might start with the observation that the medical establishment can be sclerotic and a barrier to progress. Then one would see that it is important to engage directly with those impacted by the epidemic and enlist a diversity of viewpoints in searching for evidence. Furthermore, a proper understanding of the 1854 and 1866 cholera epidemics would lead one to be on alert for the possibility of a disease of the remedy — that somehow unwittingly, some step towards scientific progress might have unleashed unintended consequences. Finally, the 1854 and 1866 cholera epidemics teach one to examine autism in its political, economic, cultural, and historical context while specifically examining the possible role of corporations and capitalism in the rise of the disorder. And yet, generally speaking those are not the lessons that public health authorities take from John Snow, Henry Whitehead, and the removal of the Broad Street pump handle. More often than not the story is made to fit existing cognitive biases — "visionary scientist working alone and science as a system that is self-correcting and always improving".

3.3 Three American regimes of science in the 20th century.

Krimsky (2004), Angell (2005), Hess (2007), Michaels (2008a), Mirowski (2011), and Gøtzsche (2013) examine more recent trends in science and medicine and find that every step in the scientific process (in the U.S.) is now shaped by corporate influence. I devote chapter 5 to exploring the details of the current mode of production in science.

For the purposes in this chapter, I want to focus on the work of Philip Mirowski in *Science-Mart* (2011) because he takes a longer historical view than some of these other critical authors, his periodisation is better, and he looks at science and medicine in their economic and political context.

Mirowski is Professor of Economics and Policy Studies and the History and Philosophy of Science at the University of Notre Dame. In *Science-Mart* (2011) he gives a political economic history of corporate influence on science starting in 1890. To begin with he notes that 'history of science' is a misnomer. The proper term is 'histories of sciences' plural in each instance because neither history nor science are monolithic (Mirowski, 2011, p. 88).

Mirowski (2011) argues that there were three radically different phases (what he calls 'regimes') of American scientific research: 1890 to WWII, the 'Captains of Erudition' regime; WWII to 1980, the Cold War regime; and from 1980 to the present, the 'Globalized Privatization' regime. For each regime he tracks changes in the approach to science across six domains: the evolution of the corporate form, government policy towards corporations, government science policy, who are the science managers, changes in higher education, and the pivotal disciplinary science of that era. Taking each regime in turn:[4]

The 'Captains of Erudition' regime from 1890 to WWII was characterised by scientific innovation inside large corporate R&D labs; the expansion of corporate prerogatives

[4] All of the material in the next three paragraphs comes from a table in Mirowski (2011) pp. 94–95.

from patents to giving employers ownership over the research performed by employees; very little government science policy; science driven by the charismatic directors of corporate labs; universities focused mainly on teaching; and chemistry and electrical engineering as the pivotal scientific disciplines of the era (Mirowski, 2011, p. 94).

By contrast, during the Cold War Regime from World War II to 1980, Mirowski (2011) argues that large firms diversified; military contracts formed a sort of *de facto* national industrial policy; there was a huge expansion of federal military funding and control of science; the military were the primary managers driving innovation in universities, corporate labs, and at think tanks; higher education expanded (particularly after the war) with an eye toward turning out democratic citizens; and physics, operations research, and formal logic were the pivotal scientific disciplines of this era (p. 94).

According to Mirowski (2011), starting around 1980, the scientific paradigm changed again in the United States. Mirowski characterises the era from 1980 to the present as the 'Globalized Privatization Regime.' During this period, corporations have outsourced R&D and spun off in-house labs; antitrust laws have been weakened and intellectual property rights vastly expanded; publicly funded research has been privatised; global corporations control research at universities, contract research organisations, and start-ups; universities and professors have neglected teaching in favour of research and developing patentable intellectual property in partnership with private firms; and biomedicine, genetics, computer science, and economics are the pivotal disciplinary sciences (Mirowski, 2011, p. 95).

The catalyst for this shift to the new Globalized Privatization Regime in science was the Bayh-Dole Act of 1980 in the U.S. which ‘allowed universities and small businesses to own patents on discoveries made with government R&D funding’ (Mirowski, 2011, p. 21). Other countries soon adopted similar legislation (Mirowski, 2011, p. 21).

Prior to Bayh-Dole, government funded research, to the extent that it was not classified, became part of the commons, free to be used by anyone (Mirowski, 2011). Under Bayh-Dole, knowledge and discovery could now be privately owned, so individual professors, departments, and universities rushed to patent their discoveries and find ways to commercially profit from their inventions (Mirowski, 2011). Thus (I note that) several hundred years after the British parliament enclosed public lands through various legislative acts, the U.S. Congress similarly enclosed public scientific knowledge and awarded it to private intellectual property holders to profit from as they wish.

As knowledge is increasingly privatised, collaboration becomes much more difficult because now one must obtain a license for everything from certain cell lines to a wide range of research methods (Mirowski, 2011). As a result, so called Material Transfer Agreements (MTAs) have proliferated in universities (Mirowski, 2011). MTAs are contracts that stipulate royalty rates for the use of research tools and specify who will own the outputs of scientific research (Mirowski, 2011). Professors, universities, and corporations all demand MTAs from each other in order to work together (Mirowski, 2011). Mirowski (2011) writes, ‘MTAs were essentially absent in most university setting before 1980’ (p. 142). He continues, ‘...MTAs can contain a forbidding array of controls and restrictions over prospective research still to be carried out by anyone who signs them’ (p. 155). These controls and restrictions include ‘reach through’ clauses

whereby the patent holder of the research tool is given ownership rights to any discoveries resulting from the use of said tool; confidentiality rules whereby the original patent holder can forbid publication of unfavourable results of research processes involving the patented material; and prohibitions on disclosure of any discoveries related to the safety or efficacy of the research tools (Mirowski, 2011, p. 155).

Similarly troubling developments have happened in privatised corporate research. Mirowski (2011) shows that many of the same trends that we have seen in traditional manufacturing over the last 30 years have also occurred in the manufacturing of knowledge — contracting out (p. 137), offshoring (p. 223), and deskilling (p. 228). Pharmaceutical companies had long been frustrated by the fact that academic research scientists were too slow and sometimes published results that hurt profits. So starting in the 1980s and then accelerating in the 1990s, pharmaceutical companies started to work with so-called ‘contract research organizations’ (CROs) (Mirowski, 2011).

CROs are private science labs-for-hire that specialise in clinical trials (Mirowski, 2011). CROs emphasise speed and give pharmaceutical companies control over the research process (Mirowski, 2011). Unfavourable studies are killed and unfavourable data are never published (Mirowski, 2011). CROs have radically shifted the biomedical landscape from ‘figuring out what was specifically wrong with the patient to the efficient and timely production of standardized data for FDA protocols’ (Mirowski, 2011, p. 231).

The use of CROs raises ethical and safety issues that have thus far been ignored by regulators. ‘Foreign trials offer the freedom to adjust the protocols to achieve the

preconceived answer one seeks' (Mirowski, 2011, p. 375). In an interview with Petryna [2007] a CRO scientific officer stated:

> 'In my recruitment strategy, I can use subject inclusion criteria that are so selective I can "engineer out" the possibility of adverse events being seen. Or, I can demonstrate that my new drug is better by "engineering up" a side effect in another drug. That is the big game of clinical trials' (Mirowski, 2011, p. 375).

As much as 80% of all clinical trials are now conducted in CROs in foreign countries with China as the CRO industry leader (OIG [2010] in Mirowski 2011, p. 232).

One result of the privatisation of scientific research is that the pipeline of truly novel therapies, drugs, and innovations in science has begun to dry up (Mirowski, 2011). Mirowski (2011) notes, 'the initiation of a serious decline in the number of [New Drug Applications] NDAs in the United States dates from roughly 1983' (p. 211). From 1989 to 2000, the FDA reports only 15 percent of all approved drugs were real innovations (what are called 'new molecular entities' NMEs) (Mirowski, 2011, p. 214).

The privatisation of the scientific commons also increases the tendency toward Cartesian reductionism. Mirowski (2011) observes:

> In order to assert control over biological innovation and research tools, it becomes necessary for theory to stabilize discrete objects of ownership in accordance with the reigning rules of the property regime. Under the

> sign of commercialized science, those combinations of theory + empiricism that conform to the arbitrary definitions of the commodity will clearly be preferred to those that stress complexity and interrelatedness of phenomena (p. 206).

Mirowski (2011) suggests that the production of ignorance may be the goal, not the unfortunate byproduct of this shift towards a globalised privatisation regime in science (p. 343). He writes, 'The current modern regime of science organization in many respects is not a new knowledge economy as much as it is an engine of agnogenesis' (Mirowski, 2011, p. 318). The slowing down and freezing up of scientific discovery is not accidental (even if some of the participants are unwitting or unaware of the larger dynamics at work). Rather, the legislative enclosure that has produced this result has been extremely profitable for a handful of well-positioned professors, universities, and corporations.

In the concluding chapter to *Science-Mart* Mirowski (2011) writes: 'It will probably take a system crash before the leaders of today's universities will admit [that] the current wave of commercialized knowledge production has proven unsustainable on its own terms' (p. 316). A strong case can be made that the autism epidemic is that system crash. By analogy, the surge in autism cases is akin to New Orleans following Hurricane Katrina: an emergency hits and the system has no capacity to respond because it has been hollowed out by corporate interests. Professors, universities, medical journals, and regulators have often turned their attention from doing good science to doing profitable science. And preventing autism is not profitable. Few of the people in a position to respond can respond appropriately because they have committed themselves to a

different purpose. Even if they wanted to respond they could not because the research tools that they need have been encumbered by the privatisation of scientific knowledge.

3.3.1 A different view of the Bayh-Dole Act

In contrast to Mirowski's dim view of the Bayh-Dole Act, many in the scientific community see it as a great catalyst for progress. The argument is that scientific discoveries do no good if locked away in a university — their only value comes from commercial applications in the world that make life better for people. Said differently, the Bayh-Dole Act properly aligns incentives between scientific research and the needs of the public; corporations and academic researchers are compensated according to the value that they produce for society.

The Economist in 2002 wrote that the Bayh-Dole Act is 'possibly the most inspired piece of legislation to be enacted in America over the past half-century... More than anything, this single policy measure helped to reverse America's precipitous slide into industrial irrelevance' ('Innovation's Golden Goose', para. 2). Schacht (2012) writing for the Congressional Research Service points out that research funding only accounts for about 'one-quarter of the costs associated with bringing a new product to market' (p. i). Patents awarded to universities soared following the passage of the Bayh-Dole Act: 'in 1980, 390 patents were awarded to universities, by 2009, the number increased to 3,088' (Schacht, 2012, p. 9). In-house reports prepared for the Biotechnology Innovation Organization and the Association of University Technology Managers (AUTM) claim that over the twenty years span of 1996–2015 (inclusive) the Bayh-Dole Act led to the creation of up to 12,000 new companies, 4.3 million jobs, $1.3 trillion in

economic activity, and the development of over 200 new FDA approved vaccines and drugs (AUTM, 2016; Pressman, Yuskavage, & Okubo, 2017).

Others are less sanguine. Heller and Eisenberg (1998) in a widely cited article in *Science* argue that the Bayh-Dole Act led to the creation of an 'anticommons'. They write, 'A proliferation of intellectual property rights upstream may be stifling life-saving innovations further downstream in the course of research and product development' (Heller & Eisenberg, 1998, p. 698). Heller and Eisenberg (1998) spurred a growing field of anticommons studies including economic modeling (Buchanan & Yoon, 2000), books (Heller, 2008; Burk & Lemley, 2009; Heller, 2010), and the creation of the Commons Strategies Group to support the development of commons research around the world. Others point out that the data with respect to Bayh-Dole is decidedly mixed. With the academic landscape transformed into a series of monopolies over each part of the scientific process, the federal courts have been tied up with patent suits and university spending on litigation increased 5-fold from 1991 to 2002 (Leaf, 2005). Furthermore, the cost of prescription drugs skyrocketed — 13% a year for two decades (Leaf, 2005).

The champions of Bayh-Dole do not focus on autism, the rise in chronic illness, nor the inability of government, universities, or the market to prevent and cure such diseases. In-house estimates of economic impacts are notoriously unreliable. Touting new FDA approvals, which are overwhelmingly 'me-too' drugs, does not provide much information on impact (there is no way to know how many new molecular entities would have been created in the absence of Bayh-Dole). If one focuses on patents and profits, then Bayh-Dole is an overwhelming success. But it is more than a little

incongruous to celebrate the revenues that have flowed to academic researchers even as the number of new molecular entities has slowed and epidemics like autism have stumped science and medicine for three decades.

But this conflict over Bayh-Dole is instructive because like the debate over autism itself, it is not about data and evidence per se. Rather the conflict reflects prior decisions about first principles — the philosophy of science that one uses to approach the material and the political economy preferences that one brings to the debate. Bayh-Dole is an ideal fit for those who think that private property, profits, and markets are the key to innovation and economic success. By contrast Bayh-Dole is seen as problematic to those who believe that the commons, free exchange of information, and widescale cooperation are the best ways to promote innovation and the best health outcomes for society.

3.4 Conclusion

In this chapter I argued that Kuhn's (1962) *Structure of Scientific Revolutions* is an idealised model that is not applicable to the biological sciences. I reviewed Wootton's (2006) history of medicine and showed that many important breakthroughs and innovations languished for decades or even centuries because they threatened established interests and many early innovators were ostracised by their peers and driven to an early death. I argued that the 1854 and 1866 London cholera epidemics offers important lessons for the autism epidemic, namely: the medical establishment might be a barrier to progress; enlist a diversity of viewpoints; look out for a disease of the remedy; and examine autism in its political, economic, cultural, and historical context (including the possible role of corporations and capitalism in the rise of the

disorder). Finally I reviewed Mirowski (2011) who argues that the Bayh-Dole Act of 1980 led to a privatisation of the scientific commons and radically reshaped nearly every step of the scientific process. This has enriched corporations (particularly in biotech) and a small number of academic researchers and institutions while impeding scientific progress. Furthermore, I argued that this privatisation of the commons has left the scientific and medical community ill-prepared to respond to the autism epidemic because profit motives may undermine a focus on public health. In the next chapter I examine the sociological literature on toxic chemical disasters and long-term toxic chemical exposures to glean further lessons for understanding the autism epidemic.

Chapter 4

Case studies in toxic chemical disasters and long term toxic chemical exposures

4.0 Introduction

Over the last fifty years, social scientists have developed a large literature on patterns associated with toxic chemical disasters and long term toxic chemical exposures. This literature can help us to think about the political economy of the autism epidemic. In this chapter, I start with a focus on the work of Michael Reich (1991) who shows that toxic chemical disasters tend to follow a similar pattern as the shockwaves from the initial disaster ripple through society (4.1). Then I focus on three case studies of long term toxic chemical exposure over the last century: asbestos (4.2.1), lead (4.2.2), and tobacco (4.2.3). I show that the public health system is often extremely slow to respond to well known threats to human health when powerful economic actors are involved. I conclude with a section on Rachel Carson's (1962) *Silent Spring* and the lessons that the campaign against DDT might offer to those interested in autism prevention (4.3).

4.1 The sociology of toxic chemical disasters

There is a large literature on the sociology of toxic chemical disasters including Erickson (1977), Levine (1982), Edelstein (1988), Clark (1989), Picou (1990), Brown (1990), Reich (1991), Lerner (2006, 2010), and Kroll-Smith and Couch (2009). Reich (1991), in a study of three major chemical disasters on three separate continents, found that in spite of differences in cultures and contexts, all three societies experienced a

similar dynamic following the catastrophe. At first the toxic disaster was treated as a nonissue: a private trouble for individuals and their families (Reich, 1991). Later as victims connected disparate pieces of information about the cause and then organised and struggled for redress, the disaster became a public issue (Reich, 1991). Finally, the disaster became a political issue when politicians and various institutions were forced to respond (Reich, 1991). Reich (1991) is building on the work of Lukes (1974) who is building on the work of C. Wright Mills [1956, 1959], amongst others, in developing this analysis.

Reich (1991) writes, ‘four key factors determine the nature of contamination: the invisibility of the toxic agent, the nonspecificity of toxic symptoms, the geographical distribution of victims, and the difficulties of identifying the causative substances’ (p. 145). In every case, the particular features of autism make mobilisation difficult. There are no biomarkers for autism; it is determined solely by behavioral characteristics. So unlike a toxic cloud or an oil spill, in the case of autism the causative substances are mostly invisible. Autism is a spectrum rather than a single disorder, so the toxic symptoms are nonspecific. People on the autism spectrum represent one to two percent of the global population but they are distributed all over the world and in all races, ethnicities, and classes which makes organising more difficult. And there are likely not just one but many different causative substances which makes it more difficult to establish the aetiology of the disorder.

4.2 Case studies in long term toxic chemical exposures

While there is fairly good evidence that autism is caused by chemical exposures, the autism epidemic is not the result of a one-time spill or accident. Rather it appears to be the result of business as usual under a regulatory framework that claims to balance corporate profits and human health, but in fact invariably gives preference to corporate interests. Closer analogies to the autism epidemic come from the study of asbestos, lead, and tobacco. With accidents at chemical plants, one can sometimes make the case that no one could have predicted this outcome. But with asbestos, lead, and tobacco, doctors and scientists have known for decades that these products were deadly. And yet production and use continue anyway.

4.2.1 Asbestos

Over the last thirty years, a number of investigative reporters, doctors, and social scientists have studied the history of asbestos including Brodeur (1985); Castleman and Berger (1996); Schneider and McCumber (2004); McCulloch and Tweedale (2008); and Miyamoto, Morinaga, and Mori (2011). A number of interesting patterns emerge across these various studies including the fact that: 1.) the vast majority of people in positions of authority, whether in politics or medicine, overlook, downplay, or ignore death and disease in their midst rather than confronting toxic polluters; 2.) early whistleblowers invariably suffer repression and loss of economic livelihood; and 3.) public health institutions can sometimes slow the pace of the catastrophe or provide some amelioration but are generally unable to stop a public health crisis caused by a corporate

polluter in spite of a century of progressive reforms and the growth of public health institutions in this era.

Schneider and McCumber (2004) provide an overview of the last 100 years of asbestos research (and all of the sources and quotes in this paragraph come from their text, pp. 80–82). Castleman [1996] notes that in 1897, a physician in Vienna wrote that pulmonary problems in asbestos weavers and their families were the result of dust inhalation. In 1918, the Commerce Department published a study called, ‘Mortality from Respiratory Disease in Dusty Trades’. The author Frederick Hoffman, an employee of Prudential Insurance on loan to the government for the project, made it clear that the dangers of asbestos were widely known. Hoffman [1918] wrote, ‘In the practice of American and Canadian life insurance companies, asbestos workers are generally declined on account of the assumed health-injurious conditions of the industry’. Brodeur [1985] cites a 1932 letter from the U.S. Bureau of Mines to asbestos manufacturer Eagle-Picher that states: ‘It is now known that asbestos dust is one of the most dangerous dusts to which man is exposed’. Furthermore, ‘according to the U.S. military’s own estimation, almost as many military personnel were killed from exposure to asbestos in World War II than by the enemy’ (Schneider & McCumber, 2004, p. 82).

Many people in positions of authority knew about the dangers of asbestos and did nothing about it. Companies that mined asbestos knew that their workers were dying from various lung ailments; companies that used asbestos in their products knew that dust in the factory was injuring and killing workers; and doctors for these companies, insurers, and community leaders knew as well (Schneider & McCumber, 2004). But almost invariably, those who speak out in the early days of widespread toxic

contamination are vilified and suffer enormous economic harm. In Libby, Montana, site of one of the world's largest vermiculite mines, a local doctor, Richard Irons, figured out in the mid-1970s that workers in the mine were developing lung diseases from asbestos (Schneider & McCumber, 2004). But the mine owner, W.R. Grace 'exerted tremendous influence on Libby's medical community. It donated heavily to St. Joseph's Hospital and always kept an executive on the hospital board' (Schneider & McCumber, 2004, p. 122). After seeing evidence of lung problems in chest x-rays of eleven mine worker patients in a row, Irons contacted W.R. Grace executives to alert them to what he was finding (Schneider & McCumber, 2004, p. 123). Grace subsequently stopped sending mine workers to his practice and shortly thereafter St. Joseph's Hospital accused Irons of drug use and revoked his hospital privileges thereby ending his medical practice in Libby (Schneider & McCumber, 2004, p. 124). It took another twenty-two years before an investigative reporter from the *Seattle Post-Intelligencer* stumbled upon the story and wrote the articles that led to an investigation that resulted in compensation for some asbestos victims and the partial cleanup of the town (Schneider & McCumber, 2004, p. 183).

By the 1930s, it was known that asbestos causes asbestosis, by the 1940s it was established that asbestos causes lung cancer, and by the 1960s it was shown that asbestos causes mesothelioma (McCulloch & Tweedale, 2008, p. 9). The impact of all of these illnesses has been catastrophic worldwide:

> The International Labour Organization (ILO) and the World Health Organization (WHO) have recently stated that asbestos kills at least 90,000 workers worldwide each year at present. According to one report,

> the asbestos cancer epidemic could take at least five million (and possibly as many as ten million) lives before asbestos is banned worldwide and exposures cease (McCulloch & Tweedale, 2008, p. 11).

In spite of these catastrophic health impacts, asbestos has not been banned in the United States and production levels continue to be as high today as they were in the 1960s when the direct link between asbestos and mesothelioma was established (McCulloch & Tweedale, 2008). They note that:

> Between 1900 and 2004, world asbestos production was approximately 182 million tonnes. Of this total, 143 million tonnes were produced after 1960 [Virta, 2006]. Put another way, nearly 80 percent of world asbestos production in the twentieth century was produced after the world learned that asbestos could cause mesothelioma! (McCulloch & Tweedale, 2008, p. 14).

McCulloch and Tweedale (2008) explain that continuing production in spite of known catastrophic effects is simply a matter of power: '…asbestos has proved to be so enduring, because the industry was able to mount a successful defence strategy for the mineral — that still operates in some parts of the world' (p. 15). The strategy consisted of 'concealment and, at times, misinformation that often amounted to a conspiracy to continue selling asbestos fibre irrespective of the health risks' (McCulloch & Tweedale, 2008, p. 15). McCulloch and Tweedale's (2008) analysis suggests that in some ways we live under a sort of modern feudalism, where a handful of powerful actors can engage in

long term toxic trespass, as long as they have enough resources to hire skilled product defence attorneys and a good public relations team.

4.2.2 Lead Poisoning

Like asbestos there is an extensive literature on the history of lead poisoning including Needleman (1991), Warren (2000), Denworth (2009), and Markowitz and Rosner (2013). An interesting picture emerges from the study of more than one hundred years of lead poisoning. Specifically, the evidence shows that toxicology has evolved considerably over the last century. Yet, in spite of improved science, public health as an institution is in retreat, seemingly unable to address the root causes that caused the problem in the first place.

The level of lead (in the blood) considered 'safe' has changed dramatically over the course of the last fifty years. Markowitz and Rosner (2013) write:

> From the 1960s through the early 1990s, blood lead levels considered dangerous to children declined from 60 to 10 μg/dl. And more recent research indicates that even the lower blood lead level considered safe in the 1990s offers children inadequate protection. In fact, the CDC in mid-2012 lowered its level of concern—the level at which children should be considered at risk—to 5μg/dl, thereby increasing the estimated number of endangered children from 250,000 to 450,000. Even this may not be a safe level. The CDC's Advisory Committee on Lead Poisoning

> Prevention itself acknowledged that there may not be any ‘safe’ level of lead exposure for children (p. 218).

The study of lead poisoning upends many of the long-standing theories in toxicology and epidemiology. Markowitz and Rosner (2013) point out that:

> Our common-sense assumptions, long held by toxicologists as well as the general public, that the higher the level of a poison, the more damage it causes, may not always be true. New research shows that the most serious damage from lead occurs at some of the lowest levels of exposure, often in utero or in the first years of life, when the neurological structures of the brain are forming. For example, compared to children with virtually no evidence of lead in their blood, the greatest effect of lead on IQ occurs in children with blood lead levels below 5 μg/dl.... Similarly, endocrine disruptors such as bisphenol A have their greatest impact on physiological structures at the lowest levels of bioaccumulation if exposure occurs at critical moments in fetal development. This raises troubling issues for toxicology and for society, because these data imply that other toxins may also defy the traditional dogma that the ‘dose makes the poison’ and that ‘lowering exposures lowers the risk’ (p. 218).

Markowitz and Rosner’s (2013) account is about more than lead poisoning, it is about the failures more broadly of public health as a discipline. They write, ‘More than thirty-five studies were done during the 1980s and 1990s about various lead-abatement

strategies' (Markowitz & Rosner, 2013, p. 229). In spite of the evidence, 'policy makers were unwilling to commit the needed resources to finally remove lead from children's homes, and the courts were unwilling to hold accountable the companies responsible for this ecological and human tragedy' (Markowitz & Rosner, 2013, p. 229). Figert and Bell (2014) lament that global clinical trials have reduced 'public health strategies from a broad array of disease prevention efforts to one seeking to improve the health of populations with pharmaceuticals' (p. 456).

Corporate interests, not human health, continue to be the overriding force determining regulatory outcomes. Scientists have known for at least 100 years that lead is toxic; lead poisoning is a preventable disease; and yet both policymakers and the courts refuse to hold industry responsible for the harms they have caused thereby ensuring 'that future generations of children will be sacrificed as well' (Markowitz & Rosner, 2013, p. 231). Bruce Lanphear underscores this point when he writes, 'unless it serves the needs of private enterprise, public health is incapable of controlling the causes of chronic disease and disability' (in Markowitz & Rosner, 2013, p. i).

4.2.3 Tobacco

The literature on the centuries-long battle against tobacco includes Kluger (1996), Kessler (2001), Brandt (2007), McGarity and Wagner (2008), Michaels (2008a), and Oreskes and Conway (2010). Like asbestos and lead, many people have known for a long time that tobacco was carcinogenic and deadly. Michaels (2008a) notes that 'by the eighteenth century, doctors were writing about the oral tumors of the mouth and throat that seemed to afflict smokers' (p. 4). Early campaigns against smoking encountered

widespread media capture by cigarette makers. Furthermore, the medical establishment was both part of the problem and part of the (as yet still incomplete) solution.

In 1938, a study by Pearl at Johns Hopkins University suggested that smoking increased mortality (Michaels, 2008a, p. 4). But newspapers at the time were heavily dependent on advertising from cigarette makers and so other than the Associated Press, most newspapers ignored the story (Michaels, 2008a, p. 4). One muckraking journalist, George Seldes, became so enraged by what he saw as media self-censorship that he started his own newsletter in 1941 called 'In Fact' to publicise stories 'linking tobacco to disease and premature death' (Michaels, 2008a, p. 5).

Five studies came out in 1950 showing that smoking caused lung cancer, but statisticians and the medical establishment remained unconvinced (Michaels, 2008a, p. 5). They asked,

> What was the mechanism by which the tobacco smoke caused cancer? Were there other factors associated with both lung cancer and tobacco that might be responsible? Was there something in one's constitution (which today we would explain as genetic) that increased both lung cancer risk and propensity to smoke? If so, then smoking would not cause lung cancer; a third factor would cause them both. Smoking apparently increased risk not just of lung cancer but of a host of other diseases as well. To some researchers steeped in infectious disease epidemiology, it seemed implausible that many different diseases could be associated with a single cause (Michaels, 2008a, p. 5).

Looking back, the degree to which the tobacco industry was able to co-opt doctors to promote their product is astonishing (Kluger, 1996). Both doctors and (later) favourable studies could be bought for a price, much like any other commodity (Kluger, 1996). Far from the image that science and medicine would like to project of rationality and objectivity, for the most part, in the midst of a massive public health crisis, the scientific and medical communities showed that they were susceptible to outside pressure and a desire for personal financial enrichment (Kluger, 1996).

4.2.4 Patterns that cut across asbestos, lead, and tobacco

There are also patterns that cut across all three of these toxic products. The first is that, in the early phase of the crisis, which can sometimes stretch on for decades, there is a strong tendency to blame the victim. With asbestos, when mine workers showed signs of lung problems, they were blamed for smoking and generally having an unhealthy lifestyle (Schneider & McCumber, 2004). With lead, children suffering from lead poisoning were blamed for bad behaviour and their parents were blamed for everything from being single parents, to lack of discipline, to lack of proper moral values (Warren, 2000). And with tobacco, as the science connecting smoking with lung cancer became crystal clear, cigarette makers crafted a clever legal maneuver to put warning labels on cigarette packages — which shifts the blame onto smokers (for choosing to ignore the warnings) and thereby gave cigarette makers some form of liability protection for about thirty years (Michaels, 2008a, p. 10).

The second pattern that shows up in all three of these cases is the essential role of legal discovery. Case after case involving asbestos, lead, and tobacco shows that discovery in preparation for a trial unearthed the documents that showed the extent of the problem and the corporate attempt to cover it up. In writing about lead poisoning, Markowitz and Rosner (2013) explain that their account of 'industry's role in the development of a public-health tragedy would not have been possible without litigation, which brought to light literally hundreds of thousands of pages of company documents' (p. xiii). In the absence of discovery we might very well still have asbestos in home insulation, lead in paint and gasoline, and the tobacco industry never would have settled with the states for $265 billion in related health care costs. An industry that could avoid discovery could potentially pollute for an indefinite period of time.

Also in the case of asbestos, lead, and tobacco, some new technology came along that enabled better detection. Initially, in every case it was assumed that only those exposed to high doses, usually at the factory, with a genetic predisposition were susceptible to illness or death from the product. But better detection methods showed that even minute doses were toxic, even to otherwise healthy people exposed anywhere. So for example in the case of asbestos, the U.S. Environmental Protection Agency previously conducted all of their tests of asbestos content in ore and dust using polarized-light microscopy (PLM); but by the late 1990s a more sophisticated testing method had been developed, transmission electron microscopy (TEM) (Schneider & McCumber, 2004). When dust and ore from the Libby vermiculite mine were tested using PLM they usually came back with no readings for asbestos; when the same samples were tested with TEM, nearly 100% came back positive for asbestos (Schneider & McCumber, 2004, p. 16). In the case of lead, by the mid 1990s, 'technological advances had led to routine tests that

were capable of inexpensively identifying much lower levels of lead in children's blood' (Markowitz & Rosner, 2013). It is not clear what the breakthrough technology will be for detecting the causes of autism. But the fact that the U.S. federal government is primarily funding research on the genetic causes of autism, even though this theory is increasingly discredited, surely does not help.

4.3 The Lessons from *Silent Spring*

By most accounts, Carson's (1962) *Silent Spring* produced a profound shift in how people around the world think about environmental issues. In this section I will discuss the lessons from *Silent Spring* because I think they may offer some important insights for how society should respond to the autism epidemic.

When *Silent Spring* came out in 1962, chronicling the harmful effects of DDT and other insecticides, it faced a large, powerful, and profitable industry, and a sceptical court system. In the ten years prior to the publication of *Silent Spring*, four other books had come out on the dangers of pesticides and yet none of them made a dent in public opinion nor an impact on regulation (Paull, 2013, p. 7). Yet *Silent Spring* was a catalyst for a sea change in public opinion and a dramatic shift in the regulation of chemicals in the U.S. (Griswold, 2012). Following the publication of the book and Senate testimony by Carson, President Kennedy directed his Science Advisory Committee to follow up on Carson's claims (Stoll, 2012). By 1963, the committee had largely validated Carson's work (Lear, 1997; Stoll, 2012). Support for greater regulation of toxicants was bipartisan. President Nixon created the Environmental Protection agency in 1970, and by 1972, the EPA had phased out most uses of DDT. Today *Silent Spring* is credited by

many with igniting the modern environmental movement (Griswold, 2012). Three lessons emerge from the publication of *Silent Spring* that may be useful as we think about the autism epidemic.

First, Carson (1962) presents not just an alternative account of DDT, she presents an alternative ontology of how the world works. Carson (1962) points out the reductionist thinking of the U.S. Department of Agriculture (USDA) in targeting specific insects, while missing the impact of pesticides on ecosystems. What she shows is that the USDA and state aerial spraying programs killed thousands of larger animals including fish, birds, and raccoons and they were often ineffective at eradicating the targeted insects. Carson (1962) overcomes Cartesian reductionism by looking at every level of an ecosystem and the interactions between them. She starts with living systems in water and moves up through soil to the role of worms and their interaction with decomposing leaves and plants before discussing birds and then larger animals including humans. And she shows how introducing a toxicant at any level of that system impacts every other layer in the system. In the book, Carson (1962) does not push for new regulation (although she did later in Senate testimony). Rather she advocates for a complete change in worldview — from chemical pest management targeted toward killing individual species to biological pest management focused on healthy ecosystems.

Second, Carson's work was reviled by the U.S. Department of Agriculture when it came out (Lear, 2007). Contrary to the smooth shifting of gears between different paradigms implied by Kuhn (1962) in actual practice those who challenge existing paradigms face ostracism, bullying, intimidation, and economic coercion. The important point here is

that the USDA saw their mandate as protecting corporate interests rather than public health.

Finally, when President Kennedy's Science Advisory Committee urged comprehensive reforms in the regulation of pesticides, they had not clearly established causation. They proceeded out of an abundance of caution. What this shows is that waiting for proof of causation is a political choice. The responses to the 1854 London cholera epidemic and the bird and fish die-offs associated with DDT show that one can stop an epidemic even in the absence of establishing causation. It is only the hegemony of a certain sort of corporate ideology in our current era (and laws that emerge from that sort of ideology) that makes one think that one has to establish causality first.

There is an interesting footnote in connection with Rachel Carson's legacy. A small but vocal faction of the scientific community maintains that Carson is one of the great villains in history. Guided by a mix of a positivist philosophy of science, political libertarianism, and a belief that big chemical companies rarely do harm, they maintain that the banning of DDT led to millions of unnecessary human deaths from malaria, particularly in the developing world (Ames & Krovoza, 1992; Trewavas et al., 2012; Offit, 2017). This view overlooks the fact that a large body of evidence suggests that DDT and its metabolites are associated with a range of adverse health effects including breast cancer, diabetes, and neurodevelopmental disorders in children (Eskenazi et al., 2009). Furthermore, mosquitos had already developed resistance to DDT by the time of the ban, a number of suitable substitutes now exist, and interventions like mosquito nets offer effective protection against malaria without the toxic trade offs (Stone, 2006). But the notion persists because, as I showed in chapter 2, ideology shapes how one sees the

evidence. Some of the same actors who see Carson as a villain also defend the producers of toxic triggers associated with autism.

4.4 Conclusion

In this chapter I reviewed the work of Reich (1991) who showed that toxic chemical disasters tend to follow similar patterns — at first they are a private trouble; as victims begin to organise and gain publicity, the disaster becomes a public issue; and as the crisis grows and politicians are forced to respond it becomes a political issue. I also pointed out that the particular facets of the autism epidemic make organising more difficult. Then I reviewed three case studies in long term toxic chemical exposures — asbestos, lead, and tobacco. I showed that there are similarities between the dynamics in connection with each of these cases and the autism epidemic. And I showed that there are patterns that cut across all three case studies — initially there is a strong tendency to blame the victims, legal discovery is key to paradigm shifts, and technological innovation eventually enables better detection of harms at lower doses. I concluded with an analysis of *Silent Spring*. I argued that Carson presented an alternative ontology of how the world works (and that this contributed to her lasting impact), that she was reviled by the USDA and many in the science community who worked to protect corporate interests, and that establishing causation is a political choice but not essential for stopping an epidemic.

Chapter 5

The capitalist conquest of science and medicine

5.0 Introduction

Editors from several of the top science journals in the world have recently published withering critiques of the current state of scientific research and the practice of medicine. Published over the course of a decade, they highlight a series of troublesome patterns that appear to be growing worse.

Richard Smith (2005) 'was an editor for the *BMJ* for 25 years' and served for 13 years as 'the editor and chief executive of the BMJ Publishing Group... which published some 25 other journals' (p. 364). In 2005, Smith published an essay, in *PLoS Medicine*, titled, 'Medical Journals are an Extension of the Marketing Arm of Pharmaceutical Companies'. In the essay he cites data [from Lexchin, Bero, Djulbegovic, & Clark, 2003] showing that 'studies funded by a pharmaceutical company are four times more likely to have results favourable to the company than studies funded from other sources' (Smith, 2005, p. 365). He argues that peer review is 'ineffective' and 'prone to bias and abuse' (Smith, 2005, p. 365). He concludes by suggesting that 'journals should perhaps stop publishing [clinical] trials' altogether and instead 'concentrate on critically describing them' (Smith, 2005, pp. 365–366).

Drummond Rennie (2007), who served for thirty years as deputy editor of first *The New England Journal of Medicine* (*NEJM*) and then the *Journal of the American Medical Association* (*JAMA)*, writes, 'The pharmaceutical companies, by their arrogant

behaviour and their naked disregard for the well-being of the public, have lost our trust. The FDA, by spinelessly knuckling under to every whim of the drug companies, has thrown away its high reputation, and in so doing, forfeited our trust' (pp. 1011–1012).

DeAngelis and Fontanarosa (2008) editor in chief and executive deputy editor respectively of *JAMA* write, 'The profession of medicine in every aspect — clinical, education, and research — has been inundated with profound influence from the pharmaceutical and medical device industries. This has occurred because physicians have allowed it to happen, and it is time to stop' (p. 1833).

Marcia Angell (2009) writes:

> It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of *The New England Journal of Medicine* (para. 29).

Richard Horton (2015) editor-in-chief of *The Lancet* writes:

> The case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue. Afflicted by studies with small sample sizes, tiny effects, invalid exploratory analyses, and flagrant conflicts of interest, together with an obsession for pursuing fashionable

> trends of dubious importance, science has taken a turn towards darkness (p. 1380).

These are not the opinions of some Luddite fringe. These are the editors of the most influential medical journals in the world. In their capacity as editors they have a bird's eye view of the scientific and medical professions and they are alarmed by what they see. Science and medicine have reached unprecedented levels of power and influence in society. And yet many of those who know the industry best, report that science as an institution is facing multiple internal crises that raise serious doubts about the validity of much of the scientific literature.

It is doubtful that there was ever an era when the scientific process was pure, disinterested, and untainted by outside influence (Mirowski & Van Horn, 2005, p. 523). But the scientific community has changed considerably since the consolidation of medicine around biosciences in the 1920s (Collyer, 2010). The development of randomised controlled trials that proved the effectiveness of antibiotics in the 1940s gave the scientific community a unique claim upon epistemological superiority over and against other schools of thought (Wootton, 2006). However, Krimsky (2004), Angell (2008), Mirowski (2011), and Gøtzsche (2013) argue that corporate influence over science and medicine has intensified since 1980 and led to structural changes that have diminished the quality of scientific output. My aim in this chapter is to show how conflicts of interest have come to shape every step in the scientific and medical research process in the U.S. and I will argue that this is foundational to understanding what is happening with autism today.

Sociologist of science Robert C. Merton, in his 1942 journal article ‘Science and Technology as a Democratic Order’, describes a set of four norms that he argues represent the ‘goals and methods’ of science and are described as ‘binding’ upon scientists (p. 269). Today they are ‘known by the acronym CUDOS’ which stands for ‘communism, universalism, disinterestedness, and organised scepticism’ (Turner & Mccreery, 2015). Communism is the ‘common ownership of goods’ with goods in this case defined as the ‘substantive findings of science’ (Merton, [1942], 1973, p. 273). Universalism is the idea that truth-claims ‘are subjected to pre-established impersonal criteria: consonant with observation and with previously confirmed knowledge’ (Merton, 1973, p. 270). Disinterestedness is ‘a distinctive pattern of institutional control of a wide range of motives’ (Merton, 1973, p. 276). Organised scepticism is ‘the temporary suspension of judgment and the detached scrutiny of beliefs in terms of empirical and logical criteria’ (Merton, 1973, p. 277). As I will show below, actually existing scientific practices often violate some or all of these Mertonian norms of science.

In attempting to describe an entire system it is difficult to know where to begin. I aim to describe a system in constant flux and look at it in its historical, economic, and political context. As a way of organising the material, I will examine the problems by sector looking at financial conflicts of interest (COI)[5] in university scientific research, corporate scientific research, scientific journals, government agencies, and the medical profession — while recognising that many of these trends, patterns, and crises overlap. The distinction between different sectors of the economy that I make in this chapter is somewhat artificial. The profit motive and its distorting effects run throughout all of

[5] I will often shorten ‘conflicts of interest’ to COI in this chapter. COI should be understood to be plural and to represent financial conflicts of interest unless otherwise noted. Some scholars abbreviate it as COIs but unless it is in a direct quote I prefer to use COI.

these different sectors. The real distinction is between discovery oriented science (which may or may not have use values) and profit oriented science (searching for exchange values). And there is less and less discovery oriented science in our current era (Mirowski, 2011).

In this chapter I mostly rely on studies in biomedicine because biomedicine is connected with three of the possible environmental triggers described in chapter 1 (acetaminophen, selective serotonin reuptake inhibitors, and vaccines). But there is plenty of evidence that the mode of production in connection with the other possible autism triggers — especially plastics, flame retardants, and pesticides — is similar to the mode of production in biomedicine. Historically, large pharmaceutical companies often had a pesticide and chemical division organised under the same corporate parent and that structure continues today at Bayer. Novartis and Zeneca spun off their agrichemical divisions to create Syngenta in 2000. Furthermore, the producers of the seemingly disparate chemicals that I review in this thesis *see themselves* as all operating in the same industry as evidenced by the fact that energy, plastics, pesticides, and pharmaceutical companies all contribute and serve together as trustees of lobbying groups such as the American Council on Science and Health (Kroll & Schulman, 2013). Finally, regulatory agencies that have purview over these different sectors and products seem to operate in a similar manner (and have similar sets of problems).

In this chapter I will show that science and medicine are especially vulnerable to the distorting influence of capitalism. Even though this point is obvious to social scientists like Mirowski, Navarro, or Michaels, it runs counter to the popular perception of science as disinterested and somehow separate from the rest of the economy. Science

and medicine have a unique epistemic position that gives them extraordinary power and the science and medical communities, particularly in the autism debate, often attempt to use their power to shield themselves from popular, political, or media scrutiny. Furthermore, the science and medical communities have failed to construct adequate ethical safeguards to prevent COI and correct problems as they occur. The result is that science and medicine are increasingly beholden to and work in service of capital in ways that violate scientific norms and jeopardise the well-being of society.

In this chapter I will show that COI pervade university research (5.1), private research (5.2), scientific journals (5.3), government agencies (5.4), and the medical profession (5.5). This leads to studies that are not replicable and high levels of iatrogenic injury and death from treatments that are not safe (5.6). Far from its popular image and self-image as objective, science and medicine today have weaker COI rules than the financial system and the courts (5.7). The thread that runs through this chapter is that COI are *fatal* to good science. I will argue that the influence of capitalism on science and medicine makes it much more difficult to respond to the autism epidemic because the institutions that should be focused on prevention and cures are often focused on profit instead. The evidence presented in this chapter will show once again that there are political economy issues that must be solved prior to or simultaneously with public health efforts to respond to the autism epidemic.

5.0.1 Definitions of conflict of interest

There are several competing definitions of conflict of interest in the literature. Thompson (1993) defines a conflict of interest as ‘a set of conditions in which

professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)' (p. 573). Resnik (2007) defines a conflict of interest as 'a situation in which the individual has financial, personal, professional, or political interests that are likely to compromise his or her judgment or decision-making related to the performance of his or her ethical, legal, or professional obligations' (p. 112). Schafer (2004) emphasises the primacy of the physician's duty to the patient when he writes:

> A person is in a conflict of interest situation if she is in a relationship with another in which she has a moral obligation to exercise her judgment in that other's service and, at the same time, she has an interest tending to interfere with the proper exercise of judgment in that relationship (p. 19).

I find that the word 'unduly' in Thompson (1993) and 'likely' in Resnik (2007) are equivocal and unhelpful. I prefer Schafer's (2004) definition because it establishes a hierarchy between moral duty to the patient and individual (usually financial) interests.

Elliott (2008) notes that 'Some of the major sources of financial COIs for contemporary academic and government researchers include consulting fees with private companies, grants or contracts to fund university research projects, honorariums, gifts, equity holdings, managements positions with start-up companies, and revenue streams from intellectual property' (p. 4).

5.1 Financial conflicts of interest in university scientific research

As I showed in the chapter 3, Mirowski (2011) argues that the passage of the Bayh-Dole Act in 1980, which allows government-funded researchers to patent their discoveries, led to the increasing privatisation of university research science. One of the results is that financial conflicts of interest have become endemic to medical schools and academic scientific research. Angell (2009) writes, 'A few decades ago, medical schools did not have extensive financial dealings with industry, and faculty investigators who carried out industry-sponsored research generally did not have other ties to their sponsors. But schools now have their own manifold deals with industry and are hardly in a moral position to object to their faculty behaving in the same way' (para. 15).

Campbell et al. (2007) found that 60% of medical school department chairs had a personal relationship with industry (from serving on a board to serving as a consultant) and 67% of medical schools received financial support from drug companies. In an odd bit of mental compartmentalisation, 'more than two-thirds of department chairs perceived that having a relationship with industry had no effect on their professional activities, but 72% view a chair's engaging in more than one industry related activity as having a negative impact on a department's ability to conduct independent unbiased research' (Campbell et al., 2007, p. 1779). Tereskerz, Hamric, Guterbock, & Moreno (2009) surveyed the faculty at the 33 U.S. universities that receive the most research funding (p. 79). At those institutions, 66% of researchers received financial support from industry (Tereskerz et al. 2009). Male researchers were more than three times more likely to receive financial support from industry than female researchers — 79% vs. 23% respectively; 'full professors (51%)... were significantly more likely to receive

overall industry support than associate professors (25%) or assistant professors (23%)' (Tereskerz et al., 2009, p. 4).

Even prestigious schools of public health have become entangled with financial conflicts of interest. The tobacco, asbestos, vinyl, and other toxic industries have a long history of hiring professors of public health from esteemed universities to produce research favourable to the industry (Michaels, 2008a; Heath, 2016). For example, when Patricia Buffler, former dean of the UC Berkeley School of Public Health and world renowned researcher into childhood leukemia, died suddenly of a stroke at age 75, it was discovered that she had long held lucrative consulting deals with some of the very industries she was tasked with evaluating (Heath, 2013b). She made $360,000 serving as an expert witness on behalf of lead-based paint manufacturers and she made more than $2 million for her seventeen years on the board of pesticide giant FMC Corp (Heath, 2013b). Buffler never disclosed her work with FMC nor her ownership of FMC stock in her published journal articles (Heath, 2013b). Buffler also consulted for 'Dow Chemical, DuPont, Union Carbide, Shell Oil, Goodyear, and Atlantic Richfield' (Heath, 2013b). In addition, the American Industrial Health Council, an industry-funded group that lobbied against 'excessive' regulation of carcinogens, hired Buffler to critique a public health study conducted by the Harvard School of Public Health in connection with the leukemia cluster in Woburn, Massachusetts (depicted in the book and movie *A Civil Action*) (Heath, 2013b). She called the study 'sophisticated but biased' because of its use of volunteers to help collect survey data in spite of the fact that they had all received training in the appropriate research techniques (Heath, 2013b).

The UC Berkeley School of Public Health is not unique in having staff with COI. The Harvard Center for Risk Analysis (HCRA) is housed within Harvard's T. H. Chan School of Public Health and since its inception in 1989 it has been funded by many of the largest producers of toxic chemicals in the world including the American Chemistry Council, the Business Roundtable, ExxonMobil, Dow Chemical Company, Dupont, General Electric, Phillip Morris, and the Society of the Plastics Industry (Vogel, 2009, p. 562). The grants from these companies are usually listed as 'unrestricted' but when these companies face regulatory or legal hurdles they often commission HCRA to produce a report or study, that comes with the imprimatur of one of the nation's most prestigious universities, that portrays their product or industry in a favourable light (Vogel, 2009).

Corporations that produce toxic chemicals that need an expert to testify on their behalf or need a study to defend their product in regulatory proceedings or in court can also hire environmental consulting firms including Gradient, Exponent, Ramboll Environ, or ChemRisk that are often staffed with current and former professors of public health from prestigious universities (Heath, 2016). These firms are pejoratively referred to as 'rented white coats' by environmental groups because regardless of the issue, they consistently produce scientific results favourable to industry. Gradient Corporation staff sometimes include former and/or present day faculty at the Harvard School of Public Health (Heath, 2016). Heath (2016) writes,

> Gradient belongs to a breed of scientific consulting firms that defends the products of its corporate clients beyond credulity, even exhaustively studied substances whose dangers are not in doubt, such as asbestos, lead,

> and arsenic. Gradient's scientists rarely acknowledge that a chemical poses a serious public health risk. The Center for Public Integrity analyzed 149 scientific articles and letters published by the firm's most prolific scientists. Ninety-eight percent of the time, they found that the substance in question was harmless at levels to which people are typically exposed (para. 13).

In response to criticism of such close ties to industry, many universities have moved to develop guidelines to manage conflicts of interest. Angell (2009) notes that such guidelines are 'highly variable, generally quite permissive, and loosely enforced' (p. 3). Indeed there is often no sanction for failing to disclose a conflict of interest and no evidence that such policies have reduced corporate influence on campus or improved the quality of scientific research output (Mirowski, 2011, p. 236).

Zinner, Bolcic-Jankovic, Clarridge, Blumenthal, and Campbell (2009) note that 'life science faculty with industry research support were more productive than faculty without such support on virtually every measure [number of publications, publication trends score, journal impact factor, number of service activities]' (p. 1814). Yet, saying that industry funded scientists are more productive is a circular argument — it is not surprising that those who receive more corporate support are able to be more productive in a system shaped by corporations to reward those who participate on their terms.

5.2. Changes in Corporate Science

In *Morbid Symptoms*, Panitch and Leys (2009) write, 'Any serious political economy of health under capitalism must be centred on the fundamental contradiction involved: health and health care are use values *par excellence*, of limited interest to capital unless it can convert them into exchange values' (p. 3). Preventing autism provides use value to individuals, families, communities, and nations. But preventing autism has almost no exchange value (indeed following the recommendations of Project TENDR to ban or severely restrict a range of toxicants would cost industry money). Yet science and medicine under capitalism are dedicated to exchange values.

George W. Merck, the President of Merck and Co. from 1925 to 1950, once said,

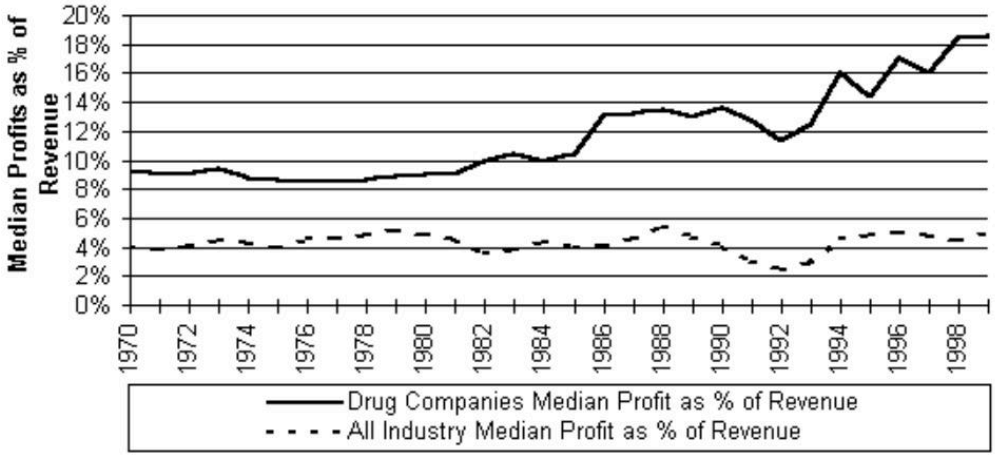
> 'We try to remember that medicine is for the patient. We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been' (in Kessel, 2014, p. 988).

Even if the statement was mostly for public relations purposes, it echoed the rhetoric of the Fordist era bargain — that some concessions that benefit the larger community (usually in connection with higher worker pay or health and retirement benefits) would be rewarded with higher long-run profits (Jessop, 1992). Kessel (2014) argues that the culture inside pharmaceutical companies has changed radically in our current era. He writes:

> Over time, however, there has been a shift in ideology of corporations [such] that the only social responsibility is to increase profits and enhance investor returns, and pharma has followed this mantra. As Jurgen Drews, the former head of Roche research, candidly stated in 2003, in the pharmaceutical business today 'the ethics of successful business have replaced those of medicine. The supreme loyalty of today's companies is not primarily directed at patients and their physicians but at shareholders. Consequently, the most influential figures in today's pharmaceutical companies are no longer the heads of R&D but the heads of marketing and finance' (Kessel, 2014, p. 984).

The pharmaceutical industry has long been more profitable than the Fortune 500 average but pharmaceutical industry profitability further increased in the twenty years after the passage of the Bayh-Dole Act in 1980 (Public Citizen, 2000).

Figure 5.1: Profitability of Fortune 500 Drug Industry and All Fortune 500 Industries; Profits as a % of Revenue (1970–1999)



Source: Public Citizen (2000).

But it all seems unsustainable. A 2013 Harris Poll found that only 10% of people surveyed have a favourable view of pharmaceutical companies. Legislative manoeuvres to extend patents and a focus on ‘me-too drugs’ have produced fat profits in the short and medium term but few truly novel new inventions that could sustain the industry over the long term (Mirowski, 2011). Regulatory capture leads to soaring prices for prescription drugs that consume a growing proportion of American incomes. At the same time, the outsourcing, deskilling, and offshoring of production have led to quality concerns (Harris, 2008b; ‘FDA says Chinese Pfizer plant hid failures’, 2015) and a number of high profile disasters such as when the FDA pulled the blood thinner heparin following reports of 785 serious injuries and 81 deaths linked to counterfeit ingredients sourced from China (Harris, 2008a, para. 1).

It would seem that the only way that high profit margins can last amidst rising public anger and declining quality and effectiveness of one’s products is through ever-increasing advertising (to try to change public sentiment) and aggressive capture of regulatory agencies and politicians (to head off regulation) — which, as I will show below, is essentially what is happening now. But that seems unsustainable as well. As the gap grows between what one sees and hears in the media and from the political class versus one’s actual lived experience of the world I imagine that would set off a whole host of destabilising tendencies (for individuals and entire societies) — from pessimism to cynicism to nihilism.

5.3 The crises in scientific journals

Smith (2003) acknowledged, ‘All journals are bought — or at least cleverly used — by the pharmaceutical industry’ (p. 1205). There is growing awareness that the practices of actually existing scientific journals violate the Mertonian norms of science: COI are widespread (5.3.1); COI shape study design and skew research results (5.3.2); the practice of ghost, gift, guest, and honorary authorship is widespread (5.3.3); peer review offers little quality control and introduces bias (5.3.4); most studies are not reproducible (5.3.5); and even when problems are identified scientific journals seldom issue corrections or retractions (5.3.6). Scientific publishing is very profitable, but it appears to be increasingly unable to produce reliable scientific results.

5.3.1 Financial conflicts of interest in scientific journals: advertising, reprints, special issues

Krimsky, Rothenberg, Stott, and Kyle (1996) studied 1,105 authors, who appeared in 789 articles, published in 14 major medical journals in 1992 (p. 395). They found that at least one lead author had at least one conflict of interest in connection with 34% of the articles examined (Krimsky et al. 1996, p. 395). Krimsky and Rothenberg (2001) revisited this issue and reviewed the 1,396 highest ranked science and medical journals. Of these, over 200 had conflict of interest policies. But when the authors reviewed 61,134 of the articles in these publications, only 327 (0.5%) had any statements listing a financial interest of the authors related to the subject matter of the publication (Krimsky & Rothenberg, 2001). Krimsky (2004) writes that, ‘journals neither police nor evaluate author compliance with their guidelines’ (p. 171).

Drug companies advertise heavily in medical journals and that advertising works: print advertising in medical journals has been shown to increase sales [O'Connell, 2001]; advertising in medical journals is seen as just as effective as the work of pharmaceutical sales representatives for 'announcing a new product' or a new use of an existing product [Association of Medical Publishers, 2000]; one study showed a return on investment of $2.22 to $6.86 (U.S.D.) per dollar spent on journal advertising [Neslin, 2001]; 'another industry study of 45 advertising campaigns found that journal advertising returned U.S. $3.05 for unique products and U.S. $2.46' for products competing with a rival [Liebman, 2000] (Fugh-Berman, Alladin, & Chow, 2006). Drug companies spent $326 million on advertising in medical journals in 2010 (Kornfield, Donohue, Berndt, & Alexander, 2013, p. 2).

Glassman, Hunter-Hayes, and Nakamura (1999) found that the *Annals of Internal Medicine (AIM)*, the *Journal of the American Medical Association (JAMA)*, and the *New England Journal of Medicine (NEJM)* had almost as many advertising pages as text pages. Lexchin and Light (2006) found that advertising in *AIM* supplies 12.9 per cent of the budget of the America College of Physicians, advertising in *JAMA* supplies 10.4 per cent of the budget of American Medical Association, and advertising in *NEJM* supplies 21.3 per cent of the budget of the Massachusetts Medical Society. In all three cases, corporate advertising exceeded the contributions from membership fees and assessments for these professional medical associations (Lexchin & Light, 2006, p. 1445). Special issues and inserts in academic journals have lower editorial standards and bring in additional advertising revenue (Sismondo, 2009, p. 183).

Lundh, Barbateskovic, Hróbjartsson, and Gøtzsche (2010) found that in 2005-2006, the sale of reprints generated 41% of *The Lancet's* income. Richard Horton, editor of *The Lancet* explains how it happens:

> Then the conversation might go: 'It is likely that the company will want to buy several hundred thousand reprints' and of course several hundred thousand reprints might translate into half a million pounds, a million pounds revenue to the journal. There is an implicit connection between the submission of a paper and the revenue that comes into a journal (UK, House of Commons, Health Committee, 2005, pp. 243–244).

Armstrong (2006) shows that Merck bought, from *NEJM,* 900,000 reprints of an article on a favourable Vioxx trial. Smith (2006b) estimates the profit from this purchase at $450,000. The editors of *NEJM* have since come under sharp criticism for their failure to issue an immediate correction when it was revealed that Merck omitted key information about heart attack risk from the article (Armstrong, 2006). Merck withdrew the drug from the market in 2004 and *NEJM* only issued an expression of concern in an editorial in 2005 — four years after editors were first made aware of problems with the data (Armstrong, 2006).

Under editors Kassirer and Angell, *NEJM* had some of the most stringent conflict of interest guidelines of any medical journal. For a time they even banned conflicts of interest for all review articles and editorials. In 2000, the Massachusetts Medical Society that owns the *NEJM* appointed Jeffrey Drazen as editor. Drazen received financial consideration from 21 drug companies between 1994 and 2000 (Smith, 2006b,

p. 380) and was censured by the FDA for touting a new asthma drug over and above its proven effects (Gottlieb, 2000). In 2002, Drazen along with executive editor Gregory Curfman bemoaned the fact that, as a result of the strict COI rules they inherited from previous editors, from 2000 to 2002 the *NEJM* was only able to publish one drug therapy article (Drazen & Curfman, 2002, p. 1901). So Drazen and Curfman announced that the *NEJM* would relax their COI guidelines. Henceforth, authors would be permitted up to $10,000 a year from a single source (doubling the previous limit; multiple COI are permitted but they each have to be below $10,000), and stated that these were ‘guidelines, not rigid rules’ (Drazen & Curfman, 2002, p. 1902).

5.3.2 Conflicts of interest shape study design and skew results

Sismondo (2008b) reports that ‘pharmaceutical company funding of clinical trials is strongly associated with published results favoring those companies’. The phenomenon is called the ‘funding effect’ and there is a vast literature that documents the extent of the practice.

Stelfox, Chua, O’Rourke, and Detsky (1998) examined 70 articles in the medical literature published between March 1995 and September 1996 on the safety of calcium-channel antagonists. They found that ‘authors who supported the use of calcium-channel antagonists were significantly more likely than neutral or critical authors to have financial relationships with manufacturers of calcium-channel antagonists. (96 percent vs. 60 percent and 37 percent, respectively)’ (Stelfox et al., 1998, p. 101). ‘Supportive authors were also more likely than neutral or critical authors to have financial

relationships with any pharmaceutical manufacturer, irrespective of the product (100 percent vs. 67 percent and 43 percent, respectively)' (Stelfox et al., 1998, p. 101).

Djulbegovic et al. (2000) examined 136 RCTs in connection with multiple myeloma published from 1996 to 1998. Seventy-four per cent of the RCTs sponsored by for-profit entities supported the new therapies versus just 53% when the study was sponsored by a nonprofit organisation (Djulbegovic et al., 2000).

Yaphe, Edman, Knishkowy, and Herman (2001) analyzed 314 randomised controlled trials published between 1992 and 1994 in five top medical journals (*Annals of Internal Medicine, BMJ, JAMA, Lancet*, and *NEJM*). Industry funded 209 RCTs and of those, 181 (87%) had positive findings and 28 (13%) had negative findings (Yaphe et al., 2001). By contrast, 96 RCTs did not have industry funding and of those, 62 (65%) had positive findings and 34 (35%) had negative findings; nine studies were categorised as uncertain; and the differences between the outcomes by funding source were statistically significant (Yaphe et al., 2001). The increased positive outcomes appeared whether the support was in the form of money, staff time, or free therapeutic agents (so the amount or type of the contribution did not matter — just whether there was any support at all) (Yaphe et al., 2001). And there was no difference between the five different journals (i.e. no journal was better at weeding out positivity bias than another) (Yaphe et al., 2001).

Als-Nielsen, Chen, Gluud, and Kjaergard (2003) studied 370 drug trials included in Cochrane Collaboration meta-analyses (studies of studies) and found that 'conclusions were significantly more likely to recommend the experimental drug as treatment of

choice in trials funded by for-profit organizations alone compared with trials funded by non-profit organizations' (p. 925). Once again the size of the contribution did not matter — both small contributions (such as simply providing the drug) and large contributions (funding the whole study) increased the likelihood that the drug would be recommended (Als-Nielsen et al., 2003).

Friedman and Richer (2004) examined 193 articles published in *NEJM* and 205 articles published in *JAMA* in 2001 and found that 'depending on the COI criteria used, 16.6% to 32.6% of manuscripts had one or more author with COI' (p. 51). They 'observed a strong association between those studies whose authors had COI and reported positive findings' (Friedman & Richer, 2004). When measured against the International Committee of Medical Journal Editors [2001] COI criteria, 'authors with COI were 10 to 20 times less likely to present negative findings than those without COI' (Friedman & Richer, 2004, p. 51).

Bekelman, Li, and Gross (2003) aggregated the results of eight meta-analyses that evaluated 1,140 original studies. They found that studies with industry sponsorship were more than three times more likely (OR = 3.6) to reach pro-industry conclusions than studies that were not sponsored by industry (Bekelman et al., 2003). Lexchin, Bero, Djulbegovic, and Clark (2003) examined 16 studies that looked at 'the relationship between funding source and the outcomes of clinical trials'; 13 of those 'found that clinical trials and meta-analyses sponsored by drug companies favored the product produced by the funder' (p. 5). Yank, Rennie, and Bero (2007) in a study of 124 meta-analyses found that meta-analyses that had ties to a drug company were more than five times more likely to report favourable conclusions (OR = 5.11; CI: 1.54, 16.92).

Sismondo (2008a) reviewed 19 articles on the relationship between industry funding and research outcomes and found that 17 articles reported a strong positive correlation. Lundh, Sismondo, Lexchin, Busuioc, and Bero (2012) examined the data in 48 papers published between 1948 and 2010 on the funding effect and found a statistically significant association between industry sponsorship and 'favorable efficacy results (RR = 1.32; CI: 1.21, 1.44), harms results (RR = 1.87; CI: 1.54, 2.27), and conclusions (RR = 1.31; CI: 1.20 to 1.44)' (p. 1). Lundh, Lexchin, Mintzes, Schroll, and Bero (2017) reviewed the literature from 2010 through February 2015 and added 27 new studies (to the 48 examined previously) on the funding effect and found that 'industry sponsored studies more often had favorable efficacy results, (RR = 1.27; CI: 1.17, 1.37) (25 papers) (moderate quality evidence), similar harms results (RR = 1.37; CI: 0.64, 2.93) (four papers) (very low quality evidence), and more often favorable conclusions (RR = 1.34, CI: 1.19, 1.51) (29 papers) (low quality evidence)' (p. 2). Moreover, 'in industry sponsored studies, there was less agreement between the results and the conclusions than in non-industry sponsored studies (RR = 0.83; CI: 0.70, 0.98) (six papers)' (Lundh et al., 2017, p. 2).

Resnik and Elliott (2013) argue that financial conflicts of interest can influence the selection of research problems or questions, study design, data collection, data analysis, the interpretation of data (overstating the significance of data or understating risks), and publication (favourable results are much more likely to be sent out for publication) (pp. 188–190). Michaels (2008b) writes, 'Within the scientific community, there is little debate about the existence of the funding effect, but the mechanism through which it plays out has been a surprise' (para. 6). Many people initially assumed that the funding effect was the result of outright fraud and data manipulation (Michaels, 2008b). Clearly

fraud is a *part* of the story — McGoey (2007) documented how the makers of Seroxat hid the increased risk of suicide from British drug regulators. Later in this chapter I will show how the makers of Vioxx hid the increased heart attack risk from studies submitted to the FDA. But as Smith (2005) notes, fraud is crude and often detectable. Furthermore, the evidence suggests that research methods in industry funded studies are as good or better than independently funded studies (Djulbegovic et al., 2000; Als-Nielsen et al., 2003; Lexchin et al., 2003). There are many ways to set up a research study to produce a desired outcome (it is not clear whether this manipulation is conscious or unconscious but it is bias all the same). Smith (2005) argues that the most effective way to influence a study is through asking research questions in a certain way that privileges one approach over another. Other common techniques include:

> ...testing one's drug against a treatment that either does not work or does not work very well; testing one's drug against too low or too high a dose of the comparison drug because this will make one's drug appear more effective or less toxic; publishing results of a single trial many times in different forms to make it appear that multiple studies reached the same conclusion; and publishing only those studies or even parts of studies that are favourable to one's drug, and burying the rest (Michaels, 2008b, para. 10).

But that creates an untenable situation. For example, over 100 independent studies of bisphenol A (BPA) found harms from even low dose exposures while none of the nearly two dozen studies funded by the chemical industry identified such harms (vom Saal & Welshons, 2006, p. 61). As I will show below, Environmental Protection Agency (EPA)

regulators in the U.S. are required by Congress to weigh all of the available evidence. So biased studies are mixed in with unbiased studies which muddies the pool of evidence and makes regulation more difficult.

Bias also shows up in metastudies, where decisions about what to include and what to exclude as well as how to weight different factors and which endpoints to examine all make an enormous difference on the study outcome (Michaels, 2008b, para. 11). So for example, the National Toxicology Program sponsored two metastudies of the health effects of BPA and they reached two different conclusions because of differences in sampling and weighting of different studies (Michaels, 2008b, para. 11).

5.3.3 Ghost, gift, guest, and honorary authorship

As pharmaceutical companies shifted much of their research funding to CROs over the last twenty years, it created a problem because the managers of the CROs rarely have the necessary academic degrees nor social standing to get published in top science and medical journals. And yet articles in top science and medical journals are a key marketing tool in outreach to doctors and the public. So pharmaceutical companies began asking academics to affix their names to studies written by pharmaceutical company ghost-writers. ‘Honorary’ (also sometimes called ‘guest’ or ‘gift’) authorship is defined as ‘naming, as an author, an individual who does not meet authorship criteria’ (Rennie & Flanagin, 1994). Ghost authorship is defined as ‘failure to name, as an author, an individual who has made substantial contributions to the research or writing of the article’ (Rennie & Flanagin, 1994). The full extent of ghost writing in the scientific and medical literature is unknown because it is secret by design (Ngai, Gold, Gill, &

Rochon, 2005). ‘Most of the articles that have been identified as ghost written were revealed as such only after investigative work by lawyers, journalists, or scientists’ (Ngai et al., 2005, p.106). Sismondo (2007) estimates that ‘approximately 40% of journal reports of clinical trials of new drugs’ are written by ghost writers employed by pharmaceutical companies, not the listed author. Other studies described below have lower estimates. ‘Ghost authorship is often employed to mask conflicts of interest’ (Ngai et al., 2005). Yet this practice is commonplace throughout academic publishing and rarely policed by most universities (Mirowski, 2011). Honorary and ghost authorship are two facets of a vast restructuring in the mode of production in science over the last few decades. In this section I will review the literature on how marketing concerns largely drive the scientific process from study design through execution and dissemination of the results.

In a previous era, research came first and then marketing. Now, the evidence suggests, marketing starts the process — either in-house at pharmaceutical companies and/or through a range of contractors including advertising agencies, medical education and communications companies (MECCs), and/or publication planners — who guide a research study from conception, through publication, regulatory approval, and marketing (Sismondo, 2009). These firms aim to produce results that get published in the best journals in the shortest amount of time and then they broadly share these results with regulators, doctors, and the public in order to boost sales and profits for their sponsors (Sismondo, 2009).

Publication planning has evolved beyond the ghost writing of the earlier era — it is now a vertically integrated information manufacturing machine that guides every step of the

process. ‘Publication planning can and should start even before the research does, contributing to research design, mapping out key messages, and identifying papers for different audiences and journals, and potential authors on those papers. The focus is communication, and the research is created with communication in view’ (Sismondo, 2009, p. 175).

There are more than 50 publication planning firms, some with hundreds of employees, and even two international associations of publication planning professionals (Sismondo, 2009, pp. 172–174). Some publication planning firms are independent, some are owned by CROs, and some are divisions of major publishing houses (Sismondo, 2009, p. 182). Petersen (2002) writing in the *New York Times* discovered that three of the world’s largest advertising agencies (Omnicom, Interpublic, and WPP) have bought or invested in CROs directly (para. 5).

An essential step in this new mode of knowledge production is to find a Key Opinion Leader (KOL) who will agree to attach his or her name to the study in order to get it published in a high impact factor journal (Sismondo, 2009). ‘A KOL is a well-known specialist, highly regarded by peers, who... can influence other physicians and who has experience with the product’ (Sismondo, 2009, p. 185). Ideally, the KOL has an existing relationship of some kind with the pharmaceutical company (Sismondo, 2009, p. 186). KOLs can include doctors, editors at medical journals, and academics (Sismondo, 2009).

Why would leaders in the field agree to attach their names to studies that they did not write? The evidence suggests such honorary, gift, or guest authorship is relatively easy, somewhat lucrative, and there is almost never any sanction even if caught (which, given

the secret nature of the arrangement, rarely happens). Petersen (2002) finds evidence that some academics sign on for as little as $1,000 to $1,500 per article. Sismondo (2009) estimates the going rate at around $2,500 per article.

It appears that the dynamic here is about more than just the money. In the competition to improve university, department, and individual rankings, those who play the honorary/gift/guest writing game earn publishing credits for ‘authoring’ articles which can ‘then translate into promotion, tenure, grants, and so on’ (Moffatt & Elliott, 2007, p. 29). Such success presumably also impacts social capital including standing, respect, and esteem in the eyes of colleagues. And those who do not play along in a system in which pharmaceutical industry funding is influential in every step of the process, may find themselves falling further and further behind.

Flanagin et al. (1998); Yank and Rennie (1999); Mowatt et al. (2002); Healy and Cattell (2003); Gøtzsche et al. (2007); Ross, Hill, Egilman, and Krumholz (2008); and Wislar, Flanagin, Fontanarosa, and DeAngelis (2011) all conducted original research that showed widespread evidence of honorary, guest, gift, and ghost authorship. Melander, Ahlqvist-Rastad, Meijer, and Beermann (2003) found widespread evidence of multiple publication (publishing the same article, worded slightly differently, in several journals), selective publication (only publishing studies that are favourable to one’s product), and selective reporting (omitting key data from a study) in connection with studies of five SSRIs.

Defenders of the status quo tend to describe the trend towards honorary, guest, gift, and ghost authorship as ‘new styles of authorship’ which reflect the decentralised nature of

modern scientific research. By contrast, Moffatt and Elliott (2007) argue that honorary, guest, gift, and ghost authorship are designed to conceal conflicts of interest for the purpose of marketing and profit.

5.3.4 Problems with peer review

Peer review is one of the gold standards of academic publishing. Yet leading figures in science and medicine are sharply critical of the process and raise doubts as to its effectiveness and scientific validity. Smith (2006a) writes:

> Peer review is impossible to define in operational terms (an operational definition is one whereby if 50 of us looked at the same process we could all agree most of the time whether or not it was peer review). Peer review is thus like poetry, love, or justice.... [W]e have little evidence on the effectiveness of peer review, but we have considerable evidence on its defects. In addition to being poor at detecting gross defects and almost useless for detecting fraud, it is slow, expensive, profligate of academic time, highly subjective, something of a lottery, prone to bias, and easily abused (p. 178).

Peters and Ceci (1982) selected 12 papers published in prestigious journals, changed the names and institutions listed for the authors, and ‘resubmitted [them] to the same journals that had originally refereed and published them’ (p. 187). ‘Sixteen of the 18 referees (89%) recommended against publication and the editors concurred’ (Peters & Ceci, 1982, p. 187). In the scientific community, favourable treatment toward well-

established names in the field is referred to as the ‘Matthew Effect’ (Merton, 1968) based on the Biblical passage, Matthew 13:12: ‘For to those who have, more will be given, and they will have an abundance; but from those who have nothing, even what they have will be taken away’ (New Revised Standard Version).

Schroter et al. (2008) reviewed three studies on the ability of reviewers to detect errors (Nylenna, Riis, & Karlsson, [1994]; Baxt et al., [1998]; and Godlee et al., [1998]) and found that the majority of reviewers missed most of the major errors that were deliberately inserted. Schroter et al. (2008) then inserted nine major errors into three test papers and sent them to 607 peer reviewers at the *BMJ*. After marking up the first paper, reviewers then underwent a short training in how to detect methodological errors. ‘At baseline (Paper 1) reviewers found an average of 2.58 of the nine major errors’ (Schroter et al. 2008, p. 507). Following the short training course, ‘the mean number of errors reported was similar for the second and third papers, 2.71 and 3.0, respectively’ (Schroter et al. 2008, p. 507).

Jefferson, Alderson, Wager, and Davidoff (2002) in a metastudy on peer review concluded that, ‘The practice of peer review is based on faith in its effects, rather than on facts’. Lee, Sugimoto, Zhang, and Cronin (2013) in a more recent metastudy of papers on peer review found bias in connection with institutional prestige, affiliation, nationality, as well as confirmation bias, conservatism, bias against interdisciplinary research, and positivity bias (pp. 7–10).

Ioannidis (2005b) writes, ‘Prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their findings, thus

condemning their field to perpetuate false dogma' (p. 698). Wilson (2016) writes, 'If peer review is good at anything, it appears to be keeping unpopular ideas from being published' (para. 19).

Smith (2006a) provides a list of recommended reforms to improve peer review, but, like so many policy prescriptions, he is doubtful that they will be implemented. He writes,

> So peer review is a flawed process, full of easily identified defects with little evidence that it works. Nevertheless, it is likely to remain central to science and journals because there is no obvious alternative, and scientists and editors have a continuing belief in peer review. How odd that science should be rooted in belief (Smith, 2006a, p. 182).

Reform proposals that are quickly forgotten and a tendency to stick with traditional systems even when they have been shown to be inadequate or error-prone have become troublesome hallmarks of the modern scientific era. Peer review, that starts out looking like the very essence of objective science, is in fact social, and prone to abuse, distortion, and bias; its gatekeeping role can be used to improve quality but it can also serve to protect existing power structures in science and medicine.

5.3.5 The crisis of reproducibility

Widespread problems in the quality of scientific research have led to what is called the 'crisis of reproducibility'.

C. G. Begley is the former global head of Hematology and Oncology Research at Amgen. Over the course of a decade, Begley and other researchers at Amgen attempted to reproduce 53 landmark studies in the field (‘landmark’ is not defined in the paper) (Begley & Ellis, 2012). Extraordinary efforts were taken to reproduce the exact conditions of the initial study — in some cases the studies were even reproduced in the original lab under the direction of the original investigators (Begley & Ellis, 2012). However, scientific findings were confirmed in only six (11%) out of 53 cases (Begley & Ellis, 2012, p. 532).

Sharon Begley (2012) of Reuters followed up with C. G. Begley (no relation) and discovered that many of the original study authors, as a condition of participating in the replication study, required the Amgen scientists to ‘sign a confidentiality agreement barring them from disclosing data at odds with the original findings’. C. G. Begley explained that as a result, ‘the world will never know’ the 47 studies that are not replicable (S. Begley, 2012).

How does this happen? It appears to be a combination of permissive standards as well as a tendency for science journals to seek out sensational stories. C. G. Begley recounts that he met with the principal investigator of one of the non-reproducible studies (S. Begley, 2012).

> ‘We went through the paper line by line, figure by figure’, said [C. G.] Begley. ‘I explained that we re-did their experiment 50 times and never got their result. He said they’d done it six times and got this result once, but put it in the paper because it made the best story’ (S. Begley, 2012).

Cosgrove, Vannoy, Mintzes, and Shaughnessy (2016) point out that the FDA regulatory process allows this sort of cherry-picking of positive data and omission of failed trials. The same drug that receives FDA approval as safe and effective via this cherry-picking approach could also fail a systematic review that looks at all of the evidence (Cosgrove et al., 2016, p. 261).

In a similar set of experiments, three scientists from Bayer Healthcare compared published data against the results from 67 in-house projects (Prinz, Schlange, & Asadullah, 2011). Forty-seven of the 67 projects were from the field of oncology. They found that:

> ...only in ~20–25% of the projects were the relevant published data completely in line with our in-house findings.... Surprisingly, even publications in prestigious journals or from several independent groups did not ensure reproducibility. Indeed our analysis revealed that the reproducibility of published data did not significantly correlate with journal impact factors, the number of publications on the respective target or the number of independent groups that authored the publications (Prinz et al. 2011, p. 713).

Prinz et al. (2011) argue that the non-reproducibility of much of the published research is widely known in scientific circles. They write:

> Our findings are mirrored by ‘gut feelings’ expressed in personal communications with scientists from academia or other companies, as well as published observations. An unspoken rule among early-stage venture capital firms that ‘at least 50% of published studies, even those in top-tier academic journals, can’t be repeated with the same conclusions by an industrial lab’ (Prinz et al. 2011, p. 713).

The problem of lack of reproducibility sets off a cascade of harmful effects. Begley and Ellis (2012) write, ‘Some non-reproducible preclinical papers had spawned an entire field, with hundreds of secondary publications that expanded on elements of the original observation, but did not actually seek to confirm or falsify its fundamental basis’ (p. 532). Many of these non-reproducible studies also lead to clinical trials which means that people are subjected to medicines that do not work (Begley & Ellis, 2012, p. 532).

In 2005, John Ioannidis published two ground-breaking articles on the crisis of reproducibility. Ioannidis (2005a) focused on 49 of the mostly highly cited (over 1,000 citations) original clinical research findings during the period 1990–2003. Forty-five studies in the sample reported effective interventions (Ioannidis, 2005a, p. 218). ‘Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had a larger effect size than in the subsequent study, 20 (44%) were replicated, and 11 (24%) were not subject to replication studies’ (Ioannidis, 2005a, p. 218). In the study, five out of six non-RCTs were problematic (contradicted or reported larger effects than were replicable) versus just 9 out of 38 RCTs (Ioannidis, 2005a, p. 218).

Ioannidis (2005b) 'Why Most Published Research Findings are False' created a mathematical model to estimate the likelihood that any given research study will be true.[6] His model factored in estimates of power, bias, and pre-study odds to create a range of estimates. His model predicts that 85% of 'adequately powered RCTs with little bias and 1:1 pre-study odds' are correct; 23% of 'underpowered but well-performed phase I/II RCTs' are correct; 20% of 'adequately powered exploratory epidemiological studies' are correct; and about 1/10th of 1% of 'discovery oriented exploratory research with massive testing' (nutrition and genetic studies with large numbers of variables) are correct (Ioannidis, 2005b, p. 700). It is important to point out that Ioannidis is presenting a theoretical model here. Actual real world results, including the efforts of Begley and Ellis (2012) and Prinz, Schlange, and Asadullah, (2011) show that even widely respected RCTs in the real world are not replicable at much higher rates than suggested by Ioannidis' (2005b) model. What this tells us is that lots of low quality evidence is routinely passed off as legitimate in ways that are profitable for corporations but harmful for the public.

5.3.6 Even when massive problems are identified, scientific journals seldom issue corrections or retractions

In the 1950s, a poor African American tobacco farmer named Henrietta Lacks developed cervical cancer (Skloot, 2017). Samples of her cancerous cells were cultured and turned into a popular and profitable cell line called HeLa that is still used in scientific research today (Skloot, 2017). But it turns out her cell line was too successful and combined with inadequate lab practices, HeLa has contaminated a wide variety of

[6] It has since become the most downloaded article in the history of *PLoS Medicine* (Freedman, 2010).

cell lines and raised questions about the validity of an enormous range of subsequent scientific research (Oransky & Marcus, 2016). HeLa contamination is just the tip of the iceberg as far as contamination of popular cell lines:

> Recent estimates suggest that between 20 percent and 36 percent of cell lines scientists use are contaminated or misidentified — passing off as human tissue cells that in fact come from pigs, rats, or mice, or in which the desired human cell is tainted with unknown others. But despite knowing about the issue for at least 35 years, the vast majority of journals have yet to put any kind of disclaimer on the thousands of studies affected (Oransky & Marcus, 2016, para. 2).

The conclusions of thousands of studies are potentially invalid as a result of this contamination.

> Nearly 5,800 articles in 1,182 journals may have confused HeLa for HEp-2; another 1,336 articles in 271 journals may have mixed up HeLa with INT 407. Together, the 7,000-plus papers have been cited roughly 214,000 times, *Science* reported last year. And that's just two cell lines. All told, more than 400 cell lines either lack evidence of origin or have become cross-contaminated with human or other animal cells at some point in their laboratory lineage (Oransky & Marcus, 2016, para. 4).

Casadevall, Steen, and Fang (2014) conducted a study of 2,047 articles in the PubMed database that had been retracted as of May 3, 2012. Casadevall et al. (2014) found that

the vast majority of retractions, 1,624 (79%), were the result of scientific misconduct defined as ‘data fabrication, data falsification, plagiarism, and duplicate publication’ (p. 3848). They analysed the remaining 423 (21%) articles that had been retracted due to error. To their surprise, they only found 6 (1.4% of the papers retracted due to error) attributed to contamination of cell lines or use of inappropriate cells (Casadevall et al., 2014, p. 3849). They noted that this low number was in spite of the fact that the problem of cell line contamination is widespread and well known. They conclude, ‘the paucity of retractions attributed to contaminated cell lines suggests that the literature contains many unretracted but potentially erroneous studies’ (Casadevall et al., 2014, p. 3849). Indeed if Oranksy and Marcus (2016) are correct, the number of articles that should be retracted numbers in the tens of thousands.

It does not take a lot of imagination to figure out why scientific journals might be reluctant to retract the thousands of papers tied to contaminated cell lines. Millions of dollars, jobs, and status are on the line for the academic and corporate researchers and the journals themselves. Yet the unwillingness of journals to issue retractions for articles they know are based on false premises, suggests that economic, social, and personal factors sometimes outweigh objectivity at even the best scientific journals.

5.4 Capture of regulatory agencies

Laffont and Tirole (1991) argue that the theory of regulatory capture begins with Marx. While they do not elaborate on Marx’s particular contribution, it seems clear that Marx and Engels’ ([1848], 2004) argument in the *Communist Manifesto* that ‘The executive of the modern state is but a committee for managing the common affairs of the whole

bourgeoisie' and many themes in their larger *oeuvre* presaged more recent theories of regulatory capture. Following the growth of the regulatory state in the U.S. as part of Roosevelt's New Deal and with the end of World War II a number of political scientists and economists developed theories of regulation including Huntington (1952), Bernstein (1955), and Downs (1957). Progressives often view regulation as a tool for reining in corporate excesses and harms. Chicago school theorists including Stigler (1971) and Peltzman (1976) counter that regulation and regulatory agencies are often designed by corporate lawyers, lobbyists, and executives to favour corporate interests (which is more in line with Marx's view as well).

Carpenter and Moss (2013) define regulatory capture as 'the result or process by which regulation, in law or application, is consistently or repeatedly directed away from the public interest and toward the interests of the regulated industry, by the intent and action of the industry itself' (p. 13). Below I will present evidence that the key regulatory agencies in the Federal government that have purview over some aspect of the autism epidemic (CDC, FDA, NIH, and EPA) are all captured pursuant to the definition from Carpenter and Moss (2013). In spite of their differences, each institution is characterised by unresolvable contradictions that are built into the design of the institution and/or are added over time. Evidence of regulatory capture in these institutions includes corporate influence over the decisions of advisory committees, front line scientists, and senior managers. Corporate donations to elected officials also result in pressure from above on regulators to bow to corporate interests.

5.4.1 Centers for Disease Control and Prevention

The U.S. Communicable Disease Center was founded July 1, 1946 as a branch of the U.S. Public Health Service with a mission to control malaria (Parascandola, 1996). In the early years the key staff were entomologists (scientists who study insects) and engineers and the agency focused on the application of DDT and other pesticides to more than 6 million homes (CDC, 2016a). Over the years the CDC expanded to take on the Epidemic Intelligence Service (to deal with Cold War concerns over biological warfare), veterinary diseases, and sexually transmitted diseases (CDC, 2016a). It was renamed the National Communicable Disease Center effective July 1, 1967, the Center for Disease Control on June 24, 1970, the Centers for Disease Control effective October 14, 1980, and the Centers for Disease Control *and Prevention* (CDC) effective October 27, 1992 (National Archives, n.d.). Like the FDA, the CDC has made an enormous contribution to public health over the years. But there are concerns that it has become captured by corporate interests in recent years. Importantly, autism falls within the CDC's ambit. As of yet, the agency does not use the word 'epidemic' in connection with autism in spite of the rising prevalence numbers and does not acknowledge that autism is preventable in spite of the consensus statements (described in chapter 1) by leading epidemiologists that argue that autism is likely caused by environmental triggers.

COI are endemic to the CDC. Levinson (2009) in a report for the Office of the Inspector General wrote, 'We found that CDC had a systemic lack of oversight of the ethics program for SGEs [special government employees — the official designation for advisory committee members]' (p. iii). Ninety-seven per cent of disclosure forms filed

by SGEs were incomplete and 13 per cent of SGEs did not even have a disclosure form on file (Levinson, 2009).

COI are by design at the CDC. According to Lenzer (2015) in 1983, 'the CDC was authorised to accept "gifts" from industry and other private parties' (p. 1). In 1992, Congress introduced more possibilities for conflict of interest by creating the non-profit CDC Foundation which opened its doors in 1995 (Lenzer, 2015). The legislation that created the CDC Foundation allows private donors to create and fund programs at the CDC, 'endow positions at the CDC, and even place individuals to work at the CDC, paid through "private funding"' (Informed Consent Action Network, 2017a, p. 27). Overall the CDC accepted $42,433,855 in gifts in 2016 and $662,785,857 since its inception in 1995 (CDC Foundation, 2016a). Bayer, Merck, the Pfizer Foundation, and the Sanofi Foundation all give to the CDC Foundation (CDC Foundation, 2016b).

In 2016, the CDC's budget was about $7 billion, so outside funding is just a small fraction of the total. So then why allow outside funding of the CDC at all? From a corporate perspective, the CDC Foundation represents an extraordinary opportunity. For a relatively small investment of money, they can get a foot in the door and integrate themselves into the government bureaucracy and produce outputs that have the imprimatur of an ostensibly neutral government body. But from a scientific perspective such donations violate Mertonian norms of universalism, disinterestedness, and organised scepticism. The moment the CDC accepts any outside funding it becomes a conflicted party subject to the funding effect and such funding raises doubts as to the scientific integrity of their work.

Lenzer (2015) highlights three case studies of COI at CDC. Between 2010 and 2015 the CDC Foundation accepted over $26 million from corporations that make products that ‘test for or treat hepatitis C infection’ (Lenzer, 2015, p. 2). In August 2012, the CDC issued guidelines ‘recommending expanded (cohort) screening of everyone born between 1945 and 1965 for hepatitis C virus’ (Lenzer, 2015, p. 2). But Koretz, Lin, Ioannidis, and Lenzer (2014) argue that the expanded screenings are not scientifically justified. Nine of the 34 members of the working group that wrote the guidelines had a financial relationship with the manufacturers of hepatitis C tests or treatments (Lenzer, 2015, p. 2).

A similar pattern emerged in connection with an antiviral drug called oseltamivir, produced for Roche, for treatment of symptoms associated with the flu: Roche funded the CDC’s ‘Take 3’ flu campaign; the third step in the Take 3 campaign is ‘take antiviral medicine if your doctor prescribes it’; the CDC then posted a study sponsored by Roche to its website recommending antiviral drugs such as oseltamivir for flu (Lenzer, 2015, p. 2). The CDC failed to include the Cochrane Collaboration review on its website that showed that oseltamivir does not reduce pneumonia nor fatalities from the flu (Lenzer, 2015, p. 2). Indeed the FDA warned Roche that it could not promote oseltamivir as reducing pneumonia and death because it had never provided evidence to support such claims yet the CDC’s Take 3 campaign was seen as promoting off label use of oseltamivir for flu (Lenzer, 2015, p. 2).

The third case study from Lenzer (2015) is the most troubling. Twenty thousand young men who worked in sugar cane fields in Central America have died in an ‘epidemic of chronic kidney disease’ (Ramirez-Rubio, McClean, Amador, & Brooks, 2013). The

most likely causes according to Ordunez et al. (2014) are agrochemicals (including glyphosate-based herbicides like Roundup) used in the fields and the horrendous working conditions. In 2014, the sugarcane industry gave $1.7 million to the CDC (Lenzer, 2015). And the CDC is now conducting a longitudinal study, for an as yet undetermined period of time, *to examine genetics and biomarkers in children that might predispose them to later kidney failure* (Lenzer, 2015, pp. 2–3). Researching long-shot genetic explanations over and against investigating environmental causes that might threaten corporate interests has become standard practice at the CDC — particularly in connection with autism.

5.4.2 Food and Drug Administration

Throughout the Progressive Era (1890s to 1920s) in the United States, muckraking journalists like Samuel Hopkins Adams and Upton Sinclair brought the nation's attention to problematic corporate conduct in connection with the nation's medical and food supplies (Buenker, Burnham, & Crunden, 1986; FDA, 2009a). In 1902, following the deaths of thirteen children in St. Louis who received diphtheria antitoxin contaminated with tetanus spores, Congress passed the Biologics Control Act to regulate vaccines (HHS, n.d.). In 1906, Congress passed the Pure Food and Drug Act, that banned the interstate transport of food or drugs that had been adulterated (FDA, 2009a). Drugs now required labels that listed the ingredients and purity standards were also established (FDA, 2009a). Enforcement of the act was the responsibility of the U.S. Department of Agriculture's Bureau of Chemistry which later became the Food, Drug, and Insecticide Administration and this name was eventually shortened to the Food and Drug Administration (FDA) in 1930 (FDA, 2014a). Today the FDA regulates 'food,

drugs, biologics, medical devices, electronic products that give off radiation, cosmetics, veterinary products, and tobacco products' (FDA, 2018). Harris (2008b) estimates that the FDA regulates the products in connection with twenty-five per cent of all consumer spending in the U.S. There is no question that the FDA has saved millions of lives and improved health and safety for U.S. citizens. But there are growing concerns that the FDA has become captured by corporate interests (Gøtzsche, 2013, p. 109). If it is ultimately determined that autism is the result of iatrogenic injury it would represent an extraordinary regulatory failure by the FDA. For the sake of brevity, I will limit my analysis here to studies on regulatory capture of the FDA published beginning in 2000.

A study by *USA Today* found that the FDA is riddled with financial conflicts of interest (Cauchon, 2000). They found that, 'more than half of the experts hired to advise the [U.S.] government on the safety and effectiveness of medicine have financial relationships with the pharmaceutical companies that will be helped or hurt by their decisions' (Cauchon, 2000, p.1). The financial conflicts of interest 'include stock ownership, consulting fees, research grants, a spouse's employment, and payments for speeches and travel' (Cauchon, 2000, 'Types of Conflicts', para. 1). The *USA Today* analysis examined conflicts of interest at 159 FDA advisory committee meetings from January 1, 1998 to June 30, 2000. They found that:

- at 92% of meetings, at least one member had a financial conflict of interest.
- At 55% of meetings, half or more of the FDA advisers had conflicts of interest....

- At 102 meetings dealing with the fate of a specific drug, 33% of the experts had a financial conflict (Cauchon, 2000, para. 8).

Adding a 'consumer representative', a frequent reform proposed by those worried about the influence of commercial interests on drug regulation, was of no help. *USA Today* showed that 'even consumers' and patients' representatives on the committees often receive drug company money' (Cauchon, 2000, 'Number of Drug Experts Available is Unlimited', para. 6). The FDA is prohibited from using experts with COI if they do not have a waiver; but waivers are routine — during this period, the FDA granted 803 COI waivers (Cauchon, 2000). Advisory committees are extremely powerful. During the two year period under review, the FDA followed the advisory committees' recommendations in every instance except one — 'the FDA approved the flu drug Relenza in July 1999 despite an advisory committee voting 13–4 against approval' (Cauchon, 2000, 'Powerful Panels', para. 1).

In December 2000, the *Los Angeles Times* published an investigation by David Willman (who was later awarded the Pulitzer Prize for his work on this series) into seven drugs that had been approved by the FDA that were later withdrawn after a combined 1,002 fatalities. Willman (2000) notes that for decades the FDA had been known for a cautious and slow approach to approving new drugs; but pharmaceutical companies took advantage of the AIDS crisis to push for faster drug reviews. The 1992 Prescription Drug User Fee Act (PDUFA) requires pharmaceutical companies to pay $309,647 to the FDA for each new drug application (the fee represents about half of the actual cost of a review) (Willman, 2000). But in return, the PDUFA called on the FDA to review drugs within six months to a year — more than twice as fast as before

(Willman, 2000). The result was a dramatic speed up in new drug reviews and a massive increase in the percentage of drugs approved (Willman, 2000). The agency hired more medical officers to help with the workload but they did not hire more investigators to monitor safety once those drugs were on the market (Willman, 2000). Wood, Stein, and Woosley (1998) note that the 1992 PDUFA and its reauthorisation in 1997 prohibited the FDA from spending user fees 'on post-marketing surveillance or other drug-safety programs' (p. 1852). Following the PDUFA, FDA staff (who subsequently left the agency) described a 'sweatshop environment' where scientists were pressured to approve drugs and were reprimanded by senior administrators if they raised safety concerns in connection with the data submitted by the companies (Willman, 2000, 'Lost Faith in the System', para. 20). Willman (2000) writes,

> In 1988, only 4% of new drugs introduced into the world market were approved first by the FDA. In 1998, the FDA's first-in-the-world approvals spiked to 66%. The drug companies' batting average in getting new drugs approved also climbed. By the end of the 1990s, the FDA was approving more than 80% of the industry's applications for new products, compared with about 60% at the beginning of the decade (para. 9).

If the new drug works, rapid approval means patients can enjoy the health benefits sooner than under the previous system (Psaty, Furberg, Ray, & Weiss, 2004, p. 2622). But the worry is that as speed has increased, the quality of the reviews has decreased. As I will discuss in a separate section below on iatrogenic injury and death (5.6), for many people this flood of new drugs comes at an enormous cost.

> More than 250,000 side effects linked to prescription drugs, including injuries and deaths, are reported each year. And those 'adverse-events' reports by doctors and others are only filed voluntarily. Experts including Strom [Founding Chair of the Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania] believe the reports represent as few as 1% to 10% of all such events (Willman, 2000, 'Lost Faith in the System', para. 32).

In response to the embarrassing revelations published by *USA Today* and the *Los Angeles Times*, the House Government Reform Committee held hearings ('House Investigates', 2001). The FDA drafted new conflict of interest disclosure policies (Lurie et al. 2006, p. 1922). But there is little evidence that this new guidance reduced conflicts of interest.

An internal FDA report in 2002 found that 'one-third of staff members surveyed did not feel comfortable expressing contrary scientific opinions'; 'a third felt negative actions against applications were "stigmatized" within the agency'; and some drug reviewers stated, 'that decisions should be based more on science and less on corporate wishes' (Adams, 2002).

A 2003 report from the Office of Inspector General of the Department of Health and Human Services (HHS) found that 66% of reviewers in the FDA's Center for Drug Evaluation and Research (CDER) 'lacked confidence in the FDA's safety monitoring of marketed prescription drugs' and '18% had felt pressure to approve a drug despite reservations about its quality, efficacy, or safety' (HHS, 2003).

A Government Accountability Office (2006a) report found that the ‘FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues’.

In 2006, the Union of Concerned Scientists sent a survey to 5,918 FDA scientists (997 completed and returned the survey) and they found that:

- 18.4% said that they ‘have been asked, for non-scientific reasons, to inappropriately exclude or alter technical information or their conclusions in a FDA scientific document’;
- 40% fear retaliation for voicing safety concerns in public;
- 61% knew of cases where ‘Department of Health and Human Services or FDA political appointees have inappropriately injected themselves into FDA determinations or actions’.
- Only 47% think the ‘FDA routinely provides complete and accurate information to the public’.
- 81% agreed that the ‘public would be better served if the independence and authority of FDA post-market safety systems were strengthened’.
- 70% disagree with the statement that FDA has sufficient resources to perform effectively its mission of ‘protecting public health and helping to get accurate science-based information they need to use medicines and foods to improve their health’ (Union of Concerned Scientists, 2006).

Strom (2006) highlights some of the effects of the sped-up drug approval process:

- 51% of drugs have label changes because of major safety issues discovered after marketing [US General Accounting Office, 1990];
- 20% of drugs get new black box warnings[7] after marketing [Lasser et al. 2002]; and
- 3% to 4% of drugs are ultimately withdrawn for safety reasons [Bakke, Manocchia, de Abajo, Kaitin, & Lasagna, 1995].

The 2007 FDA Amendments Act capped the number of COI waivers the FDA could grant in a given year; but the 2012 FDA Safety and Innovation Act removed all caps which undermines any meaningful attempt to prevent COI on advisory committees (Wood & Mador, 2013).

Downing et al. (2012) found that the FDA approves drugs faster than the European Medicines Agency. Downing et al. (2014) 'found that the majority of pivotal trials in drug approvals involved fewer than 1,000 patients and lasted six months or less' (which is ideal for measuring benefits but inadequate to measure harms with long latency periods). Downing et al. (2017) examined the '222 novel therapeutics approved by the FDA between 2001 and 2010'. They found that by 28 February 2017, 32% (71) had a major safety event that required a black box warning, a safety communication about the drug's dangers, or withdrawal from the market. Lupkin (2017) points out that the FDA adverse events reporting system is voluntary so it undercounts the actual number of harms (para. 9). Caleb Alexander, co-director of the Johns Hopkins Center for Drug Safety and Effectiveness said:

[7] See definition in Glossary, p. xii.

> ‘All too often patients and clinicians mistakenly view FDA approval as [an] indication that a product is fully safe and effective. Nothing could be further form the truth. We learn tremendous amounts about a product only once it’s on the market and only after use among a broad population’ (in Lupkin, 2017, para. 18).

Pham-Kanter (2014) studied the voting behaviour of 1,379 FDA advisory committee members over the period of 1997–2011. She found that advisory committee ‘members who served on advisory boards solely for the sponsor were significantly more likely to vote in favour of the sponsor (OR = 4.97, p= 0.005)’ (Pham-Kanter, 2014, p. 447).

It does not appear to matter which party controls the White House, conflicts of interest at the FDA persist under both Republican and Democratic administrations. Walker (2014) in a study for the *Wall Street Journal* found that:

> In panels evaluating devices involved in cardiology, orthopedics and gynecology from 2012 through 2014 [years 4 to 6 of the Obama administration], a third of 122 members had received compensation — such as money, research grants or travel and food — from medical-device companies, an examination of databases shows.... The FDA disclosed roughly 1% of these corporate connections (para. 4).

In addition to the fees that the FDA collects from the companies that they are charged with regulating, Congress further opened the door to conflicts of interest through creating the non-profit Reagan-Udall Foundation in 2007 to support the work of the

FDA (Greenfieldboyce, 2012). While Reagan-Udall staff claimed that 'core operating expenses would be accepted from the government, individual donors, or other nonprofits' most pharmaceutical companies have set up non-profit foundations that enable them to engage in these sorts of donations. Indeed when the Reagan-Udall Foundation was struggling with funding during the early years, the Pharmaceutical Research and Manufacturers of America (PhRMA) Foundation provided a $150,000 grant (Greenfieldboyce, 2012). Furthermore there are interlocking boards of directors between the Reagan-Udall Foundation and companies the FDA is supposed to regulate. So for example, Garry Neil, is 'an executive at Johnson & Johnson who is chairman of the PhRMA Foundation's board of directors and also a member of Reagan-Udall's board' (Greenfieldboyce, 2012). While the dollar amounts flowing into the foundation at this point are still low ($4 million in 2015 according to the most recent financial statement from the RUF), the best available research on the funding effect shows that any conflicted contribution changes research outcomes.

5.4.3 National Institutes of Health

'The NIH traces its beginnings to the Laboratory of Hygiene, founded in 1887 within a Navy hospital on Staten Island in New York' (Willman, 2003). Initially, it led the federal response to cholera, diphtheria, tuberculosis, and smallpox (Willman, 2003). 'In 1938 it was renamed the National Institute of Health and moved into its present 300-acre headquarters in Bethesda, Maryland' (Willman, 2003). Today NIH is the main institution through which the U.S. federal government conducts health research (NIH, 2016b). NIH's budget in 2016 was $32.3 billion (NIH, 2016b). 'More than 80% of the NIH's funding is awarded through almost 50,000 competitive grants to more than

300,000 researchers at more than 2,500 universities, medical schools, and other research institutions in every state and around the world' (NIH, 2016b).

In 2016, $216 million from the NIH budget was earmarked for autism research (NIH, 2016a). By way of contrast, $7.8 billion in 2016 was earmarked for genetics research across all health categories (NIH, 2016a). The Director of the National Institute of Mental Health chairs the Interagency Autism Coordinating Committee (IACC) that spearheads the federal response to ASD (IACC, n.d.).

In December 2003, the *Los Angeles Times* published an investigation by David Willman into financial conflicts of interest at the NIH. He discovered,

> In November 1995, then NIH Director Harold E. Varmus wrote to all institute and center directors, rescinding 'immediately' a policy that has barred them from accepting consulting fees and payments of stock from companies. The Varmus memo also 'scuttled other restraints affecting all [NIH] employees, including a $25,000 annual limit on outside income, a prohibition on accepting company stock as payment and a limit of 500 hours a year on outside activities' (Willman, 2003, 'Temptations Abound', para. 21).

Many 'top scientists at NIH received substantial honoraria and stock options from biomedical firms that, in some cases, doubled their government salaries' (Krimsky, 2004, p. xi). Far from the disclosure and transparency that is often touted, most of these deals were kept secret. Willman found that:

> NIH officials now allow more than 94% of the agency's top-paid employees to keep their consulting income confidential.... A survey by the [*Los Angeles*] *Times* of 34 other federal agencies found that all had higher percentages of eligible employees filing reports on outside income.... The trend toward secrecy among NIH scientists goes beyond failure to report outside income. Many of them routinely sign confidentiality agreements with their corporate employers, putting their outside work under tight wraps (Willman, 2003, 'Hidden From View', para. 1–3).

A subsequent editorial by the *Los Angeles Times* stated: 'the NIH has become an arm of commerce, a place where objective science is being trampled in a stampede for market share. Its scientists brazenly collect paychecks and stock options from biomedical companies, and they do so with the blessing of their leaders. With the collusion of those leaders, they are moving swiftly to conceal the sources of their outside incomes from the public' ('Subverting U.S. Health', 2003, para. 3). Congressional hearings prompted the Department of Health and Human Services to encourage disclosure but senior officials were still allowed to collect income from outside consulting (Krimsky, 2004, p. xi).

The Foundation for the National Institutes of Health (FNIH) offers a way for corporations to give directly to NIH. In 2017, pharmaceutical giants Amgen, AstraZeneca, Bristol-Myers Squibb, Johnson & Johnson, Novartis, and Pfizer each gave more than $5 million and they have all contributed for 15 years or longer; vaccine

producers GlaxoSmithKline, Merck Sharp & Dohme, and Sanofi each gave in the $2.5 to $5 million range and have been donating every year for at least 16 years; other notable donors include alcoholic beverage giants Anheuser-Busch InBev, Carlsberg Breweries, and Heineken in the $1.5 to $2 million range (FNIH, 2017). In 2012, the National Football League gave what was supposed to be an unrestricted grant of $30 million to FNIH for brain research (Farmer, 2017). But Congressional investigators learned that behind the scenes the NFL worked to prevent funding from going to a noted brain researcher, Robert Stern, who was critical of the NFL's approach to brain injury (Farmer, 2017). Following the Congressional inquiry, the NIH allowed the contract to expire after spending $14 million of the promised $30 million (Farmer, 2017). Similar concerns were raised about the contributions of brewers to studies in connection with alcohol consumption (Rabin, 2018). The fear is that many of these grants are not in fact unrestricted and instead are just 'the nose under the tent' by which corporations come to influence scientific research and health policy. Because government has the ability to tax, it does not have to rely on such donations to fund scientific research (unlike non-profits, academia, or even corporations). The fact that FNIH chooses to permit such funding schemes, in spite of the way that they interfere with scientific objectivity, raises troubling questions about the aims and purposes of the program.

5.4.4 Environmental Protection Agency

The creation of the U.S. Environmental Protection Agency was one of the great victories of the environmental movement that began in the U.S. in the late 1950s. Congress passed the National Environmental Policy Act (NEPA) in 1969; amongst other things it established the President's Council on Environmental Quality (CEQ) and

required environmental impact statements in connection with all actions of the federal government (Eccleston, 2008). In 1970, President Nixon created the Environmental Protection Agency to consolidate the various federal environmental tasks into a single cabinet level department (EPA, 1992). The stated mission of the EPA is ‘to protect human health and the environment’ and it does that through ‘writing and enforcing regulations based on laws passed by Congress’ (EPA, 2016). If mercury, endocrine disruptors, flame retardants, and pesticides are implicated in the autism epidemic as suggested by the epidemiological evidence presented in chapter 1, then it would represent an extraordinary regulatory failure by the EPA.

In 2013, David Heath and Ronnie Greene at the Center for Public Integrity along with the PBS Newshour published an investigation into the EPA’s failure to regulate hexavalent chromium — a toxic chemical that is in the drinking water of an estimated 70 million Americans (and brought to the public’s attention through the film *Erin Brockovich*). Heath and Greene (2013) argue that EPA scientists believe that there is clear evidence that hexavalent chromium is carcinogenic and were ready to announce their findings in 2011; but industry has managed to delay the report ever since (which also delays stricter drinking water standards that would be triggered by completing its risk assessment). Three of the five scientific advisory panel members who voted to delay the report had worked on behalf of the chromium industry in the court cases connected with the contamination in Hinkley, California (Heath & Greene, 2013, para. 11). A fourth scientist also served as a consultant to the American Chemistry Council in connection with Hinkley chromium studies (Heath & Greene, 2013, para. 11).

COI on EPA advisory panels are extensive and troubling. Heath and Greene (2013) found that EPA does not even ask scientists if they have a COI:

> Instead, it turns that job over to private companies, which handle conflict-of-interest reviews in secret. All of the information the vendors collect, including financial disclosure forms is 'considered private and non-disclosable to EPA or outside entities as required by law'.... What is more, the ethics guidelines are not binding on contractors, and the EPA handbook says the agency should not override decisions on conflicts of interest ('EPA Farms Screening to Consultants', para. 3).

At the FDA, the burden of proof is on the makers of food and drugs to show that their products are safe (and as shown above, that system is riddled with COI that sometimes lead to the approval of unsafe products). But with chemicals including pesticides that are regulated by the EPA, the burden of proof is on the agency to prove that the chemical is harmful (Heath, 2013a). The Integrated Risk Information System (IRIS) is the EPA's toxic chemical assessment program (Heath & Greene, 2013). IRIS gives the veneer of regulation. But as a result of relentless industry interference that takes advantage of mechanisms for delay that are built into the assessment process, the EPA rarely completes an assessment which means there is almost no regulation of most chemicals in the U.S. (Heath & Greene, 2013). To briefly sketch the problem: 'There are more than 80,000 chemicals available for commercial use; the EPA over the past 30 years has assessed the health risks of only 570; these scientific assessments are necessary before any new regulation can be enacted' (Heath, 2015). '700 new chemicals hit the market each year'; 'a typical review takes six to eight years'; and 'it took 27

years for the agency to issue a partial assessment of dioxin' (Heath & Greene, 2013). When EPA Administrator Lisa Jackson took office in 2009 she pledged to complete 50 assessments a year. The EPA has never come close to that goal. It completed 14 toxic risk assessments in 2009, 14 in 2010, six in 2011, and just three in 2012 (Heath & Greene, 2013). Compare that with the FDA's near perfect record of completing drug reviews on time over that same period and one starts to get a more complete picture of corporate influence on the regulatory process. To put it simply: pharmaceutical companies want fast approvals and chemical companies want slow or no regulations and both industries get exactly what they want under the current system.

In toxic risk assessments, the EPA is expected to review all of the available evidence. At first that might seem reasonable but it creates all sorts of opportunities for corporations to cloud the pool of evidence through the use of 'rented white coats'. CROs are not limited to testing drugs. There are also CROs that will perform all manner of toxicity studies on behalf of chemical companies. So for example, when it looked like the EPA was about to impose further limits on the use of hexavalent chromium, the American Chemistry Council announced that it had hired a CRO called ToxStrategies to conduct a $4 million study of the health effects of hexavalent chromium on animals (Heath & Greene, 2013). This bought the manufacturers more time, and, given ToxStrategies reputation for producing results favourable to industry, it likely bought helpful data too (Heath & Greene, 2013).

In response to the Heath and Greene (2013) investigation, the EPA announced new rules to prevent COI including publicly posting the names of scientific advisory panel members prior to meetings (Heath, 2013a). The EPA noted that 'the new steps do not

change existing standards for assessing conflicts, but instead, add sunshine to the process' (Heath, 2013a).

In 2014, for the sixth year in a row, the EPA failed to complete its assessment of arsenic, thereby allowing two arsenic containing pesticides to remain on the market (Heath, 2014). In 2014, the EPA completed just one toxic risk assessment (Heath, 2015). In 2015, 'the EPA missed its own deadlines for completing risk assessments for atrazine, glyphosate, and imidacloprid', three widely used toxic agrichemicals (Burd, 2015). As mentioned in chapter 1, the increased use of glyphosate is closely correlated with the increase in autism prevalence rates. Atrazine is an endocrine disruptor and endocrine disruptors have been implicated in the autism epidemic as well (Hertz-Picciotto, 2011).

5.4.5 A different view of regulatory conflicts of interest

Davis (2014) lists five main arguments that have been developed over the years by conservative legal scholars, free market social scientists, and various scientific interests in support of allowing COI and opposed to regulating or even disclosing such conflicts.[8] First, McComas et al. [2005], Ackerley [2007], and Sullivan [2011] argue that government has difficulty finding unconflicted experts because of the 'shared pool dilemma' — academia, government, and corporations all want access to the best researchers so they are all drawing from the same shared (finite) talent pool. Next, Lurie et al. [2006] and Ackerley [2009] claim that even if experts on advisory panels do have a conflict there is no evidence that these conflicts produce changes in voting patterns. Third, Philipson and Sun [2010], Woodcock [2011], and Epstein [2012] argue that COI

[8] All of the references in the next two paragraphs come from Davis (2014).

rules might delay patients' access to (potentially lifesaving) treatments. Fourth, Herper [2012] portrays COI rules as driving up the cost of new drug development (to an average of $4 billion to as much as $11 billion per drug) which hinders economic competitiveness. Finally, Epstein [2012] and Eschenbach and Hall [2012] claim that COI rules are burdensome and that the FDA would be better served by *more* collaboration with conflicted experts rather than less.

Davis (2014) shows that those who favour stronger rules to limit COI build their case around five counterarguments (p. 1618). First, there is overwhelming evidence that COI change voting patterns in ways that ultimately harm the public [Mansell, 2006; Biddle, 2007; Lenzer & Epstein, 2012; Zuckerman, 2013]. Second, COI rules can work in industry's favour if they prevent a competitor from using its position on an advisory committee to harm the interests of a rival firm [Silverman, 2007; Begley, 2012]. Third, industry's estimates of new drug development costs are vastly overstated (closer to $55 million per drug) [Light & Warburton, 2011]; pharmaceutical companies spend 19 times more money on marketing than they do on basic research (Light & Lexchin, 2012). Fourth, it is not entirely clear that the shared pool dilemma exists when, depending on the medical subfield, 30% to 50% of the academic researchers do not have a COI [Lenzer & Brownlee, 2008; Zinner et al., 2009; Mendelson et al., 2011]. Finally, rushing drugs to market that have not been adequately tested poses both financial and health risk to patients their families (Davis, 2014, p. 1618).

5.4.6 Capture of Elected Officials

The capture of regulatory agencies is made possible by the capture of elected officials. The pharmaceutical/health products industry spent over $4 billion between 1998 and 2018 to lobby elected officials and candidates, more than any other industry (Center for Responsive Politics, 2018, 'Pharmaceuticals/Health Products'). The number of pharmaceutical company lobbyists increased from 729 in 1998 to 1,803 in 2008, before declining somewhat to 1,440 in 2018 (CRP, 2018, 'Pharmaceuticals/Health Products'). In 2018, 919 (63.8%) of the lobbyists employed by the pharmaceutical industry had previously 'worked in Congress or another branch of the federal government' (CRP, 2018, 'Pharmaceuticals/Health Products'). The corporate conquest of the courts in the U.S. is also extensive, particularly in connection with toxic tort cases (Mirowski, 2011; Cranor, 2016). There is fairly good evidence that the pharmaceutical industry has captured traditional media as well. In non-election years, television news in the U.S. derives an estimated 70% of its revenue from advertisements for pharmaceutical products (Kennedy, 2014).

5.5.0 Conflicts of interest amongst medical school students, doctors, and professional medical associations

Conflicts of interest also shape the practices of medical schools (5.5.1), doctors (5.5.2), and professional medical associations (5.5.3) in ways that lead to bias (5.5.4) although there are some doctors who contest this claim (5.5.5).

5.5.1 Capture of Medical School Students

Capture of the medical profession begins while students are still in medical school. Sierles et al. (2005) surveyed 1,143 third-year students at eight U.S. medical schools. 'Mean exposure for each student was 1 gift or sponsored activity per week. Of respondents, 762/818 (93.2%) were asked or required by a physician to attend at least 1 sponsored lunch' (Sierles et al., 2005, p. 1034). Third-year medical students had faith in their ability to resist bias, but less faith in their colleagues. 'Regarding attitudes, 556/808 (68.8%) believed gifts would not influence their practices and 464/804 (57.7%) believed gifts would not affect colleagues' practices' (Sierles et al., 2005, p. 1034). Perhaps most interesting, third-year medical students saw these conflicts of interest as their due. 'Of the students [who responded to this particular question], 553/604 (80.3%) believed that they were entitled to gifts' (p. 1034).

Austad, Avorn, and Kesselheim (2011) conducted a systematic review of 32 studies on 'medical students' exposure to the drug industry'. They found that 'up to 90% of surveyed students in their clinical years had received educational materials such as textbooks or journal reprints from industry' (Austad et al., 2011, p. 3). Medical students' exposure to the drug industry was highest in the U.S. where two studies showed that '100% of students had at least one interaction with industry' (Austad et al., 2011, p. 3). 'Contact with the pharmaceutical industry increased over the course of medical school' (Austad et al., 2011, p. 3). 'Almost two-thirds of students reported that they were immune to bias' but once again these same respondents were significantly less likely to believe the same about their medical school colleagues or doctors (Austad et al., 2011, p. 3). 'Students who interacted with PSRs [pharmaceutical sales representatives] were

more likely than those who did not meet with PSRs to report positive perceptions of industry marketing (OR = 2.974) and were less likely to perceive this marketing as negative (OR= 0.408)' (Austad et al., 2011, p. 3). Sierles et al. (2015) conducted a follow up study and discovered that exposures and attitudes had shifted, 'students were significantly less frequently exposed to interactions (1.6/month versus 4.1/month), less likely to feel entitled to gifts (41.8% versus 80.3%), and more apt to feel gifts could influence them (44.3% versus 31.2%)' (p. 1137).

5.5.2 Capture of doctors

While COI in universities, science and medical journals, and regulatory agencies are extraordinary, they pale in comparison to the financial conflicts of interest involving doctors.

There is an extensive social science literature on gift giving, reciprocity, and influence going back five decades.

> Mauss [1967], argues that gifts create strong dispositions or obligations to reciprocate, especially if they involve extended relationships and more than mere economic transfers. Mather [2005] shows that physicians are subject to these obligations, and that through gift-giving pharmaceutical companies become accepted parts of physicians' social landscape; and gifts to physicians have measurable effects, even though most physicians believe themselves immune from influence [Wazana, 2000] (Sismondo, 2008b, p. 1911).

The Pew Charitable Trusts published a study in 2013 titled, ‘Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients’. The data are extraordinary. In 2012, the pharmaceutical industry spent more than $27 billion on drug promotion; $24 billion (89%) of that total was spent on marketing to physicians while $3 billion (11%) was spent on advertising to consumers (including those ubiquitous television commercials in the U.S. that end with ‘Ask your doctor if [X drug] is right for you’); and $15 billion (62.5%) of the $24 billion spent on marketing to physicians is spent on what is called ‘detailing’ — the well-dressed pharmaceutical sales representatives who show up in doctors’ offices bearing gifts, free samples, and copies of the latest studies (Cegedim Strategic Data, [2012], in Pew, 2013, p. 1).

Campbell et al. (2007) finds that 94% of physicians have financial relationships with the pharmaceutical and medical device industries. Rockoff (2014) finds that drug companies employed 102,000 sales representatives in 2005 but that the number of sales representatives shrank to 63,000 by 2014, mostly as a result of consolidation in the healthcare field whereby more doctors now work directly for hospitals or health maintenance organisations (para. 7).

The pharmaceutical industry is heavily involved in continuing medical education. ‘In 2011, the pharmaceutical and medical device industries provided 32 percent of all funding for continuing medical education courses in the United States — $752 million out of $2.35 billion’ (Accreditation Council for Continuing Medical Education, [2011], in Pew, 2013). Many of the same medical education and communications companies (MECCs) described above that shepherd a study through all phases of publication also

deliver the continuing medical education courses required for doctors. Via MECCs, pharmaceutical companies have turned CME into lavish commercials, in which studies designed, managed, and often ghostwritten by the MECCs are presented to doctors as cutting edge objective research.

Elliott (2004) writes,

> Why is it so hard to bring about change? Partly because change is in nobody's financial interest. In the case of medical education, the funding operation is seamless. Not only does pharma fund the MECCs who organize the CME, the academics who deliver the CME, and the offices that certify the CME, it also funds the professional societies that require the CME. Specialty groups like the American Psychiatric Association and the American Academy of Family Physicians are heavily dependent on industry funds. Pharma even helps write the accreditation guidelines. Nearly half of the membership of the task force which produced the original ACCME [Accreditation Council for Continuing Medical Education] standards governing industry support of CME came from industry itself (p. 21).

The philosophy of science has long grappled with (and been unable to resolve) the fact that we are always part of the system we would like to measure so there never is a 'true', 'outside', 'objective' position from which to measure 'reality'. The capture of the medical profession by pharmaceutical companies is a capitalist variant on this problem

in that doctors are rarely outside of an ontological and epistemological reality created by pharmaceutical companies to serve their profit interests.

5.5.3 Capture of Professional Medical Associations

The capture of doctors also includes professional medical associations (PMAs) where corporate funding is pervasive. PMAs are extremely influential because they ‘inform members of new and established diagnostic treatment procedures’, ‘issue detailed practice guidelines’, and ‘define ethical norms for their members’ (Rothman et al., 2009, p. 1367).

Only a handful of professional medical associations release detailed information about their finances. ‘As non-profits, they must disclose their tax returns but not their specific sources of funding’ (Ornstein & Weber, 2011). In response to a *New York Times* investigation (O’Connor, 2015), Coca-Cola agreed to reveal all of its corporate sponsorships covering the period 2010–2015. Over that five year period, Coca-Cola gave ‘the American Academy of Family Physicians $3.6 million, the American College of Cardiology $3.2 million, the American Academy of Pediatrics nearly $3 million, the American Cancer Society $1.9 million, Brigham and Women’s Hospital $1.2 million, and the American Diabetic Association $1.1 million’ (Belluz & Oh, 2015). In all, Coca-Cola gave ‘$21.8 million to scientific research and $96.8 million to support health and well-being partnerships’ (Belluz & Oh, 2015). Many of the largest PMAs only bring in a fourth or less of their annual budget from membership dues; advertising and corporate sponsorship often make up the rest (Lexchin & Light, 2006). As the most extreme example, the Massachusetts Medical Society takes in nearly eight times more money

from advertising in the *NEJM* than they do in membership dues (Lexchin & Light, 2006). The American Academy of Pediatrics has a Friends of Children Fund that enables them to take in corporate contributions. Infant formula makers Abbott Nutrition, Mead Johnson Nutrition, and Nestlé as well as vaccine makers Merck and Sanofi are among the biggest contributors (American Academy of Pediatrics, 2018).

'Panels that write clinical guidelines — the documents that govern the diagnosis and treatment of patients' have also been found to be riddled with COI (Taylor & Giles, 2005). An investigation by *Nature* found that 35% of the authors of clinical guidelines 'declared financial links to relevant drugs companies, with around 70% of panels being affected' (Taylor & Giles, 2005). The researchers cautioned that 'this is likely an underestimate as it relies on authors' own declarations' (Taylor & Giles, 2005, p. 1070).

5.5.4 How financial conflicts of interest lead to bias and the inadequacies of disclosure as a remedy for conflicts of interest

The information in this section will focus on how COI lead to bias amongst doctors. But the same dynamics likely apply to COI in other areas of science and medicine including medical school faculty, editors of academic journals, regulators, and politicians.

In the case of clinical trials in connection with Vioxx, Seroxat, and Fen-Phen there appears to have been outright fraud on the part of doctors in hiding catastrophic side effects in order to boost sales and profits. But there are multiple mechanisms by which conflicts of interest lead to bias and often they are subtle or subconscious (Cain, Loewenstein, & Moore, 2005, p. 119).

For more than thirty years social scientists have been studying the problem of how conflicts of interest lead to bias.[9] 'Physicians typically report that they are not biased by financial arrangements with pharmaceutical companies, although a large body of research suggests that they are' (Dana & Loewenstein, 2003, p. 254). Palmisano and Edelstein [1980] found that 'medical students recognize gifts as more problematic for other professions than they are for medicine'. McKinney et al. [1990] found that 'most physicians do not perceive themselves as biased, [however] they admit that conflicts of interest might compromise *other* physicians' decisions'. Randall [1991] showed that many pharmaceutical companies ban 'their own employees from accepting even small gifts' lest it influence their behaviour. A survey of physicians by Steinman et al. [1991] found '61% reported that "promotions don't influence my practice" while only 16% believed the same about other physician's practices'. Orlowski and Wateska [1992] found that physicians who attended continuing medical education seminars sponsored by pharmaceutical companies were more likely to prescribe the sponsored drug; prior to attending the event 95% of those surveyed reported that the seminars would not influence their behaviour. Spingarn et al. [1996] tracked physicians who attended grand rounds (in-house master classes at a hospital) given by a representative from a pharmaceutical company. They found that physicians who attended were more likely to recommend the sponsored drug than physicians not in attendance — even though many of the physicians who attended could not recall the name of the sponsor [Spingarn et al., 1996]. Patients too exhibit remarkably asymmetrical perceptions of bias. Gibbons et al. [1998] found that while gifts from pharmaceutical companies to doctors were generally seen as problematic, patients believed that other doctors were more likely to be

[9] The sources in this paragraph all come from Dana and Loewenstein, (2003), p. 254.

influenced than their own doctor. In every case listed above, perceptions of bias were self-serving and were contrary to the scientific evidence on how bias works.

In response to high profile scandals and numerous studies that show how conflicts of interest lead to (often subconscious) bias, institutions tend to respond by implementing policies to limit the size of gifts and/or require disclosure. But there is no evidence that either of these strategies is effective in reducing bias (Dana & Loewenstein, 2003). McKinney et al. [1990] and Steinman et al. [2001] show that physicians think that accepting small gifts is more ethical than accepting large gifts. But Dana and Loewenstein (2003) argue that the size of the gift does not matter. They explain that regardless of the size of the gift, 'judgments are subject to an unconscious and unintentional self-serving bias.... Furthermore, individuals are generally unaware of the bias, so they do not make efforts to correct for it or to avoid conflicts of interest in the first place' (Dana & Loewenstein, 2003, p 252).

Disclosure is not the panacea that many make it out to be and in many cases may actually increase bias. Part of the problem is that recipients of conflicted advice have no effective way of appropriately discounting information to take account of the potential for bias. Camerer, Loewenstein, and Weber (1989) and Wilson and Brekke (1994) show that people are generally unable to unlearn, ignore, or suppress information in their decision making process even when they are told it is inaccurate. Psychological experiments demonstrate that disclosure can actually increase bias via 'strategic exaggeration' and 'moral licensing' (Cain et al., 2005). If an advisor believes that disclosure may cause their evidence to be discounted, they might be tempted to exaggerate claims in order to counteract that discounting (Cain et al., 2005, p. 115).

‘Although disclosure might warn an audience to cover its ears, it also may encourage advisors to yell even louder’ (Cain et al., 2005, p. 115). In their own experiments, Cain et al. (2005) build on the work of Crawford and Sobel [1982] to show that disclosure increases bias through what they call ‘moral licensing’. Cain et al. (2005) write, ‘Insofar as disclosure is perceived to level the strategic playing field, it may leave the advisor feeling less compelled to toe the ethical line and look out for the interests of those receiving their advice’ (p. 7).

Elliott (2004) writes,

> It is time to admit that as a remedy for conflict of interest, disclosure has been an utter failure. Disclosure is an empty ritual designed to ease the consciences of academics unable to wean themselves from the industry payroll. Its only purpose is to serve as a warning signal, like a fire alarm in a burning building. Disclosure does nothing to fix the underlying problem of pharma funding, which is not secrecy but power. It does patients no good to be told that doctors, researchers, and regulators are all in pharma’s pocket if there is nothing they can do about it (p. 22).

Disclosure as a remedy for bias persists precisely because it is ineffective. If disclosure reduced bias then pharmaceutical companies would not be getting a return on their $24 billion a year investment in marketing to physicians and there would be no point in making such expenditures in the first place.

5.5.5 A different view of conflicts of interest involving doctors

Rosenbaum (2015a, 2015b, 2015c), a national correspondent for the *New England Journal of Medicine*, is not especially concerned about doctors accepting funding and gifts from industry.

In part one of a three part series regarding conflicts of interest published in the *NEJM*, Rosenbaum (2015a) explains that tragedies such as the death of Jesse Gelsinger (a healthy volunteer who died during a gene therapy trial directed by a medical school professor with a COI) and disasters such as Merck's Vioxx along with record fines of GSK, Pfizer, Eli Lilly, Abbott Laboratories, and AstraZeneca, create a certain 'affective impression' that unfairly shapes the perception of all physician-industry interactions (pp. 1861–1863).

In part two, Rosenbaum (2015b) argues that the debate about COI has overshadowed other troublesome forms of bias including non-financial biases (listed as 'fatigue, hunger, institutional norms, the diagnosis of the last patient we saw, or a memory of a patient who died'), self-serving bias ('when we stand to gain from reaching a certain conclusion, we unwittingly assimilate evidence in a way that favors that conclusion'), 'bias blind spot' ('we're far more likely to think that drug promotions influence our colleagues than that they affect our own behaviour'), and 'anti-industry bias' (pp. 1961–1962). Regarding 'anti-industry bias', Rosenbaum (2015b) favourably quotes Epstein [2010] as writing: 'The scientists who have no such connections could easily harbour strong beliefs that new and risky drugs should be kept off the market which, in turn,

could lead them to overstate the risks and understate the benefits of these new treatments' (p. 1962).

In part three, Rosenbaum (2015c) argues that the 'conflict-of-interest movement' has cast 'industry interactions as a moral issue' and that moral reasoning interferes with rational weighing of trade-offs. She continues by arguing that those who use moral reasoning are inclined to 'invent harm' (p. 2065) and that the debate over conflicts of interest is 'disgust-driven spin' and a 'vicious gotcha cycle' that has eroded the 'public trust in medicine and science' (p. 2067).

What is odd about Rosenbaum's argument is how thinly sourced it is. In part 1, she argues, 'Finally, whatever the financial stake and however effectively it's managed, the role of bias is impossible to prove...' (Rosenbaum, 2015a, p. 1862). In part two Rosenbaum asks but leaves unanswered the question, 'Does the money introduce a bias that undermines scientific integrity?' (2015b, p. 1961). As I have shown in this chapter, there are numerous studies that show how funding shapes research outcomes. Rosenbaum (2015a, 2015b, 2015c) never uses the term 'funding effect' even though there is an entire field within science and technology studies dedicated to exploring this problem. For empirical data, Rosenbaum quotes Campbell et al. (2007), Bekelman et al. [2006], and Lurie (2006). However, Ioannidis and Gøtzsche are two of the most quoted experts in the world on the question of research bias but she makes no mention of them nor does she cite the work of the Cochrane Collaboration, Sismondo, Cosgrove, Lexchin, Lundh, or Michaels. If Rosenbaum had consulted their work she would have found that they have already provided, in abundance, the data she claims is unknowable. To be clear it does not appear that Rosenbaum is making an epistemological point about

the limits of all knowledge, proof, scientific validity, etc. Rather she is claiming that studies that counter her point do not exist when in fact they do.

Rosenbaum unwittingly demonstrates that many debates about science are not scientific at all (insofar as the debate is not especially concerned with data, methods, or the results of empirical investigation). Instead they are debates about identity, power, and ideology.

5.6 High levels of iatrogenic death and injury in our current system

Conflicts of interest, fraud, and questionable scientific data result in high levels of iatrogenic injury and death. Gøtzsche (2013) writes,

> Our [prescription] drugs kill us on a horrific scale. This is unequivocal proof that we have created a system that is out of control. Good data are available, [Weingart et al., 2000; Starfield, 2002; and Lazarou et al. 1998], and what I have made out of the various studies is that around 100,000 people die each year in the United States because of the drugs they take even though they take them correctly. Another 100,000 die because of errors, such as too high a dose or use of a drug despite contraindications.... The European Commission has estimated that adverse reactions kill about 200,000 EU citizens annually (at a cost of €79 billion).... This means that in the United States and Europe: [prescription] drugs are the third leading cause of death after heart disease and cancer... In addition to all the deaths, millions of people experience serious, disabling drug injuries every year' (pp. 259–260).

It is important to underscore here that Gøtzsche is not talking about those who commit suicide by overdosing on prescription drugs and he is also not talking about illegal drug use. These are fatalities from drugs that have been approved as safe and effective by the FDA and the European Medicines Agency.

Makary and Daniel (2016) argue that 'medical error is the third most common cause of death in the U.S.' (p. 2). They conducted a meta-study of four existing studies [Health Grades, 2004; HHS, 2010; Classen et al., 2011; and Landrigan et al., 2010] on 'annual deaths from medical error in the U.S.' since 1999 (Makary & Daniel, 2016, p. 1). They 'calculated a mean rate of death from medical error of 251,454' people a year in the U.S. (Makary & Daniel, 2016, p. 2). They argue that this is likely an underestimate because death certificates in the U.S. use International Classification of Disease (ICD) codes that do not include categories for human or systems errors and because the studies cited only measure inpatient deaths (Makary & Daniel, 2016, p. 1). Presumably the half of Gøtzsche's (2013) prescription drug fatality estimate attributable to (usually hospital) error also shows up in Makary and Daniel's (2016) estimate. By either measure there is a remarkable level of preventable death and injury from our current system of capitalist medicine.

5.7 Science and medicine eschew the sorts of basic protections against corruption used by other institutions

The U.S. Securities and Exchange Commission requires financial statements from publicly traded firms to be audited by independent accounting firms (USSEC, 2016,

§1110). No wise investor would put his or her money into a firm without this protection because the assumption is that the unaudited data would be fraudulent. Even then there are problems (e.g. the savings and loan crisis, Enron, the collapse of Arthur Andersen, and the global financial collapse, to name a few recent examples). Several leading figures in science and medicine (Angell, 2008; DeAngelis & Fontanarosa, 2008) have proposed having all clinical trials conducted by independent third parties, but these reforms have gone nowhere. In judicial systems around the world it is unthinkable to allow a judge, attorney, or juror to disclose a COI and then continue with the case (Krimsky, 2005). The legal system has decided that recusal is the only way to deal with COI. Yet in science and medicine, those who stand to gain financially from a discovery or invention publish their own account of the data and often that is the only information available. Angell (2008) writes, 'It is self-evidently absurd to look to investor-owned companies for unbiased evaluations of their own products. Yet many academic investigators and their institutions pretend otherwise, and it is convenient and profitable for them to do so' (p. 1071). The evidence presented above shows that the traditional safeguards in science and medicine — peer review and publication in respected scientific and medical journals, regulatory approval, and the endorsement of doctors and their professional associations — do not offer sufficient protection against bias, fraud, and the distorting influence of profit.

5.8 Conclusion

In this chapter I have shown that financial conflicts of interest are endemic in connection with university scientific research, corporate scientific practices, science and medical journals, regulatory agencies, politicians, medical school students, doctors, and

professional medical associations. These conflicts of interest distort every step of the scientific process from study design to research outcomes to marketing, postmarket surveillance, and clinical practice. Conflicts of interest lead to study results that are not replicable and high levels of iatrogenic injury and death from products that are not safe. Even those who are aware of the extent of the problem and its ramifications, continue as if these problems can somehow be managed through disclosure of COI in spite of the absence of any evidence to support this view. Scientists and doctors portray themselves as uniquely objective. However their unique epistemic position gives them extraordinary power and this power makes them unusually vulnerable to the distorting influence of profit. Science and medicine eschew the sorts of ethical safeguards against COI that are common in other industries and institutions. This lack of safeguards is by design because COI are profitable. The public depends on science and medicine to produce use values that reduce suffering and improve quality of life yet since 1980 these professions are increasingly dedicated to exchange values that produce profits.

Part II:

The failure to regulate toxicants associated with autism

Recapping the argument thus far

In chapter 1, I presented what, at first glance, appears to be an unusual case — autism is an epidemic, there is fairly good data about factors that increase autism risk, and yet the federal government in the U.S. is not acting on that data. In chapter 2, I showed that science and medicine are shaped by their social, economic, and political contexts and argued that in any scientific debate one must study the data *and* its context (and the interrelationship between the two). In chapter 3, I showed that the histories of science and medicine do not resemble the idealised model of scientific progress presented by Kuhn (1962) and that instead, these professions can remain stuck in counterproductive paradigms for decades or longer as a result of social factors including power and profit. In chapter 4, I argued that autism resembles the dynamics of other toxic chemical disasters and long-term toxic chemical exposures such as lead, asbestos, and tobacco. In chapter 5, I showed that all facets of the scientific and medical process in the U.S. are now shaped by capitalism and that this has created a series of internal crises that have left these professions ill-equipped to respond to the autism epidemic.

Introduction to Part II

In chapters 6 through 9, I will provide evidence that the current crises in capitalist science and medicine are particularly acute in connection with those toxicants associated with increased risk of autism. Space does not permit me to review the

regulatory history of all of the toxicants listed in chapter 1. Instead, I focus on four classes of possible environmental triggers that may be contributing to the total allostatic load on children and that exemplify the need for greater regulation (plastics and flame retardants, herbicides and pesticides, selective serotonin reuptake inhibitors, and vaccines). I will examine what research has been done, what research has been left undone, and how regulators have responded (or not) to scientific evidence. The regulatory patterns in connection with all of the toxicants discussed in chapters 6 through 9 are very similar: regulatory agencies routinely allow products to enter the market without adequate safety testing; even when evidence of toxicity emerges it can take decades to get any regulatory action; and the producers of these products shape key aspects of the scientific and regulatory process to their benefit.

Chapter 6

The failure to investigate possible environmental factors in general and the failure to regulate endocrine disruptors in particular in the U.S.

6.0 Introduction

This chapter has four main sections. I begin by defining key terms in toxicology (6.1). Next, I document the failure of the U.S. Congress and U.S. public health agencies to effectively investigate toxicants associated with autism (6.2). Then, I review the failure to effectively regulate endocrine disrupting chemicals including phthalates, BPA, and flame retardants (6.3). Finally, I discuss lobbying and campaign contributions by chemical and related manufacturers (6.4).

6.1 Definition of key terms

To begin this section it is important to define a number of key terms in toxicology and epidemiology. A toxic substance is simply a poison; 'any agent capable of producing a deleterious response in a biological system' (Green, n.d.). A toxin is a 'toxic substance produced by biological systems such as plants, animals, fungi, and bacteria' (Green, n.d.). A toxicant is a 'toxic substance produced by or a by-product of anthropogenic (human) activities' (Green, n.d.). 'Toxins' is often used to refer to both toxins and toxicants (i.e. both natural and anthropogenic sources of poison) (Green, n.d.).

In the environment, some toxicants are broken down quickly. Others persist for days, months, or years and may bioaccumulate if 'they are stored in fat or attach to biological

molecules like proteins' (Green, n.d.). 'If a chemical can accumulate in an organism, then it can be passed on to the animal that eats it'; as a toxicant moves up the food chain, it can become more concentrated and more potent in a process called biomagnification [or bioamplification] (Green, n.d.). So large predatory fish (like tuna) often have higher mercury content than animals lower in the food chain.

Toxins enter the human body through ingestion, inhalation, absorption through the skin, and injection (medical treatments) (Green, n.d.). The body has various ways to defend against toxic substances: saliva, stomach acid, properties of cells, and bodily organs all work to bind up, break down, prevent absorption, detoxify, sequester, store, and/or repair damage from toxins (Green, n.d.). But sometimes toxins overwhelm the body's ability to protect and repair itself and this causes harms in many different ways (Green, n.d.). Mutagens 'raise the frequency of mutations above the spontaneous rate' (Porta, 2014). Carcinogens 'induce or otherwise participate in the causation of cancer' (Porta, 2014). Teratogens produce 'abnormalities in the embryo or fetus by disturbing maternal homeostasis or acting directly on the fetus in utero' (Porta, 2014). Immunotoxins produce an 'adverse or inappropriate change in the structure or function of the immune system' (Office of Technology Assessment, 1991, p. 3). Neurotoxins are 'any substance that is toxic to neurons or to the nervous system' (OED, n.d.). Endocrine disruptors interfere 'with the normal functioning of the endocrine system and the physiological, developmental, and (especially) the reproductive processes regulated by it' (OED, n.d.). Reproductive toxins are any substance that produces 'adverse effects on sexual function and fertility in adults as well as developmental toxicity in offspring' (United Nations, 2011, p. 173).

Making matters significantly more complicated, Manikkam et al. (2012, 2013, 2014) show that various toxicants have transgenerational effects; in animal studies, certain toxic harms to a pregnant female (labelled generation F0) not only show up in her offspring (generation F1), but in the next three generations as well (labelled F2, F3, and F4). It is hard to overstate how profound a development this is. The standard cost benefit analysis (CBA) used by the EPA and other federal agencies generally only looks at the harms to generation F0; if in fact some of these toxicants harm four generations of offspring as well it means that many CBA calculations may understate actual harms by several fold. That casts doubt on 50 years worth of cost benefit analysis in connection with toxicants.

Some of these mechanisms of action are understood better than others. For example, the term ‘endocrine disruptor’ was not coined until the 1991 Wingspread Statement (Bern et al., 1992) and does not yet appear in the *Dictionary of Epidemiology* (Porta, 2014). The chemicals discussed in this thesis usually have multiple mechanisms of action in the human body. So for example, BPA is classified as a carcinogen by Canadian and European regulators but it also may cause autism through endocrine disruption and/or other mechanisms. Historically, regulation has tended to focus on carcinogens. By accident or by design U.S. regulations have often failed to keep up with new developments in toxicology (Vogel, 2013). Regulation tends to be based on the 500 year old idea from Paracelsus that ‘the dose makes the poison’; so researchers seek to identify a no observed adverse effect level (NOAEL) and then a safety factor (NOAEL-SF) is added (anywhere from 10x to 1000x) before setting a safe reference dose (RfD) (Vogel, 2013). But with some substances, such as lead, there appears to be no safe dose (Grandjean, 2010). Furthermore, with endocrine disruptors the relationship between an

exposure and an outcome can be nonlinear (what's called 'nonmonotonic') — low, intermediate, and/or high doses may be toxic and the dose response curve may be U shaped, an inverted U, or neither (Porta, 2014). (To be clear, a U shaped dose response curve starts at a low dose, not at zero. For more on non-linear dose response curves see Vandenberg et al., 2012, cited in Porta, 2014.) Regulation based on the notion of 'the dose makes the poison' has yet to catch up with the profound implications of 'no safe dose' for some substances and 'the timing makes the poison' for other substances (Vogel, 2009 and 2013).

Cranor (2013) points out an important aspect of causation that is not widely known — causal contributions do not necessarily need to be simultaneous. For example, animal studies have shown that mice exposed to one pesticide in utero do not develop Parkinson-like symptoms, but when they are exposed to a second pesticide as adults, they exhibit signs of Parkinson's disease (Cranor, 2013, p. 112). Establishing or refuting such non-simultaneous or synergistic effects in humans is nearly impossible. Institutional Review Boards would never approve human experiments to test the theory and people are always exposed to a multitude of confounding variables. So even if such effects are happening, which seems plausible, U.S. regulatory agencies would be unable to detect them.

6.2.0 Failure of the U.S. Congress and regulatory agencies to investigate toxicants associated with autism

One might hypothesise that elected officials would have an interest in preventing toxic harms to their constituents and would be rewarded by constituents for taking action to

regulate and ban toxicants. But in order to ban toxicants, one would have to know which chemicals are toxic, and often that research is simply not done. The evidence I will present below shows that Congress and various regulatory agencies either refuse to fund the sort of research that would lead to a better understanding of the relationship between various chemicals in the environment and autism or they approve the research and find other ways to scuttle the project as it proceeds. In this section, I review the failure of the National Children's Study (6.2.1), legislative changes to block research into environmental triggers in connection with the Combating Autism Act (6.2.2), and the CDC's decision to eliminate unfavourable data at the Autism and Developmental Disabilities Monitoring Network (6.2.3).

6.2.1 The failure of the National Children's Study

As the autism rate increased dramatically in the United States in the 1990s, many leading public health figures called for comprehensive research into possible environmental causes. In 1998, the President's [Clinton] Task Force on Environmental Health and Safety Risks to Children recommended a National Children's Study (NCS) and authorising legislation was included in the Children's Health Act of 2000 (Landrigan et al., 2006). The act called for a prospective cohort study that would track 100,000 children from shortly after conception through age 21 (Landrigan et al., 2006). The act called for 'a complete assessment of the physical, chemical, biological, and psychosocial environmental influences on children's well-being'; data collection to evaluate 'environmental influences and outcomes on diverse populations of children, which may include the consideration of prenatal exposures'; and consideration of 'health disparities among children, which may include the consideration of prenatal

exposures' (H.R. 4365, 2000). In other words, Congress funded exactly the sort of comprehensive epidemiological study that would enable scientists to identify the possible environmental causes of autism.

But the study never got off the ground. The NCS spent from 2001 to 2007 consulting with a range of experts and advisory committees on questions of study design. In 2007, Congress appropriated funding for a pilot called the Vanguard Study (Kaiser, 2014). In 2009, the NIH began enrolling 5,000 mother-infant pairs in 40 academic centres across the United States (Kaiser, 2014). But the program was already troubled. The original director, Peter Scheidt was ousted in 2009 for 'misleading Congress about the true cost of the study' (Tozzi & Wayne, 2014). In 2012, the NIH dropped the 40 academic centres and turned the study subjects over to private contractors (Kaiser, 2014). In 2014, after spending fourteen years and more than $1.3 billion on the study that was still in the pilot phase, Francis Collins, director of the NIH, killed the study altogether (Collins, 2014). Following the cancellation of the project, Collins and others made statements about continuing the research in some form using less expensive methods (Collins, 2014), but such promises have not come to fruition. During the fourteen years that the NCS spent unsuccessfully trying to launch the study, the autism rate increased nearly five fold from 1 in 250 to 1 in 59 (CDC, 2018).

It would be easy to blame bureaucratic incompetence for the failure of this project. But Francis Collins, who led the NIH from 2009 to 2016 (and was reappointed as head of NIH in 2017 by President Trump), previously led the Human Genome Project — so he had experience shepherding complex multibillion dollar projects to completion.

Furthermore, this is not the first time that government has shown a reluctance to explore the possible environmental causes of autism.

6.2.2 Legislative Changes to Weaken the Combating Autism Act

The Senate version (S. 843) of the Combating Autism Act of 2006 would have required the Centers of Excellence in Environmental Health and Autism to investigate, ‘a broad array of environmental factors that may have a possible role in autism spectrum disorders’ and allocated $45 million in funding for the purpose. But Representative Joe Barton (Republican, Texas) specifically objected to the language and funding in connection with environmental research in the Senate version of the bill; as chair of the House Energy and Commerce Committee he kept it from coming to the floor for a vote (O’Keefe, 2006). Eventually a compromise was reached whereby the EPA could consider but was not required to research environmental factors associated with autism (O’Keefe, 2006). Given the history of regulatory capture at the EPA, even if the EPA was required by law to investigate environmental factors it would face extraordinary pressure to protect key industries; so to strip out the mandate weakened the bill considerably. After five years and a billion dollars in spending, the Combating Autism Act did not produce any major breakthroughs in diagnosis, causation, or treatments.

6.2.3 Eliminating unfavourable data at the Autism and Developmental Disabilities Monitoring Network

Autism advocacy groups maintain that it is extremely important to track cases of regressive autism as a separate category because it may give an indication of injury

from environmental factors, particularly vaccines. Those who have studied regressive autism note that there is a spike in cases of regressive autism at 1 year and 18 months which also coincides with the vaccine schedule (Wright, 2014, para. 6). As flawed as their system of counting is, the CDC, when it began the Autism and Developmental Disabilities Monitoring (ADDM) network counted cases of regressive autism separately and found that between 13–30% of all cases of autism were characterised by regression and another 3–10% reported normal development followed by a plateau (Weisman, 2014, 'Elimination of Regression Reporting', para. 1). Then in the reports in connection with the data from 2008 and 2010 (which are reported 4 years later, so the 2012 and 2014 reports) the 'entire section of the study reporting regression breakdown was eliminated' (Weisman, 2014, 'Elimination of Regression Reporting', para. 1). It appears that the CDC simply stopped counting the data that did not fit their narrative. The CDC's 'will to ignorance' (McGoey, 2007) in connection with autistic regression stands in stark contrast to the latest research in the field that shows that regression has previously been undercounted and 'may be more the rule than the exception' for children with ASD (Ozonoff et al., 2018, p. 788).

6.3 Introduction to endocrine disrupting chemicals

In chapter 1, I showed that a number of scholars have expressed concern and called for more research regarding possible links between endocrine disrupting chemicals and adverse neurodevelopmental outcomes including autism in children (Gilbert, 2008; Landrigan, Lambertini, & Birnbaum, 2012; Bennett et al., 2016). Many of the environmental triggers described in chapter 1, including mercury, phthalates, BPA, flame retardants, pesticides, SSRIs, and acetaminophen are endocrine disruptors.

Endocrine disruption is not their only mechanism of action (many are also neurotoxins for example) and it is not clear whether endocrine disruption is the mechanism of action associated with autism although a number of signs point in that direction. In this section, I will review the avenues of exposure to phthalates (6.3.1.0), the health effects of phthalates (6.3.1.1), and the regulatory history of phthalates (6.3.1.2). Next I will review the avenues of exposure and health impacts of BPA (6.3.2.0) and the regulatory history of BPA (6.3.2.1). Then I will introduce the topic of flame retardants (6.3.3.0) show that the tobacco industry lobbied for flammability standards for furniture to head off regulation of cigarettes (6.3.3.1), discuss the prevalence and toxicity of flame retardants (6.3.3.2), review the toxicity of PBDE and newer flame retardants (6.3.3.3), show that flame retardants are not actually very good at stopping fires (6.3.3.4), and document the limited progress in changing policies in connection with toxic flame retardants (6.3.3.5). Finally, I will discuss lobbying and campaign contributions by chemical and related manufacturing (6.4). The pattern with all of the chemicals presented in this chapter is similar: products in widespread use have not been sufficiently studied, when harms are identified they do not necessarily lead to regulatory action because companies can use a combination of science-for-hire, public relations firms, political donations, and lobbyists to prevent regulation of their products.

6.3.1.0 Avenues of exposure to phthalates

‘Phthalates are industrial chemicals that are added to plastics to impart flexibility and resilience and are often referred to as plasticizers’ (CDC, 2009, p. 258). They are in a wide range of industrial and consumer products including, ‘adhesives; automotive plastics; detergents; lubricating oils; some medical devices and pharmaceuticals; plastic

raincoats; solvents; vinyl tiles and flooring; and personal-care products, such as soap, shampoo, deodorants, lotions, fragrances, hair spray, and nail polish' (CDC, 2009, p. 258). They are also a key component in polyvinyl chloride (PVC) that is used in making 'toys, pipes, plastic bags, blood storage products, and intravenous medical tubing' (CDC, 2009, p. 258). In PVC products, as much as 70% of the total product is made up of these plasticisers (ChemicalWatch, 2010). Phthalates are especially problematic because they do not permanently bind at a molecular level with the other chemicals to which they are added so over time they leach into the things they come in contact with (such as air, food, water, medicines, skin, and blood) (CDC, 2009, p. 258). Phthalates have become ubiquitous in the environment and in the bodies of animals and people (CDC, 2009, p. 258). Numerous studies, described below, show that some phthalates are harmful to animal and human health and some studies have found an association between phthalates and autism and/or autistic like traits.

Children, women, workers in industries that use these chemicals, and those undergoing medical procedures who are exposed to phthalates in medical products are among those with the highest exposures (CDC, 2009, p. 258). Phthalates enter the body through inhalation, food, and skin contact (particularly with cosmetics and personal care products marketed to women) (CDC, 2009, p. 258). Infants are additionally exposed through dust and breast milk (CDC, 2009, p. 258). Hospital patients who need blood products or an IV have direct exposures of phthalates into their bloodstream (CDC, 2009, p. 258). Tests of workers in industrial settings exposed to airborne phthalate emissions [Liss et al., 1985; Nielsen et al., 1985; Pan et al., 2006] show that 'urinary metabolite and air phthalate concentrations are roughly correlated' (CDC, 2009, p. 258).

The National Health and Nutrition Examination Survey (NHANES) during 2003–2004 found measurable levels of phthalate metabolites in the urine of the 2,636 participants; the body burden was higher in women than in men; but because the survey only enrolled people age six years and older, the burden on infants and young children was not measured (CDC, 2016b, 'Phthalates').

6.3.1.1 Health effects of phthalates

CDC (2009) presented a mixed picture of the human health effects of phthalates. They acknowledged that some phthalates have estrogenic properties [Coldham et al., 1997; Harris et al., 1997; Jobling et al., 1995] but then noted four studies showing that '*in vivo* studies did not support phthalates having estrogenic effects [Milligan et al., 1998; Okubo et al., 2003; Parks et al., 2000; Zacharewski et al., 1998]' (CDC, 2009, p. 259). The CDC acknowledged phthalates' reproductive toxicity in animals [citing Jarfelt et al., 2005; Lovekamp-Swan and Davis, 2003; McKee et al., 2004; and NTP-CERHR 2000*a*, 2000*b*, 2000*c*, 2006] (CDC, 2009, p. 258). While nearly 100% of the U.S. population have metabolites of phthalates in their urine, the CDC (2009) cautioned that, 'finding a measurable amount of one or more phthalate metabolites in urine does not mean that the levels of the metabolites or the parent phthalate cause an adverse health effect' (p. 259). As I showed in chapter 1, a number of studies that have come out since then have shown harms. Engel et al. (2010); Testa et al. (2012); Stein et al. (2013); Degroote et al. (2014); Ejaredar et al. (2015); and Kardas et al. (2016) showed an association between phthalates and autism or traits associated with autism. Other studies that explored a possible association between phthalates and autism were mixed (Miodovnik et al., 2011; Boas, Feldt-Rasmussen, & Main, 2012) or inconclusive (Philippat et al., 2015).

6.3.1.2 Regulation of phthalates

The European Commission (1999) banned six phthalates (BBP, DBP, DEHP, DIDP, DINP, and DNOP) from toys and children's products that are 'intended to be placed in the mouth'. This followed earlier moves by Denmark, Austria, Greece, Finland, Sweden, Italy, France, and Germany to restrict some or all of these phthalates from children's products (European Commission, 1999).

The European Parliament (2006) passed Regulation 1907 concerning the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) and establishing a European Chemicals Agency in Helsinki. Unlike the EPA where the burden of proof is on the agency, REACH operates under a precautionary principle of 'no data, no market' that puts the burden of proof on the company to demonstrate that its product is safe (European Commission, 2016, para. 1). The European Chemicals Agency (ECHA) administers the REACH regulations on behalf of the European Union. The ECHA reviewed the safety data on these six phthalates and recommended that 'existing restrictions should be maintained' (European Commission, 2014).

In 2008, Congress passed the Consumer Product Safety Improvement Act (Westervelt, 2015, para. 4). The legislation banned three phthalates (BBP, DBP, and DEHP) in children's products, imposed an interim ban on three other phthalates (DIDP, DINP, and DNOP) in children's toys and child care articles, and asked the U.S. Consumer Product Safety Commission (CPSC) to review the safety of phthalates (CPSC, 2014, p. 3). When the CPSC came back with its report in 2014, it recommended keeping the

permanent ban on BBP, DBP, and DEHP in children's products; adding DINP to the permanent ban but allowing DIDP and DNOP back on the market; and took no action against other phthalates or phthalate alternatives other than to recommend more study (CPSC, 2014, pp. 7–9). The report also contained a curious disclosure: 'Overall, food, beverages, and drugs via direct ingestion, *and not children's toys and their personal care products*, constituted the highest phthalate exposures to all subpopulations' (emphasis in original, CPSC, 2014 p. 3). Food, beverages, and drugs are under the jurisdiction of the FDA, so the CPSC simply suggested that the 'U.S. agencies responsible for dealing with [phthalate] exposures from food and other products conduct the necessary risk assessments with a view to supporting risk management steps' (CPSC, 2014, p. 7). So on the one hand, Congress could claim that they took decisive action toward protecting children from these toxic harms, while on the other hand, the primary avenues of exposure (and their producers) were left undisturbed.

Neither the U.S. Congress nor the European Parliament (nor the various regulatory agencies in both regions) have recommended banning phthalates as a class, preferring instead to ban or restrict individual low molecular weight phthalates while generally leaving high molecular weight phthalates on the market. But the problem remains that phthalates do not permanently bond to the chemicals they are mixed with (ATSDR, 2008). So while high molecular weight phthalates may be less toxic, they still leach out of the product into the environment, food, and people's bodies. The Lowell Center for Sustainable Production (2011) provides an overview of available alternatives to phthalates; yet many of them are not well studied and/or involve different health and environmental trade offs.

6.3.2.0 Avenues of exposures and health impacts of BPA

Bisphenol A (BPA) is a chemical compound used in the manufacture of polycarbonate plastics, epoxy resins (used in canned food liners amongst other uses), and polyvinyl chloride (Stein, Schluter, Steer, Guo, & Ming, 2015, p. 272). Polycarbonate plastics account for 70% of global demand, followed by epoxy resins (Burridge, 2011). BPA is also found in thermal paper used in receipts (Björnsdotter, de Boer, & Ballesteros-Gómez, 2017) and halogenated BPA is used as a flame retardant (Vandenberg, Maffini, Sonnenchein, Rubin, & Soto, 2009, p. 78). Six billion pounds of BPA are produced globally a year with demand increasing at 5% per annum (Burridge, 2011).

The estrogenic properties of BPA have been known since the 1930s (Vogel, 2009, p. 559). In 1993, it was discovered that BPA is an endocrine disruptor (Vogel, 2009, p. 561). Cranor (2013) writes that, 'some substances, such as DES [discussed below] or bisphenol A, can alter the expression of the genetic code without altering the genetic sequence itself' (p. 114).

Human exposure can come from contact with skin, ingestion, and/or inhalation (Stein et al., 2015). BPA is in the bodies of most Americans:

> More than 90% of the U.S. population has detectable levels of urinary BPA [Calafat et al. 2008]. BPA has also been detected in the urine and serum of pregnant women [Padmanabhan et al. 2008; Schonfelder et al. 2002; Wolff et al. 2008; Ye et al. 2008] and serum, plasma, and placenta of newborn infants [Lee et al. 2008; Schonfelder et al. 2002] (Braun et al., 2009, p. 1945).

Endocrine disrupting chemicals such as BPA ‘may pose the greatest risk during prenatal and early childhood development’ and may also act as reproductive toxins that impair fertility (National Institute of Environmental Health Sciences, ‘Endocrine Disruptors’, 2018). Braun et al. (2009) found an association between prenatal BPA exposure and early childhood aggressive behaviour. Stein et al. (2015) in a study of 46 children on the autism spectrum compared against 52 neurotypical controls found a statistically significant association between BPA and autism (p. 272). In this subsection I will review the history of BPA and the failed attempts to regulate BPA in spite of a growing body of evidence showing cause for concern.

6.3.2.1 Regulatory history of BPA

A. P. Dianin first synthesised BPA in 1891 (Vandenberg et al., 2009, p. 77). British biochemist Edward Charles Dodds discovered in the 1930s that BPA has estrogenic properties which at the time were seen as desirable as a potential medical treatment for a range of disorders (Vogel, 2009, p. 559). Dodd’s research team later discovered an even more potent synthetic estrogenic substance, diethylstilbestrol (DES) (Vogel, 2009, p. 559). In the 1940s, DES was commercialised and prescribed to women for a wide range of conditions from morning sickness to menopause and used to increase meat production in cattle (Vogel, 2009, p. 559). In 1971, DES was ‘banned for use in pregnant women after the first epidemiological studies reported rare vaginal cancers in young women exposed to DES while in their mothers’ wombs’; DES was banned in meat production 8 years later (Vogel, 2009, p. 559).

Chemists in the U.S. and Switzerland found use for BPA in epoxy resins (Vogel, 2009, p. 559). ‘Commercial production began in the early 1950s’ and uses proliferated in both industrial and consumer products (Vogel, 2009, p. 559). In 1957, scientists working at Bayer and General Electric discovered that BPA could be used to make polycarbonate plastic which ‘is strong enough to replace steel and clear enough to replace glass’ (Vogel, 2009, p. 559). The market for epoxy resins and polycarbonate plastics grew quickly and ‘reached half a billion pounds [about 227 million kilo] by the late 1970s’ (Vogel, 2009, pp. 559–560).

In 1977, the National Cancer Institute launched what was supposed to be a 2-year animal study to try to determine whether BPA causes cancer (Vogel, 2009, p. 560). At the same time, the General Accounting Office (GAO) was conducting a study [Hart, 1979] on the quality of the private labs used for government cancer research and they found widespread problems throughout the system (Vogel, 2009, p. 560). The worst lab in the study was Litton Biotechnics with violations including, ‘maintenance problems, poor quality-control measures, and poor pathology practices’ (Vogel, 2009, p. 560). Litton Biotechnics was the private contractor conducting the BPA carcinogenesis study (Vogel, 2009, p. 560). Yet the GAO report did not lead to changes in the BPA study and in 1982, the National Toxicology Program (NTP, which had since taken over the national Carcinogenesis Bioassay Program) released the final report (Vogel, 2009, p. 560). The report found ‘no convincing evidence’ of carcinogenicity, *with the exception of leukemia* (NTP, [1982], p. ix in Vogel, 2009, p. 560). The study stated:

> That ‘bisphenol A is not carcinogenic’ should be qualified to reflect the facts that leukemia in male rats showed a significant positive trend, that

> leukemia incidence in high-dose male rats was considered not significant only on the basis of the Bonferroni criteria, that leukemia incidence was also elevated in female rats and male mice, and that the significance of interstitial-cell tumors of the testes in rats was dismissed on the basis of historical control data (NTP, [1982], p. ix in Vogel, 2009, p. 560).

When is it appropriate to use a Bonferroni adjustment? This may seem like venturing unnecessarily into the statistical weeds, but the inappropriate use of Bonferroni adjustments is a key point of contention in regulating toxic chemicals in general and in regulating toxicants in connection with autism in particular (see, e.g., Donzelli, Schivalocchi, & Battaggia, 2017). Bonferroni adjustments are used when multiple tests or comparisons are conducted for the same study and are used to reduce the possibility of Type I errors (false positives) (Nakagawa, 2004, p. 1044). They are calculated as follows: 'The formula for the error rate across the study is $1 - (1 - \alpha)^n$, where n is the number of tests performed. [α is the type 1 error rate, used to test the null hypothesis, usually set at .05.] However, the Bonferroni adjustment deflates the α applied to each.... The adjusted significance level is $1 - (1 - \alpha)^{1/n}$' and a quick way to estimate that is just α/n (Perneger, 1998, p. 1236). So if a Bonferroni correction was applied to a trial testing $n = 10$ hypotheses with an $\alpha = 0.05$, then statistical significance would not be achieved until $\alpha < 0.005$. One can instantly see the problem — in this example, a Bonferroni adjustment makes it 10 times more difficult to find a statistically significant association.

Bonferroni adjustments are widely seen as controversial (Perneger, 1998; Moran, 2003; Nakagawa, 2004). 'There is no formal consensus for when Bonferroni procedures should be used' (Nakagawa, 2004, p. 1044). Perneger (1998), states that Bonferroni

adjustments ‘are, at best, unnecessary and, at worst, deleterious to sound statistical inference’ (p. 1236). Of particular concern, Bonferroni adjustments decrease Type I errors (‘false positives’) by *increasing* Type II errors (‘false negatives’) (Perneger, p. 1236). While any errors are problematic, generally speaking, the makers of toxic chemicals have a vested interest in preventing Type I errors whereas environmental groups are more concerned with preventing Type II errors. So when Litton Biotechnics found a statistically significant association between BPA and leukemia, and then used a controversial statistical tool that increases Type II errors that rendered the result insignificant, it raised concerns. Of course there are also defenders of Bonferroni adjustments (Holm, 1979; Rice, 1989) and the courts in the U.S. have often been receptive to the use of Bonferroni adjustments precisely because they reduce Type I errors (Schachtman, 2014). Whether one sees this statistical technique as valid then depends on a host of earlier decisions one makes about theory and method.

In spite of the problems with the Litton Biotechnics lab and problems with their BPA study, when the Environmental Protection Agency (EPA) moved to set a regulatory safety standard for BPA in 1988 this was the study that they used (Vogel, 2009, p. 559). ‘Considering BPA to be a noncarcinogen, the EPA used the lowest dose from the [Litton] carcinogenesis study as the “lowest observed adverse effect level” and divided this number by an uncertainty factor of 1000 to determine a reference dose of 50 µg/kg of body weight per day’ (Vogel, 2009, p. 559). This was also the reference dose adopted by the FDA and remains the current safety standard (Vogel, 2009, p. 559).

The term ‘endocrine disruptors’ was coined in 1991 at a meeting of leading scientists put together by Theo Colborn and J.P. ‘Pete’ Myers, at the Wingspread Conference

Center in Wisconsin (Vogel, 2009, p. 561). But the idea had been developing for several decades. For example, Carson (1962) wrote at length about the impact of toxicants on the hormonal system. 'In 1996, Congress passed the Food Quality Protection Act (which amended the Federal Insecticide, Fungicide and Rodenticide Act) and an amendment to the Safe Drinking Water Act. Both amendments included language directing the EPA to establish a testing and screening program for endocrine disruptors' (Vogel, 2009, p. 561). Twenty years later this is still a work in progress (and will be discussed in more detail below).

In 2000, the EPA asked the NTP to 'review the research on the health effects of low doses of estrogenic compounds, including DES and BPA' (Vogel, 2009, p. 561). 'The NTP's [2001] *Report of the Endocrine Disruptors Low Dose Peer Review*... concluded that there was credible evidence for effects from BPA exposure at or below the safety standard' (Vogel, 2009, p. 562). The NTP report largely concurred with the findings of a leading critic of BPA safety, Frederick vom Saal at the University of Missouri and noted that his findings on low dose effects had also been replicated by another laboratory (Vogel, 2009, p. 562). The NTP also called for a new testing paradigm to assess low dose effects (Vogel, 2009, p. 562).

The American Plastics Council responded by hiring the Harvard Center for Risk Analysis (HCRA) to conduct a study of BPA safety on their behalf (Vogel, 2009, p. 562). The HCRA is housed within Harvard's T. H. Chan School of Public Health but as I showed in chapter 5 it receives funding from many of the largest producers of toxic chemicals in the world including the Dow Chemical Company which makes BPA (Vogel, 2009, p. 562). 'The HCRA report on BPA, published in 2004, used a "weight of

the evidence" assessment framework developed at a 2001 meeting sponsored by the Annapolis Center for Science and Policy' a corporate think tank 'founded by the former vice president of the National Association of Manufacturers and funded by tobacco giant Phillip Morris and the ExxonMobil Foundation' (Vogel, 2009, p. 562). The weight of the evidence framework is designed to favour the Good Laboratory Practice Guidelines that are standard in large corporate studies (Vogel, 2009, p. 562). Using this framework, the HRCA report concluded that two large multigenerational studies 'funded by the American Plastics Council and the Society of the Plastics Industry' provided the most relevant and reliable data (Vogel, 2009, p. 562).

vom Saal and Hughes (2005) responded with a literature review of their own.[10] Their study showed that 'by 2004 there were 115 published *in vivo* studies concerning low-dose effects of BPA, and 94 of these report significant effects. In 31 publications with vertebrate and invertebrate animals, significant effects occurred below' the EPA safe reference dose (vom Saal & Hughes, 2005, p. 96). Perhaps even more importantly, they demonstrated the extraordinary funding effect in BPA research. Of the 115 studies published between 1997 and 2004 more than 90% of government-funded studies reported significant effects from low doses of BPA whereas 'No industry-funded studies (0 of 11, or 0%) report significant effects at these same doses' (vom Saal & Hughes, 2005, p. 96).

In 2006, 38 experts on endocrine disruptors and BPA met for three days in Chapel Hill, North Carolina (vom Saal et al., 2007, p. 131). The meeting was sponsored by the National Institute of Environmental Health Sciences, the National Institute of Dental

[10] I am grateful to Vogel (2009) for first directing me to vom Saal and Hughes (2005) and vom Saal et al. (2007).

and Craniofacial Research, the EPA, and Commonweal, a foundation that works on environmental justice issues (vom Saal et al., 2007, p. 131). The meeting's final product, the Chapel Hill Consensus Statement, concluded with 'confidence', on the basis of 'hundreds of *in vitro* and *in vivo* studies', that BPA at concentrations found in the human body is associated with 'organizational changes in the prostate, breast, testis, mammary glands, body size, brain structure and chemistry, and behavior of laboratory animals' amongst other harms (vom Saal et al., 2007, p. 134).

Shortly thereafter the Center for the Evaluation of Risks to Human Reproduction (CERHR) at the NTP, hired Sciences International to conduct a literature review on BPA toxicology (Vogel, 2009, p. 562). Sciences International is a three person firm in Alexandria, Virginia that has done extensive work for the tobacco industry, consults with 50 of the largest chemical companies in the world, and in 2006 listed two BPA manufacturers, BASF and DowDupont, among its clients (Cone, 2007, para. 13). An investigative report by the *Los Angeles Times* found that the CERHP routinely hires Sciences International to write the first draft of reports, and that Sciences International also helps select members and set the agendas for CERHR's scientific review panels (Cone, 2007, para. 2). The final report found '*some concern* for effects on the brain, behavior and prostate gland in fetuses, infants and children at current human exposures to BPA' (NTP-CERHR, 2008, p. vii). The study also found, '*minimal concern* for effects on the mammary gland and an earlier age for puberty for females in fetuses, infants, and children at current human exposures to bis-phenol A...' and '*negligible concern*' for all other health endpoints measured (emphases in the original, NTP-CERHR, 2008, p. vii). In 2008, the federal government in Canada concluded that BPA

is toxic (Vogel, 2009, p. 559). In contrast, in 2009 the FDA and EPA both decided to take no action and announced plans to study BPA further (Vogel, 2009, p. 564).

In 2012, the FDA declared that ‘baby bottles and children’s drinking cups could no longer contain BPA’ (Tavernise, 2012). But they did so at the request of the American Chemistry Council which wanted to ‘boost consumer confidence’ (Tavernise, 2012, para. 2). It is odd that an industry association can just give orders to a federal agency like that. Furthermore, it was solely an act of political theatre. Following earlier bans on BPA in baby bottles and ‘sippy cups’ in Minnesota, Chicago, and Connecticut, manufacturers had already removed BPA from those products (Tavernise, 2012). So the FDA action in this case did not affect any products and allowed manufacturers to continue to use BPA in containers of baby formula and all other products (Tavernise, 2012, para. 12) while creating the impression that regulators were taking action to keep the public safe.

Meanwhile, the EPA has spent 20 years trying to develop an Endocrine Disruptor Screening Program pursuant to their mandate from Congress set forth in the 1996 Food Quality Protection Act and the amendment to the Safety Drinking Water Act mentioned above (Vogel, 2009, p. 561). They began in 1998 by forming a stakeholders panel of representatives from industry, government, and the scientific community, but notably left off the panel the leaders who had drafted the Wingspread statement in 1991 (Colborn, 2009, para. 4). By 2007, the EPA announced that they were finally ready to begin testing chemicals for endocrine disruption using a two tier system — an initial screen to identify the chemicals most likely to cause harm *in vitro* followed later by a second screen of these chemicals *in vivo* in animal studies if necessary (EPA, n.d.,

‘Endocrine Disruption’). Already at this point, prominent researchers in endocrine disruption were warning that the EPA had selected the wrong screening tests (Ambrose, 2007), and would likely miss the effects of known endocrine disruptors such as atrazine and chlorpyrifos because their measures were not sufficiently sensitive (Colborn, 2009, para. 6–7). As the EPA neared completion of their first round of screenings, the American Chemistry Council (2015) put out a statement applauding the design of the program. EPA (2017) released the first round of Tier 1 endocrine disruptor screenings and declared that no problems were found with any of the 52 chemicals tested.

If the manufacturers of BPA are correct, then government is endlessly studying and needlessly raising alarms over a product that improves people’s lives (from extending the shelf life of food to strengthening plastic safety equipment). If vom Saal and others are correct, then government, for more than 60 years, has allowed a toxic chemical with devastating health consequences into the bodies of nearly all Americans, with particular consequences for infants and children that may include autism.

Vogel (2013) argues that the battle over whether to ban BPA is asking the wrong question. If BPA is banned, another chemical will take its place and the decades-long regulatory fight will start all over again. Vogel (2013) argues that the more important fight is over the testing standards that will be used for measuring endocrine disruption. I will return to some of these themes in the next chapter.

6.3.3.0 Introduction to flame retardants

According to Birnbaum and Staskal (2004) ‘There are more than 175 different types of flame retardants, which are generally divided into classes that include the halogenated organic (usually brominated or chlorinated), phosphorus-containing, nitrogen-containing, and inorganic flame retardants’ (p. 9). There is little toxicity data for most of these chemicals but what data does exist is troubling (Birnbaum & Staskal, 2004, p. 9). For the purposes of this subsection I will focus on the handful of the most widely used flame retardants for which some data exists (PBDE, TBB, TBPH, and TPP). In this section I will show why regulation in connection with these chemicals has been slow and largely ineffective at improving public health. Indeed, regulation by the state of California helped to create the market for flame retardants in the first place and has caused it to grow over the last 40 years.

6.3.3.1 Tobacco industry fends off regulation of cigarettes by lobbying for flammability standards in furniture

The story of how flame retardants became ubiquitous in household furniture in the U.S. begins with efforts to regulate cigarettes (Callahan & Roe, 2012b). Hundreds of people die each year from fires that result from cigarette smoking — often after falling asleep while a cigarette is still smouldering (Callahan & Roe, 2012b). Starting in the 1920s, state and federal regulators tried to get tobacco companies to design ‘fire-safe’ cigarettes that would stop burning if left unattended (Callahan & Roe, 2012b). But tobacco companies believed that this would change the consumer experience of smoking and hurt sales of cigarettes (Callahan & Roe, 2012b). Over time, tobacco

companies figured out how to harness the regulatory apparatus of the state to protect cigarettes by mandating flame resistance standards for household furniture instead.

California led the way. Slater (2012) reports that in 1975, the California Bureau of Home Furnishings:

> mandated that the foam inside upholstered furniture be able to withstand exposure to a small flame, like a candle or cigarette lighter, for 12 seconds without igniting. Because foam is highly flammable, the bureau's regulation, Technical Bulletin 117, can be met only by adding large quantities of chemical flame retardants — usually about 5 to 10 percent of the weight of the foam — at the point of manufacture. The state's size makes it impractical for furniture makers to keep separate inventories for different markets, so about 80 percent of the home furniture and most of the upholstered office furniture sold in the United States complies with California's regulation (para. 5).

As part of the Tobacco Master Settlement Agreement in 1998 between the attorneys general of 46 states and the four largest U.S. tobacco companies, 13 million internal tobacco company documents were made public (Callahan & Roe, 2012b). An investigation by the *Chicago Tribune* discovered that amongst the documents were details of the tobacco industry's decades-long effort to shape regulations around flame retardants in furniture (Callahan & Roe, 2012b). Tobacco companies used the Tobacco Institute to funnel donations to fire fighting organisations to neutralise their support for safer cigarettes and get them to support flame retardants in furniture instead (Callahan

& Roe, 2012b). Peter Sparber, a former tobacco company executive, helped create The National Association of State Fire Marshals (NASFM) which, as the name suggests, is made up of the top fire officials in every state (Callahan & Roe, 2012b). In 1992 the fire marshals lobbied for federal rules for flame retardant furniture and helped to delay rules around fire-safe cigarettes (Callahan & Roe, 2012b).

In 1999, The Tobacco Institute was closed as part of the Tobacco Settlement Agreement (Callahan & Roe, 2012b). But by then the flame retardant industry had grown so large that it could fund nationwide lobbying efforts themselves (Callahan & Roe, 2012b). Producers of flame retardants used the same strategies as the tobacco industry, hired some of the same lobbyists, and funnelled money to fire marshals just as the tobacco industry had done (Callahan & Roe, 2012b). So for example, in 2007, Sparber and NASFM lobbied for federal regulations that would have required 'hazardous materials' warning labels on any couch that did not contain flame retardants, and sought to require any furniture store that sold couches without flame retardants to be declared 'hazardous occupancies' which is a 'classification usually reserved for locations handling gasoline and other highly combustible materials' (Callahan & Roe, 2012b).

California's Technical Bulletin 117, similar requirements in other states, and lobbying efforts to protect and expand such rules have been wildly successful at increasing the market for flame retardants. According to data from the Freedonia Group, worldwide demand for flame retardants has sharply increased over the last few decades from 526 million pounds in 1983 to 3.4 billion pounds in 2009 to a projected 4.4 billion pounds in 2014 (Callahan & Roe, 2012a). Three companies control 40% of the market for flame retardants: Chemtura Corp, Albermarle Corp., and ICL Industrial Products (Callahan &

Roe, 2012a). Chemtura, Albermarle, and ICL Industrial Products all fund the Bromine Science and Environmental Forum which uses Sparber as their lobbyist (Callahan & Roe, 2012b). These three firms are also the only members of an astroturf[11] group called Citizens for Fire Safety that lobbies regulators to promote flame retardant standards for furniture (Callahan & Roe, 2012a). Citizens for Fire Safety collected $17 million between 2008 and 2010 (Callahan & Roe, 2012a).

6.3.3.2 Prevalence and toxicity of flame retardants in people's bodies

Flame retardants are in almost all furniture sold in the United States. Congleton, Sharp, and Lunder (2014) found that:

> 93 percent of couches purchased after 2005 contained significant levels of flame retardant chemicals compared to 76 percent of couches purchased prior to 2005. An analysis of baby products showed a similar pattern of flame retardant use [Stapleton 2011]. Eighty percent of samples collected from 101 baby products, including car seats, baby carriers and portable mattresses, contained fire retardants (p. 8).

The increase in the use of these chemicals, primarily in furniture, has resulted in a sharp rise in flame retardant chemicals in people's bodies, particularly women and children. Callahan and Roe (2012a) report that:

[11] See definition in Glossary, p. xii.

> Blood levels of certain widely used flame retardants doubled in adults every two to five years between 1970 and 2004. More recent studies show levels haven't declined in the U.S. even though some of the chemicals have been pulled from the market. A typical American baby is born with the highest recorded concentrations of flame retardants among infants in the world (para. 13).

As the foam breaks down over time, using a couch acts like a bellows that propels dust into the room (Slater, 2012, para. 15). People then inhale or swallow that flame-retardant laced dust in the course of their normal activities. 'Scientists believe that small children may have higher exposures to flame retardants because they spend more time on the floor, where dust contaminated with these chemicals accumulates' (Congleton et. al, 2014). Stapleton, Eagle, Sjödin, and Webster (2012) confirmed 'that the levels of PBDE flame retardants on toddlers' hands predicted levels in their blood, supporting the role of hand-to-mouth contact as an exposure pathway'. Once inside the body, 'flame retardants can pass from mother to child through the placenta and through breast milk' (Slater, 2012, para. 15).

6.3.3.3 PBDE and newer flame retardants

Polybrominated diphenyl ethers (PBDEs) are often used as flame retardants (CDC, 2009, p. 311) and there is concern about their health effects, particularly their impact on the hormonal system. Several studies show the ubiquity and toxic trespass of PBDEs into the human body. Lind et al. (2003) provide a helpful introduction to the literature:

> PBDEs in breast milk were first reported in German samples by Krüger [1988] and later Swedish milk measurements were presented [Darnerud et al., 1998; Norén and Meironyté, 1998]. In the study of banked samples by Norén and co-workers, a strong increase in PBDE levels was observed from the beginning of the 1970s to 1997, but samples from 1998 and later showed decreased levels [Meironyté-Guvenius, 2002]. A recent study on breast milk from the USA gives evidence for much higher levels (ca. 200 ng/g fat compared to Swedish levels of 3–4 ng/g fat) [Päpke et al., 2001], which may indicate national differences in exposure.... Comparatively high PBDE levels have also been found in the blood serum of immigrant women in the San Francisco Bay Area [Petreas et al., 2002] (p. 186).

In chapter 1, I presented evidence that showed increasing levels of PBDE in human tissues (Sjodin et al., 2004). Gilbert (2008) expresses ‘high confidence’ that PBDEs cause learning and developmental disabilities. Messer (2010) reports that multiple animal and human studies have found that PBDE interferes with the thyroid and theorises a possible link between PDBE exposure and autism. Bennett et al. (2016) list PBDEs as a ‘prime example’ of a neurodevelopmentally toxic chemical that can contribute to ASD and other disorders.

The Environmental Working Group has released four studies on PBDE levels in women’s bodies in the United States (Congleton, 2014, p. 10). EWG (2003) in a study of 20 first time mothers found that 100% had PBDEs in their breast milk; ‘the lowest level of PBDEs in the U.S. women tested, 9.5 ppb, was higher than the highest levels

measured in Sweden, 7.7 ppb [Guvenius et al., 2003]'. EWG (2005) in a study of ten newborns found that all had PBDEs in their umbilical cord blood; 32 different types of PBDEs were detected. EWG (2008) found that 'PBDE levels in American mothers were 75 times higher than those found in European studies'. EWG (2009) tested the umbilical cord blood of 10 babies born to racial/ethnic minorities between 2007 and 2008 and 'found multiple PBDEs in every single sample'. Two PBDEs (pentaBDE and octaBDE) were to be voluntarily phased out of production in the U.S. by 2004; but other PBDEs continue to make up about 25% of all flame retardant production (CDC, 2009, p. 311).

When safety problems emerge with one flame retardant, chemical companies can reformulate it by adding a new molecule and the burden of proof falls on the EPA once again to show that it is unsafe, thus starting the safety review process all over again. Firemaster 550 was introduced to market as a safer alternative to the PBDEs they were replacing (Hawthorne, 2012). Chemtura, maker of Firemaster 550, refuses to list the ingredients calling them a trade secret (Hawthorne, 2012). Independent tests confirmed that it contains TBPH, TBB, and TPP in addition to other chemicals (Tung, Ahmed, Peshdary, & Atlas, 2017). TBPH and TBB are structurally similar to the phthalate DEHP that is banned in both Europe and the U.S. (Hawthorne, 2012). In an animal study, Patisaul et al. (2013) found that Firemaster 550 is an endocrine disruptor. The Columbia Center for Children's Environmental Health studied 25 mother-child pairs and found that 95%–100% had PBDEs, TBPH, and/or TBB on their hands; 100% of homes in the study had PBDEs, TBPH, and TBB in dust samples; and children had higher concentrations on their hands than their mothers (Cowell et al., 2017, p. 32).

6.3.3.4 Existing flame retardants do not necessarily stop fires

The regulatory fight over flame retardants appears to pit two public goods against each other — the need to prevent fires versus the need to protect people from toxic chemicals (Slater, 2012, para. 31). Chemtura points to data that show that ‘deaths [in the U.S.] caused by furniture fires dropped from 1,400 in 1980 to 600 in 2004; a 57 percent reduction’ (Slater, 2012, para. 28). However, a number of factors changed over that 25 year time period including updated sprinkler codes for apartment buildings and a decline in smoking. The evidence suggests that flame retardants currently on the market do not work nearly as well as advertised. It turns out that the ‘materials covering the foam’, not the foam itself are the key factor in reducing fires involving furniture (Congleton et al. 2014, p. 5). Many fire fighters are involved in the effort to limit the use of flame retardants in furniture because flame retardants make smoke more toxic (Callahan & Roe, 2012b, para. 17).

Furniture makers complain that flame retardants hurt their interests because flame retardants make the foam more stiff and some customers worry about possible adverse health effects (Slater, 2012, para. 32). But the makers of flame retardants have been more successful at shaping regulations and the rules have persisted.

6.3.3.5 Progress, but...

There has been some progress in regulating flame retardant chemicals but that comes with many caveats. New York broke new ground by passing a fire-safe cigarette law in 2003; by 2012 all 50 states and the District of Columbia had passed laws requiring self-

extinguishing cigarettes (National Fire Protection Association, 2011). Passing fire-safe cigarette laws opens the door to changing flammability standards for furniture.

Chemical manufacturers spent $23.2 million between 2007 and 2011 to defeat a series of proposed bills in California that would have re-written CA Technical Bulletin 117 (Slater, 2012, para. 37). In 2013, California Governor Edmund Brown Jr. bypassed the legislature by directing 'state agencies to revise flammability standards for upholstered furniture sold in the state' (Office of Governor, 2013, para. 3). The 12 second open flame standard was replaced by a standard for smouldering fires like burning cigarettes (Office of Governor, 2013, para. 6). This enables manufacturers to only treat the fabric covers rather than the foam inside (Office of Governor, 2013, para. 6). The new regulation came into effect on January 1, 2015 (Office of Governor, 2013, para. 8). Because the market is so large in California and because California's open flame standard started the nationwide trend towards flame retardants in furniture, this new regulation may cause a ripple effect nationwide.

This was seen as an important victory for those concerned about the toxic effects of flame retardants. But it may be too soon to determine the health effects of this change. Since the pattern with many endocrine disruptors is that there can be harms even at very low doses, reducing the total quantity of the chemicals while simultaneously moving them from the inside of the furniture to the outside, may have offsetting effects. Explicit regulation of toxic substances in furniture would have set a higher health standard but such toxic reviews take so long that perhaps this was the best interim solution.

After decades of attempted reforms, the Toxic Substances Control Act of 1976 was finally updated via The Frank R. Lautenberg Chemical Safety for the 21st Century Act in 2016. The new law gives the EPA the power to order companies to conduct product safety reviews for products already on the market (Eilperin & Fears, 2016, para. 10). But at the same time, the law pre-empts more aggressive state based regulation of toxic chemicals; this is problematic because states including California, New York, and Massachusetts have been the pioneers in toxics regulations over the last forty years (Eilperin & Fears, 2016, para. 11).

6.4 Lobbying and campaign contributions by chemical and related manufacturing

Chemical and related manufacturing industries spend heavily on lobbying and campaign contributions. Producers of phthalates, BPA, and flame retardants would be a subset within this larger category. From 1999 through 2018, chemical and related manufacturers spent $887 million on lobbying (Center for Responsive Politics, 2018, ‘Chemical and related manufacturing’). In 2018, they employed 321 lobbyists of which 198 formerly worked in government or were elected officials (CRP, 2018, ‘Chemical and related manufacturing’). Companies also lobby individually. ExxonMobil is one of the largest producers of phthalates in the U.S. and it spent $254 million on lobbying from 1999 to 2018 to protect all of its business interests (lobbying in connection with phthalates would have been just a small fraction of that total) (CRP, 2018, ‘ExxonMobil’). The $19.1 million that DowDupont spent on lobbying in 2016 dwarfs the lobbying expenditures of their biggest environmental opponent, the Environmental Working Group, which spent $567,452 on lobbying in 2016 (CRP, 2016, ‘DowDupont’; CRP, 2016, ‘Environmental Working Group’). Over the last 5 election cycles (2008 –

2016) chemical industries reported $98.6 million in campaign contributions (CRP, 2018, ‘Chemical and related manufacturing’). Supreme Court campaign finance rulings and new ‘dark money’ groups that do not reveal their donors make total campaign spending impossible to track (Mayer, 2016).

6.5 Conclusion

In this chapter, I defined key terms in toxicology and showed that the ancient notion of the ‘dose makes the poison’ is not always correct; depending on the toxicant, low, intermediate, and/or high doses may be toxic and the dose response curves may be non-linear. Next, I showed that NIH Director Collins killed the National Children’s Study which was the best hope for identifying environmental triggers of autism, Congress stripped language from the Combating Autism Act of 2006 that would have required additional research into environmental triggers, and the CDC eliminated data on autistic regression from the Autism and Developmental Disabilities Monitoring Network. Then, I showed that phthalates are ubiquitous in the marketplace and in the bodies of most Americans, that phthalates are endocrine disruptors, and that the U.S. Congress banned four phthalates in children’s toys without banning phthalates as a class. The primary avenues of exposure — food, beverages, and drugs, remain understudied and unregulated. Next, I showed that BPA is ubiquitous in the marketplace and in the bodies of most Americans, that BPA is an endocrine disruptor, that the funding effect is strong in the BPA literature, and that the FDA banned BPA only in baby bottles and sippy cups and only after manufacturers had already removed BPA from those products. Finally, I presented evidence that the massive increase in the use of flame retardants in furniture was the brainchild of the tobacco industry that wanted to head off regulations that would

have required self-extinguishing cigarettes. Five to ten per cent of the weight of the foam in most furniture in the U.S. is made up of flame retardants even though their effectiveness in preventing fires is questionable. Flame retardants are now ubiquitous in the bodies of Americans and many of them are endocrine disruptors. Even when dangerous flame retardants are removed from the market they are quickly replaced with slightly modified chemical compounds whose chemical properties and health effects are mostly unknown. The E.P.A.'s efforts to set up an endocrine disruptor screening program have failed to identify any health threats because they are using inadequate detection measures that are widely criticised in the field. The U.S. Congress passed chemical safety reform in 2016 that gave the EPA greater power to regulate toxic chemicals which is an important step forward; but the legislation also pre-empts more aggressive chemical safety standards in the states which is a big step backwards. In the next chapter I will review the failure to effectively regulate herbicides and pesticides.

Chapter 7

The failure to effectively regulate herbicides and pesticides

7.0 Introduction to herbicides and pesticides

In chapter 1, I showed that the herbicide Roundup and organophosphate, organochlorine, pyrethroid, and carbamate pesticides have been associated with autism. In this chapter I will provide a general history of attempts to regulate herbicides and pesticides (7.1) and discuss the downsides of the current regulatory framework (7.2). Then I will provide specific case histories of attempts to regulate Roundup (7.3), organophosphates (7.4), organochlorine pesticides (7.5), pyrethroids (7.6), and carbamates (7.7). I conclude by discussing similarities between the different chemicals listed in this chapter and in this thesis (7.8) and lobbying and campaign contributions by pesticide makers (7.9). The pattern across all of the chemicals discussed in this chapter is inadequate regulatory oversight that is the result of the extraordinary political power of chemical companies.

7.1 General history of regulation of pesticides, herbicides, fungicides, and rodenticides

Pesticides (insecticides), herbicides, fungicides, and rodenticides are often made by the same companies and are often regulated under the same statute. The term pesticides is often used as a shorthand to refer to all of these chemicals. For the sake of simplicity, in this chapter I will focus on pesticides and herbicides. But the issues raised apply to all four classes of agricultural chemicals.

Pesticides are ‘intentionally toxic’ and used on plants intended for human consumption which creates a complicated set of scientific and regulatory issues (Wargo, 1996, p. 6). Chemical pesticides have been in widespread use since the 1850s (Wargo, 1996, p. 6). By the 1900s the most commonly used pesticides were copper acetoarsenite (called Paris Green) and lead arsenate (an arsenate is a salt or ester of arsenic acid) (Wargo, 1996, p. 67). In the absence of regulation, farmers voiced concerns about variability in pesticide quality and potency not about the toxicity of these products to human health (Wargo, 1996, p. 67). Congress passed the Insecticide Act in 1910 to require certain purity standards for pesticide formulations but the act did not include any protections for human health or the environment (Wargo, 1996, p. 67). Both the Insecticide Act and the Pure Food and Drugs Act were under the purview of the U.S. Department of Agriculture (USDA) which could set tolerance limits for the amount of pesticide residues allowed on food (Wargo, 1996, p. 67). Prior to 1933, detection methods were too primitive to measure lead residues effectively (Wargo, 1996, p. 68). From 1917 to 1942 lead arsenate and calcium arsenate were the most popular pesticides used in the U.S. (Wargo, 1996, p. 67). In 1933, a new lead-detection method became available and ‘the first lead tolerance was set at 0.025 grains per pound’ (a grain is 1/7,000th of a pound) (Wargo, 1996, p. 68).

World War II provided the opportunity for the widespread testing of a range of different pesticides to protect military personnel from pests such as mosquitos in a range of different environments (Wargo, 1996, p. 70). In 1947, Congress passed the Federal Insecticide, Rodenticide, and Fungicide Act (FIFRA). It updated the purity and labelling standards from the Insecticide Act of 1910 to require ‘warning labels for certain highly toxic pesticides... [along with] instructions for use’ (Stroshane, 1999, p. 123). Under

FIFRA pesticides had to be registered with the USDA; if a pesticide was found to be particularly harmful to human health the USDA registered it as ‘under protest’ but it was still allowed on the market (Wargo, 1996, pp. 70–71). So the regulatory philosophy was labelling as risk management rather than restrictions on pesticides based on their impact on human health (Wargo, 1996, p. 71). Wargo (1996) notes:

> This approach may have done far more to protect the entitlements of the pesticide manufacturers rather than either public health or environmental quality. It sheltered manufacturers from uncoordinated state regulations, and may simply have served to provide the public with a false sense of security that pesticide risks were being well contained by USDA. The reality was that USDA registered pesticides whenever asked (p. 71).

During the war, chlorinated hydrocarbon pesticides such as DDT proved to be highly effective at killing mosquitos and a wide range of other insects; after the war they went into widespread commercial production for use in agriculture (Wargo, 1996, p. 71). By the early 1950s, there were concerns that DDT was killing other wildlife in addition to insects (Wargo, 1996, p. 72). In 1954, Congress passed the Miller Amendment to the Federal Food Drug and Cosmetics Act (FFDCA) (Wargo, 1996, p. 75). The Miller Amendment contained two conflicting principles. On the one hand, pesticide registration was only permitted so long as manufacturers could demonstrate that residues on food posed no risk to human health (Wargo, 1996, p. 75). On the other hand, regulators were instructed to ensure an ‘adequate, wholesome, and *economical* food supply’ (emphasis added) which introduced consideration of costs and benefits into the regulatory decision (Wargo, 1996, p. 75). The Miller Amendment did not give the FDA

authority to demand safety tests from manufacturers so the burden of proof and the cost of testing were still on the government (Wargo, 1996, p. 76). Furthermore, the USDA, was still in charge of evaluating the evidence of toxicity and protecting public health was not an institutional priority (Wargo, 1996, p. 76). ‘By 1966, the USDA pesticide registration division had licensed nearly sixty thousand separate products’ yet literally only had one toxicologist on staff to evaluate ‘the sufficiency of health and safety claims’ (Wargo, 1996, p. 76). Needless to say, the evaluations were likely cursory.

Congress was also of two minds when it passed the Delaney Amendment to the FFDCA in 1958. On the one hand, pesticides registered prior to 1958 and ‘generally regarded as safe’ were grandfathered in and did not require further testing (Wargo, 1976, p. 76). On the other hand, Congressman James Delaney (Democrat from New York) inserted a provision that stated, ‘The secretary shall not approve for use in food any chemical additive found to induce cancer in man, or, after tests, found to induce cancer in animals’ (Wargo, 1996, p. 76). This would have seemed to have closed the door to a range of pesticides and food additives. The reality is that pesticide tolerances had rarely been geared toward protecting human health — instead manufacturers figured out the effective dosage to kill pests, the likely amount of residues that would end up in food based on that dose, and submitted that as the recommended tolerance which was almost always approved (Wargo, 1996, p. 107). Furthermore, the Delaney Amendment had a specific carve out for pesticides — a pesticide was only considered a food additive if its residues concentrate during processing (such as tomato paste) (Wargo, 1996, p. 110).

The pharmaceutical industry wanted to continue to sell DES (diethylstilbestrol, discussed in chapter 6) to the cattle industry even though it was discovered to be

carcinogenic in the 1950s (Wargo, 1996, p. 110). So they lobbied for the 'DES proviso' a 1962 amendment to the FFDCA that permitted carcinogenic additives so long as the carcinogen was undetectable in the final food product (Wargo, 1996, p. 110). At the time, detection methods were fairly primitive. But detection methods continued to improve over the next two decades and DES was eventually banned altogether in 1979 (Wargo, 1996, p. 110). Also, the FDA had wide latitude to estimate human exposures and calculate risk and ultimately settled on permitting residues so long as they pose 'less than significant risk' which was considerably different than the absolutist spirit of the Delaney Amendment (Wargo, 1996, p. 111).

In 1970, President Nixon bypassed Congress by creating the Environmental Protection Agency (EPA) and gave it the authority to regulate pesticides (Nownes, 1991, p. 8). The FIFRA was updated in 1972 and became the Federal Environmental Pesticides Control Act (FEPCA) (Nownes, 1991, p. 8). Ostensibly, the EPA was given the power to ban pesticides that were considered unsafe but such a determination required a special review board and manufacturers were indemnified against financial losses from such decisions; if a pesticide was banned, the EPA had to buy out the remaining stocks of the pesticide using their own budget (Nownes, 1991, p. 8). In a similar vein, the EPA was required to review the safety data on pesticides registered prior to 1972, but Congress 'did not appropriate enough money for the EPA to do so' (Nownes, 1991, p. 8).

Two court cases further restricted the application of the Delaney Amendment. In *Monsanto v. Kennedy* [1979] the court ruled that 'There is latitude inherent in the statutory scheme to avoid literal application of the statutory definition of "food additive" in those *de minimis* situations that, in the informed judgement of the Commissioner,

clearly present no public health or safety concerns' (Wargo, 1996, p. 113). And the interpretation of *de minimis* was widened to include cost benefit calculations when the D.C. Circuit Court in *Alabama Power Co. v. Costle* [1979] declared, 'unless Congress has been extraordinarily rigid, there is likely a basis for an implication of *de minimis* authority to provide exemption when the burdens of regulation yield a gain of trivial or no value' (Wargo, 1996, p. 114).

In 1988, Congress amended the pesticide registration provisions of FIFRA. To make the re-registration process faster (for the 60,000 pesticides approved under previous statutes), EPA was now to review 600 active ingredients in the space of 9 years rather than reviewing each pesticide individually (Willson, 1996). Also, the indemnity provision was modified so that the U.S. Treasury, rather than the E.P.A., would pay for any losses resulting from bans on dangerous pesticides (Nownes, 1991, p. 11).

The FIFRA and the FFDCA were amended in 1996 by the Food Quality Protection Act (FQPA) (Thayer & Houlihan, 2004, p. 282). For the first time it required the EPA to separately assess risk based on the 'unique diets and vulnerabilities of children' (Thayer & Houlihan, 2004, p. 283). But as I will show in the sections below on the failure to regulate pesticides and herbicides associated with autism, these provisions are perhaps not sufficient.

Even when pesticides are banned or restricted for use in the U.S., manufacturers can continue to make them and sell them for export markets. So for example, DDT was banned by the EPA in 1972, but in 1996, the U.S. was still exporting one ton of DDT

per day (Wargo, 1996, p. 4). These pesticides can then return to the U.S. in the form of residues on imported food (Wargo, 1996, p. 4).

Three international agreements have been developed in connection with pesticides. The Basel Convention, signed in 1989 and effective as of 1992, is an attempt to limit the movement of hazardous waste from developed to less developed countries (United Nations Environment Programme [UNEP], n.d.). The Rotterdam Convention, signed in 1998 and effective as of 2004, requires signatory countries to give prior informed consent when trading any of 41 listed toxic chemicals (mostly pesticides) with other countries (UNEP, n.d.). And the Stockholm Convention on Persistent Organic Pollutants, signed in 2001 and effective as of 2004, eliminates or severely restricts 29 chemicals that have been identified as causing long term harm to health and the environment (UNEP, n.d.). In 2012, the Secretariats of the three conventions merged under the auspices of the UNEP so that they could coordinate their mutual aims (UNEP, n.d.). The United States is not a signatory to any of these agreements.

7.2 Downsides of the current regulatory framework

Aerial and ground spraying of pesticides and herbicides is wildly inefficient: ‘about 98–99.9% of the insecticides and more than 95% of the herbicides’ never reach their intended target (Miller & Spoolman, 2012, p. 145). Instead they contaminate soil, air, water, and the food we eat (Miller & Spoolman, 2012, p. 145). Over the long run, use of herbicides can lead to the development of herbicide resistant weeds (Waldman, Mulvany, Stecker, & Rosenblatt, 2017, para. 29). For most of the past 100 years, use of pesticides also led to the development of pesticide resistant insects (Shiva, 1988; Wargo,

1996; Metcalf & Horowitz, 2014). This has been an ideal business model for the makers of these agricultural chemicals — the more pesticides and herbicides applied, the faster resistance develops, the more new pesticides and herbicides one needs (Wargo, 1996). More recently there has been a collapse (as much as an 80% decline) in the populations of both beneficial and harmful insects (Stager, 2018). The cause(s) of this collapse are not well understood but pesticides are suspected (Stager, 2018). This presents a different set of problems as the disappearance of beneficial pollinators threatens the production of hundreds of different types of fruits and vegetables (Stager, 2018).

7.3 Roundup

Glyphosate-based herbicides (including Roundup) are the most used agricultural chemicals in human history (Main, 2016, para. 1; Lerner, 2016). Developed by Monsanto chemist John E. Franz, glyphosate was patented in 1974 and marketed along with a range of proprietary additional ingredients under the brand name Roundup (Franz, Mao, & Sikorski, 1997). At first it was not widely used because it killed plants indiscriminately, eliminating both weeds and crops. But that changed in the 1990s when Monsanto invented Roundup Ready™ corn and soybeans — seeds genetically engineered to survive being sprayed with their herbicide (Waldman et al., 2017). By spraying Roundup on fields planted with Roundup Ready™ seeds, ‘The weeds die, harvests expand, and expensive, laborious tillage is no longer necessary’ (Waldman et al., 2017, para. 2). Monsanto had figured out how to re-engineer the business of farming itself by substituting genetic engineering and toxicants for labour.

Use of glyphosate-based herbicides in the U.S. increased from an estimated 6 to 8 million pounds (2.72 – 3.62 million kilo) in 1987, to 240 million pounds (108.8 million kilo) in 2014 (Myers et al., 2016, pp. 2–3). ‘Every year, farmers spray, on average, almost a pound [0.45 kilo] of glyphosate-based herbicides on every acre of cropland in the U.S. and nearly half a pound [0.23 kilo] on every acre of cropland worldwide’ (Waldman et al., 2017, para. 1). As sales of Roundup increased, Monsanto found ways to counter troublesome toxicity findings and persuade regulators to allow ever-greater Roundup residues on crops entering the food supply. Today the safe limit of glyphosate residues allowed on crops is 17 times higher than what was allowed in the 1970s (Main, 2016, para. 9).

7.3.1 Roundup adjuvants

In the debate about Roundup in the popular press many people use Roundup and glyphosate synonymously. But this is incorrect. While glyphosate is one of the main ingredients in Roundup, most glyphosate-based herbicides including Roundup contain a range of additional ingredients and adjuvants that make them more toxic than glyphosate used by itself. Recall that in section 7.1 on the history of pesticide/herbicide regulation, the EPA, in an effort to clear a backlog of 60,000 agricultural chemical re-registrations, decided to study the ‘active ingredients’ in these products individually rather than each pesticide, herbicide, fungicide, or rodenticide in its actual formulation with other ingredients. But in focusing on individual parts, the EPA may have missed synergistic effects and the toxicity of the product as a whole.

Martinez and Brown (1991) first drew attention to the fact that the surfactants used in Roundup increase the toxicity of the herbicide beyond glyphosate alone.[12] Since then many additional studies have confirmed the dangers of these additional chemical adjuvants. Marc et al. (2002) showed that Roundup inhibited the cell division cycle in sea urchin embryos but that glyphosate by itself did not have an effect (p. 326). Marc, Mulner-Lorillon, and Bellé (2004) confirmed these findings for Roundup 3Plus and three other glyphosate-based herbicides (p. 245). Benachour and Seralini (2009) evaluated the toxicity of four different Roundup formulations (Express, Extra 360, Grand Travaux, and Grand Travaux Plus) in France at dilutions below standard agricultural usage, on umbilical, embryonic, and placental cells. They found that all Roundup formulations 'cause total cell death within 24 hours'; but while glyphosate was toxic, the damage was not proportional to the amount of glyphosate but rather depended on the nature of the adjuvants (Benachour & Seralini, 2009, p. 97). The adjuvant POEA by itself changes human cell permeability and is additionally toxic in combination with glyphosate (Benachour & Seralini, 2009, p. 97). Pesticide and herbicide makers like Monsanto claim that the ingredients in a formulation are confidential business information (Lerner, 2016, 'Naming the toxins', para. 5) and the EPA does not force them to disclose the ingredients on the labels. Mesnage, Bernay, and Seralini (2013) reverse-engineered nine glyphosate-based herbicides including five types of Roundup. They successfully figured out the formulations of 6 of the 9 herbicides and then tested the various ingredients alone and in various combinations. They found that each of the additives considered inert by the EPA were more toxic than glyphosate (by 1200-fold in the case of POE-15) and the combined formulations were more toxic than glyphosate alone (Mesnage et al., 2013, p. 125). Defarge et al. (2016)

[12] The structure and sources in this paragraph all come from Lerner (2016) although I reviewed each article individually and sometimes drew out additional information from them.

showed that POEA and another common glyphosate-based herbicide adjuvant called alkyl polyglucoside are endocrine disruptors at concentrations ‘800 times lower than the [standard] agricultural dilutions’ (p. 264). They also showed that glyphosate itself is an endocrine disruptor at ‘1/3 of the [recommended] agricultural dilution’ (Defarge et al., 2016, p. 264). Reached for comment, the FDA said that they have no plans to test for these herbicide adjuvants in food; the EPA also has no plans to revisit its declaration that these chemicals are inert (Lerner, 2016).

7.3.2 Attempts to regulate Roundup

The Office of Pesticide Programs (OPP) at the EPA faces the same dilemma as the FDA — by design, much of their funding comes from the industries they are charged with regulating. ‘Pesticide makers, called registrants, pay the office [OPP] to review their compounds for registration. In 2016, they provided $47 million which represented 28% of OPP’s budget. The OPP’s studies are based, by law, on data provided by pesticide registrants themselves’ (Waldman et al., 2017, para. 31).

In the 1980s, the EPA used a system that graded the carcinogenic potential of pesticides on a scale of Group A (human carcinogen) to Group E (evidence of non-carcinogenicity) (EPA, n.d., ‘Evaluating Pesticides for Carcinogenic Potential’). In 1985, the EPA classified glyphosate as a possible human carcinogen (Group C) based on evidence of tumours in mice (International Agency for Research on Cancer [IARC], 2015, para. 7). In the study, funded by Monsanto, ‘4 of 100 mice that were fed large amounts of glyphosate developed rare kidney tumors... compared with zero of 98 mice given little or no glyphosate’ (Waldman et al., 2017, para. 32). Following the decision by the EPA,

Monsanto hired 10 scientists to reanalyse the kidney tissues from the healthy mice to look for evidence of tumours (Waldman et al., 2017, para. 32). One of these scientists reported that he found cellular changes in the kidneys of one of the mice in the control group — and this was enough to render insignificant the difference between the treatment and control group (i.e. the new *p*-value > .05) (Waldman et al., 2017, para. 33). The other nine scientists signed off on the report which was submitted to the EPA (Waldman et al., 2017, para. 33). The EPA toxicology branch went back and re-examined the kidney tissues from the mice in the control group using new cross sections and concluded that the Monsanto scientists were in error and there were no tumours (Waldman et al., 2017, para. 34). In February 1986, EPA administrators overruled their own scientists and declared that glyphosate was of 'uncertain carcinogenicity' (Waldman et al., 2017, para. 35).

Reports of Roundup's toxicity continued to accumulate. Young, Ho, Glynn, and Edwards (2015) found that Roundup is an endocrine disruptor and confirmed that Roundup is more toxic than glyphosate alone. In March of 2015, the IARC (which is part of the World Health Organization) declared glyphosate as 'probably carcinogenic to humans' (Lerner, 2016, para. 6). But in November 2015, the European Food Safety Authority (EFSA) decided that glyphosate was 'unlikely to pose a carcinogenic hazard to humans' (Lerner, 2016, para. 7). The IARC and EFSA used very different methods in their systematic reviews (Lerner, 2016, para. 7). The IARC looked at studies of glyphosate-based herbicides in their actual formulations whereas the 'EFSA report included only studies looking at the effects of glyphosate alone' (Lerner, 2016, para. 8). Furthermore, 'the IARC considered only independent studies, while the EFSA report included data from unpublished industry-submitted studies, which were cited with

redacted footnotes' (Lerner, 2016, para. 8). In 2017, the State of California listed glyphosate as 'known to the state to cause cancer' (Office of Environmental Health Hazard Assessment, 2017, para. 3).

The same issues of corporate capture of academic scientists and ghost writing of academic journal articles described in chapter 5 also apply to Monsanto's approach to promoting and defending Roundup. Monsanto e-mails turned over in discovery in connection with a lawsuit against the company in California show that Monsanto staff ghost wrote an article for Henry I. Miller, a fellow at Stanford University's Hoover Institution, that appeared in *Forbes* (Hakim, 2017, para. 3). Following revelations in the *NY Times* about the provenance of the article, *Forbes* withdrew it (Hakim, 2017, para. 3). Miller is the former director of the Office of Biotechnology at the FDA so his name on the article carried a lot of weight. Other documents turned over in discovery show that Monsanto funded astroturf groups including the Genetic Literacy Project and corporate think tanks including the American Council on Science and Health that in turn attacked the EPA and the IARC on Monsanto's behalf (Waldman et al., 2017, para. 16).

Under the FQPA of 1996, the EPA must review each pesticide registration at least once every 15 years (Waldman, 2017, para. 3). The EPA convened a Scientific Advisory Panel meeting regarding glyphosate in the final month of the Obama Administration; the panel was deeply divided over the evidence of glyphosate's toxicity with eight out of 15 panel members expressing 'significant concerns' (Waldman, 2017, para. 3). Now the decision as to whether to re-register glyphosate rests with the Trump administration which has consistently sided with chemical makers (Waldman et al. 2017, para. 4).

7.3.3 Criticism and rejoinders regarding Roundup

Monsanto's website states that 'glyphosate is about half as toxic as table salt and more than 10 times less toxic than caffeine' (Waldman et al., 2017, para. 4). In an interview with *Bloomberg Businessweek*, Scott Partridge, Monsanto VP for Strategy said, 'There's never been a more studied herbicide in the history of farming. In more than 700 studies, not one has associated cancer with the use of glyphosate. And in the more than 160 countries that have registered glyphosate for use, not a single government agency has found glyphosate is a carcinogen' (Waldman et al., 2017, para. 4).

It is interesting to note that Monsanto's talking points tend to refer to glyphosate rather than Roundup thereby trying to sidestep the issue of the toxicity of the whole product (glyphosate in combination with adjuvants and other ingredients). Furthermore, glyphosate has been found to be carcinogenic by a wide range of scientists and government agencies as described above, so it is not clear how Partridge could claim otherwise.

The more complicated issue is that if one bans glyphosate-based herbicides, under the current regulatory system they might just be replaced by even more toxic alternatives. That is the fear of Andrew Kniss at the University of Wyoming who has done extensive work on the economics of agricultural chemical use (Waldman et al., 2017). Going completely organic reduces the cost of chemicals but Kniss 'showed the yields from organic farms were roughly two-thirds of those from conventional farms for corn, wheat, soybeans, and barley, and less than half for grapes, tomatoes, bell peppers, and onions' (Waldman et al., 2017, para. 24). 'Kniss did another study that found planting

genetically modified sugar beets saved farmers $200 an acre, equal to about 15 percent of their revenue, compared with planting non-GMO seeds' (Waldman et al., 2017, para. 25). In the absence of glyphosate-based herbicides, farmers would switch to other chemicals (which might be more or less toxic) or have to hire more people to weed agricultural fields by hand (Waldman et al., 2017, para. 25). Kniss said, 'Getting rid of glyphosate would have a major impact on farmers and their bottom lines. It's not like there's a risk-free scenario here' (Waldman et al., 2017, para. 25).

But perhaps this is a false dichotomy. Although many farmers think that the only choice is between Roundup and another toxic herbicide, agroecology techniques of crop rotation and planting fields with a range of different crops can be similarly effective (Shiva, 1988). 'Researchers at Iowa State University... have shown that rotating diverse crops in three- and four-year cycles and controlling weeds with limited herbicide spraying produce similar yields and profits to conventional farming — with only 1 percent of the water toxicity' (Waldman et al. 2017, para. 29). This is driven more by necessity than idealism 'because weeds are developing resistance to glyphosate[-based herbicides] at an accelerating rate' (Waldman et al. 2017, para. 29).

7.4 Organophosphates

German scientist Willy Lange discovered the toxicity of organophosphate compounds in 1932 (Petroianu, 2010, p. 776). German scientist Gerhard Schrader worked to develop organophosphates into pesticides 'to protect food for the Nazi war effort' (Lerner, 2017, para. 11). An accidental spill of a single drop in 1936 that left Schrader and his colleagues gasping for breath revealed the extraordinary effects of this class of

chemicals on the human nervous system (Lerner, 2017, para. 11). Schrader went on to lead a secret chemical weapons lab for the Nazis that turned organophosphates into nerve gas including tabun and sarin (Lerner, 2017, para. 11). After the war, German patents and government documents (including some of Schrader's research) were turned over to U.S. companies who began to synthesise organophosphate pesticides such as parathion, malathion, and azinphosmethyl (Tucker, 2006). But they were slow to take off because the organochlorine pesticide DDT still dominated the market. Once the U.S. banned most uses of DDT in 1972, organophosphates came to dominate the pesticide market. The rise in the use of organophosphates results in higher levels of those pesticide residues in the bodies of Americans. 'In the 2003–2004 National Health and Nutrition Examination Survey (NHANES), which recruits a representative sample of the U.S. adult population, 83% of pregnant women had detectable levels of urinary dimethylthiophosphate, an OP metabolite' (Woodruff, Zota, & Schwartz, 2011). The most heavily used organophosphate pesticide is chlorpyrifos and in the next subsection I will explore its tangled regulatory history.

7.4.1 Chlorpyrifos

Chlorpyrifos is a type of organophosphate pesticide developed by Dow Chemicals in 1965 (Lerner, 2017, para. 15). Manufactured by Dow and a number of smaller companies, popular brand names include Lorsban, Dursban, and Duraplex. Even though the word chlorpyrifos appears plural it is referred to in the singular — the word is a combination of *chlor-* (chlorine) + *pyri-* (pyridine) + *-fos* (which is an alteration of *phos*phorus) ('chlorpyrifos', n.d.).

The regulatory history of chlorpyrifos is similar to that described for each of these other agricultural chemicals — scientists have been aware for decades that the chemical posed a threat to human health; the EPA has studied it extensively and taken steps towards revoking its registration; and industry pressure, including efforts to shape the scientific record, has kept it on the market. Pesticide regulation also has a long history of going 'out of the frying pan into the fire' as one toxic pesticide is replaced with newer pesticides of unknown toxicity that later prove to be as harmful or worse than their predecessors — lead arsenate was replaced by DDT (and other organochlorine pesticides) which was replaced by organophosphates including chlorpyrifos (Lerner, 2017, para. 15).

As chlorpyrifos use in U.S. agriculture skyrocketed in the 1980s, some elected officials became concerned about the potential health effects of its presence in the food supply. In 1988, Congress commissioned the National Research Council to conduct a study to examine the health effects on children and infants of pesticide residues in food (Lerner, 2017, para. 16). Chaired by Philip Landrigan at the Mount Sinai School of Medicine in New York, the report [Landrigan et al. 1993] noted that 'organophosphates cause subtle and long-lasting neurobehavioral impairments' in animals (Lerner, 2017, para. 16). Acute doses are also a problem — according to the EPA, by 1996 there were 7,000 chlorpyrifos poisonings a year (Lerner, 2017, para. 17).

Dow maintained that their product was safe and cited a wealth of internal scientific documents to make their case (Lerner, 2017, para. 20). As part of litigation against Dow, plaintiffs hired Robert Sapolsky at Stanford to conduct a systematic review of the studies produced by Dow (Lerner, 2017, para. 21). Sapolsky and a team of twelve

additional scientists concluded that all of the Dow studies were flawed and 89 percent ‘had errors that broke the basic rules of science’; all of the errors worked in favour of Dow (Lerner, 2017, para. 22). Dow settled the lawsuit and later paid a $2 million fine from the NY Attorney General’s office for false advertising for claiming their product was safe (Lerner, 2017, para. 25).

In the late 1990s, Beyond Pesticides and Californians for Pesticide Reform petitioned the EPA to ban chlorpyrifos and Dow threatened to sue the EPA if they did (Lerner, 2017, para. 27). So the EPA negotiated a political compromise — Dow agreed to voluntarily withdraw chlorpyrifos for household use and the EPA agreed to allow continued use of chlorpyrifos in agriculture (Lerner, 2017, para. 27).

As it turns out, the Columbia Center for Children’s Environmental Health was conducting a study of the health effects of residential use of chlorpyrifos that began before the withdrawal of the product and continued several years after (Lerner, 2017, para. 33). The decision to withdraw chlorpyrifos from the household market created a human experiment of a kind that would not likely pass research ethics review if it had been proposed on its own. Blood samples of women and children taken before the withdrawal of the product from the market showed 70% had chlorpyrifos in their bodies; five years after the ban, the levels were undetectable (Lerner, 2017, para. 35). Children born after the ban on average weighed half a pound (0.23 kilo) more and had higher IQ and better reflexes (Lerner, 2017, para. 36). What is more, the Columbia University study found neurological harms at levels 20 times below the EPA’s safety level (Lerner, 2017, para. 40). Research teams at UC Berkeley and Mount Sinai Hospital (NY) reached similar conclusions about the detrimental health effects of chlorpyrifos on

children (Lerner, 2017, para. 40). In response, Dow developed a series of white papers to challenge the unfavourable data and set up a website called chlorpyrifos.com to distribute the information on an on-going basis (Lerner, 2017, para. 41).

Earthjustice, on behalf of a coalition of environmental and farmworker groups, sued the EPA in 2007, 2010, 2012, and 2014 to attempt to force it to ban the use of chlorpyrifos via what is called a *writ of mandamus* — an order to a government agency to fulfil their official duties (Lerner, 2017, para. 49). Dow contracted with the science-for-hire firm Exponent which promptly produced a study [Rees, Neil, Lamb, & Juberg, 2012] claiming that chlorpyrifos is safe (Lerner, 2017, para. 56). But the tide of evidence was trending decisively against chlorpyrifos — a systematic review [Muñoz-Quezadaa et al. 2013] found that 26 out of 27 independent studies on chlorpyrifos showed evidence of harm (Lerner, 2017, para. 56). In 2014, the CHARGE Study (Shelton et al., 2014) showed an association between chlorpyrifos and autism. In December 2014, the EPA issued a draft of a risk assessment that concluded that chlorpyrifos increased 'developmental disorders, attention problems, working memory loss, and intelligence deficits in children who had been exposed to the pesticide prenatally' — but the EPA still did not act to revoke the registration (Lerner, 2017, para. 52). In August 2015, the 9th U.S. Circuit ordered the EPA to finalise its risk assessment on chlorpyrifos by October 31, 2015 (Lerner, 2017, para. 53). The EPA requested and were granted an extension (Lerner, 2017, para. 555). The EPA finalised its risk assessment on November 10, 2016 — two days after the Presidential election that brought Donald Trump to power (Lerner, 2017, para. 5). The report concluded that chlorpyrifos causes neurological problems in children and that children are exposed to chlorpyrifos residues in food at levels 14,000% above the EPA safe dose (Lerner, 2017, para. 5).

President Trump appointed Mike McKenna, a Dow lobbyist, to serve on his transition team; Myron Ebell who was a contractor for Dow oversaw staff hiring for the new EPA; and Scott Pruitt, a known foe of the EPA was appointed to lead the EPA (Lerner, 2017, para. 79). On March 29, Pruitt announced that he was overruling the findings of the risk assessment and would not ban chlorpyrifos (Biesecker & Rodriguez, 2017, para. 2). Pruitt did not provide any new evidence nor indicate what evidence had caused the agency to change course (Biesecker & Rodriquez, 2017, para. 16). Dow immediately issued a statement praising the decision (Biesecker & Rodriquez, 2017, para. 18).

7.5 Organochlorine pesticides

Organochlorine pesticides are made up of carbon, hydrogen, and chlorine (Ware & Whitacre, 2004, p. 2). They are also sometimes called ‘chlorinated hydrocarbons, chlorinated organics, chlorinated insecticides, and chlorinated synthetics’ (Ware & Whitacre, 2004, p. 2). The regulation of organochlorine pesticides would seem to be one of the great success stories of the modern regulatory state. The conventional narrative is that Rachel Carson (and a number of other authors at the time) drew the world’s attention to the dangers of the organochlorine pesticide DDT; the modern environmental movement was born; and President Kennedy’s Commission pushed to ban DDT, which was accomplished, along with the creation of the EPA, under President Nixon in the 1970s. But the story is unfinished because a number of organochlorine pesticides that are chemically similar to DDT are still on the market, DDT is still produced for the export market and is still used on crops in the developing world that are exported to the U.S. market, and DDT persists in our bodies and in the environment in spite of the ban.

Woodruff, Zota, and Schwartz (2011) found that 100% of 268 pregnant women tested in the 2003–2004 National Health and Nutritional Examination Survey (NHANES) had DDE in their bodies which is a breakdown product of DDT.

From its invention in 1940 until it was banned in the U.S. in 1973, '4 billion pounds [1.81 billion kilo] of DDT were used throughout the world' (Ware & Whitacre, 2004, p. 2). Another organochlorine pesticide, Dicofol, was temporarily banned in 1986 because it is made with DDT and high levels of DDT residues remained in the final product; eventually the product was reformulated so that it contained less than 0.1% DDT and it was allowed back on the market (Sánchez, Hernando, Vaquero, García, & Navas, 2010, p. 231). As I showed in the first chapter, Roberts et al. (2007) for the California Department of Public Health found that living within 500 meters of a field sprayed with the organochlorine pesticides dicofol and endosulfan was associated with a 600% increased incidence of autism. Endosulfan was banned in 2010 (Cone, 2010a, para. 1). Dicofol was voluntarily withdrawn from the market in 2011 (Federal Register, 2011, p. 77824). Use of another chlorinated pesticide, pentachloronitrobenzene, was restricted in 2006, temporarily halted in 2010, and allowed back on the market in limited cases in 2011 (Golf Course Superintendents Association of America, 2011).

Organochlorine pesticides cross the placenta barrier and infants can be exposed to them via breast milk; 'workers can be exposed to organochlorines in the manufacture, formulation, or application of these chemicals'; and contaminated drinking water and air are other routes of exposure (CDC, 2009, p. 75). When governments have banned or restricted organochlorine pesticides, blood levels of these chemicals in the population decline (Hagmar et al., [2006], and Kutz et al., [1991], in CDC, 2009, p. 75).

7.6 Pyrethroids

Chrysanthemum flowers contain a natural insecticide called pyrethrins. Pyrethroids are a synthetic concentrated version of pyrethrins plus additional ingredients including adjuvants (CDC, 2009, p. 156). In agricultural settings, carbamates (discussed below) are increasingly being replaced with pyrethroids (CDC, 2009, p. 67). As of 2006, about 3 million pounds (1.3 million kilos) of pyrethroids are used in agriculture each year (CDC, 2009, p. 156). After Dow withdrew chlorpyrifos for indoor use, many manufacturers switched to pyrethroids (Power & Sudakin, 2007; Williams et al., 2008) and now pyrethroid-based pesticides are 'the most widely used agents for indoor pest control' (Go, Garey, Wolf, & Pogo, 1999). In part because of their relatively short half-life (21 to 28 days in the case of Permethrin, a popular pyrethroid) (Lee, Gan, Kim, Kabashima, & Crowley, 2003, p. 1) and natural analogue, pyrethroids have been seen as a safer alternative than many other pesticides. In October 2011, the EPA completed their cumulative risk assessment for pyrethroids and concluded that they 'posed health risks below the agency's level of concern' (EPA, 2011). But there are reasons to think that the evidence of harms should be revisited and updated.

Go et al. (1999) show that certain pyrethroids (sumithrin, fenvalerate) are endocrine disruptors (p. 173). Another pyrethroid, Resmethrin, was added by the State of California to the Proposition 65 list as a probable human carcinogen and other pyrethroids as of 2016 were undergoing review (Office of Environmental Health Hazard Assessment, 2016). Horton et al. (2011) found that exposure to the adjuvant piperonyl butoxide (PBO), added to pyrethroid insecticides intended for indoor use, was

associated with a 3.9 point decline on the Mental Development Index whereas airborne pyrethroid exposure did not show an effect (p. e699). The EPA re-registered PBO in 2006 with only minor restrictions (EPA, 2006). Shelton et al. (2014) and Beyond Pesticides (n.d.) have drawn attention to the toxicity of pyrethroids but as of yet these concerns have not broken through into the mainstream media nor are there any signs of Congressional action to restrict or ban this class of chemicals.

7.7 Carbamates

Unlike other pesticides that work on the surface of the plant, aldicarb (a carbamate pesticide produced by Bayer CropScience) is drawn up through the roots of the plant and deposited into the fruit. Illegal use of aldicarb on watermelon fields in California in 1985 caused the ‘largest case of pesticide food poisoning documented in North America’ — with more than 2,000 people affected — but it was allowed to remain on the market (Cone, 2010b, para. 12).

In August 2010, Bayer CropScience announced that it was voluntarily withdrawing aldicarb (brand name Temik) from the world market; they gave themselves 5 years to stop producing it and 7 years to stop distributing it (Cone, 2010b, para. 2). The EPA had recently begun to measure the health risk for children separately from adults and found that infants were consuming eight times the EPA’s safe level and children one to five years old were ingesting aldicarb residues at three times above the safe level (Cone, 2010b, para. 6).

The announcement highlighted the EPA's general impotence to protect human health. By the time of Bayer's announcement, 'aldicarb has been under special review at the EPA for more than 25 years' (Cone, 2010b, para. 16). 'The EPA relies mostly on voluntary agreements, instead of bans, to avoid lawsuits from manufacturers' (Cone, 2010b, para. 21). The seven-year timetable to withdraw it from the market means that the EPA is knowingly allowing children to be exposed to this toxic chemical at levels exceeding their own safe thresholds for the better part of a decade. Furthermore, because the EPA is simply going along with the voluntarily withdrawal of the product rather than banning the entire class of carbamate pesticides, there is nothing to stop Bayer CropScience or other manufacturers from simply reformulating the product and bringing it back on the market and starting the decades-long review process again.

7.8 Similarities between different chemicals listed in this chapter

The question naturally arises: how could five different classes of chemicals (Roundup, organophosphates, organochlorines, pyrethroids, and carbamates) all possibly produce the same outcome — autism? It is important to remember that autism is a spectrum of related disorders so the diagnosis may reflect a variety of neurotoxic effects. Furthermore, the mode of action between these different chemicals may be similar. It is not exactly clear how DDT and other organochlorine pesticides work but they appear to interfere with 'the delicate balance of sodium and potassium ions within the axons of the neuron in a way that prevents normal transmission of nerve impulses, in both insects and mammals'; so too pyrethroids are 'axonic poisons' and 'apparently work by keeping open the sodium channels in neuronal membranes'; while organophosphates and carbamates both inhibit cholinesterase which is a key enzyme in the nervous system

(Ware & Whitacre, 2004, n.p.). Furthermore, while Shelton et al. (2014) attempted to study the marginal impact of increased exposures to particular pesticides, most Americans, including all of the study subjects, likely have all five of the agricultural chemicals described in this chapter in their bodies and the cumulative and synergistic effects are unknown.

The connection between some of the pesticides and other chemicals listed in this thesis is also closer than one might think. Many of the chemicals that appear to be linked to autism are examples of bromination, chlorination, or fluorination (P. Klein, personal communication, 29 July, 2017). Many flame retardants are brominated compounds; many pesticides, vinyl chloride, and PCBs are examples of chlorination; and the selective serotonin reuptake inhibitor fluoxetine (brand name Prozac) is a fluorinated compound. Bromine, chlorine, and fluorine are all halogens, occupying column VIIA (17) of the periodic table of elements. Because fluorine, chlorine, and bromine are chemically similar to iodine (the next element in column VIIA), they can block iodine receptors in the thyroid and interfere with the normal production of thyroid hormones (P. Klein, personal communication, 29 July, 2017; Germinario, 2018).

Clearly more research is needed. But that is precisely the point. Few large scale studies of environmental effects of pesticides are ever funded; even when such studies discover important new information it rarely is sufficient for a change in policy; and additional follow-on studies are sparse as well. The entire regulatory system in the U.S. follows a perverse logic that violates ethical norms, scientific reason, and common sense: testing these chemicals on humans would be unethical and would not pass human subjects review; but the burden of proof is on the regulatory body to show that a chemical is

unsafe; so in the absence of evidence (which usually does not exist because it would be unethical to collect) the chemical is presumed safe and allowed on the market; only when animal, *in vitro*, and human (epidemiological) studies show harms will the EPA (or FDA) consider withdrawing a chemical from the market; even then it will usually only be voluntary with no financial or criminal penalties; so, in effect, even though small scale testing would be unethical, regulatory agencies (under the rules created by Congress) engage in *widescale testing*, on *the whole society*, *for decades,* all while assuring the public that the product is safe. It seems that it was only a matter of time before such a lax regulatory environment created, in the words of Grandjean and Landrigan (2014) a 'silent pandemic of neurodevelopmental toxicity' (p. 330).

To be clear, I am not calling for more human studies. If anything existing human studies conducted by pesticide manufacturers are horrific and may well violate the Nuremberg Code and the Declaration of Helsinki concerning ethical norms for human experiments (Shrader-Frechette, 2007; see also Cushman, 1998). A Congressional investigation into 22 human experiments involving pesticides found 'significant and widespread deficiencies' (Committee on Government Reform, 2005). They write, 'in violation of ethical standards, the experiments appear to have inflicted harm on human subjects, failed to obtain informed consent, dismissed adverse outcomes, and lacked scientific validity' (Committee on Government Reform, 2005). If it would be unethical to conduct a human clinical trial it is also unethical to release the product to market; so only a precautionary approach, such as the EU's Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) regulations, is consistent with international ethical norms of science and medicine.

7.9 Lobbying and campaign contributions by pesticide makers

The main trade association representing the manufacturers of pesticides and other agricultural chemicals is called CropLife America (Sourcewatch, n.d.) and it spends about $2.5 million a year on lobbying (Center for Responsive Politics, 2016, ‘CropLife America’). Individual pesticide and herbicide producers also spend heavily on lobbying and campaign contributions. In 2016 Monsanto spent $4.6 million on lobbying (CRP, 2016, ‘Monsanto’). But in some years, it spends considerably more — in 2008, Monsanto spent $8.8 million on lobbying. In the 2016 election cycle, Monsanto made $714,917 in campaign contributions; 37 out of 48 Monsanto lobbyists in 2015–2016 have previously held government jobs; and 14 members of Congress (all Republicans) own Monsanto Co. shares (CRP, 2016, ‘Monsanto’). In September 2016, German chemical giant Bayer bought Monsanto for $66 billion (Roumeliotis & Burger, 2016). Even though Bayer now controls one quarter of all seeds and pesticides produced in the world (BBC, 2016), the Trump administration assured Bayer in January 2017 that it would not face an antitrust challenge (Philpott, 2017).

7.10 Conclusion

In this chapter I argued that pesticides present a unique set of regulatory challenges because they are intentionally toxic. Early regulation focused on ensuring chemical purity rather than protecting public health. Later attempts to strengthen regulation were hampered by indemnity provisions that penalised the EPA for taking action, legislative language and judicial rulings that added in cost benefit calculations, and EPA procedures that review individual ingredients rather than the actual products. Herbicides

lead to herbicide-resistant weeds; some pesticides lead to pesticide-resistant insects; and more recently there has been a collapse in the populations of both harmful and beneficial insects which is not well understood but may be related to pesticides. Adjuvants make glyphosate-based herbicides much more toxic than glyphosate alone. But EPA reviews that focus on the ingredients separately and that ignore many widely-used adjuvants enable glyphosate-based herbicides to escape stricter regulation (in the U.S.). Use of organophosphates including chlorpyrifos soared after DDT was banned, but evidence suggests that they produce neurological harms. Chlorpyrifos was studied extensively under President Obama but the risk assessment was not finalised until after the 2016 election and the Trump administration has refused to take action against the chemical. The banning of the organochlorine pesticides DDT and later endosulfan appear to be great victories for environmental regulation but several similar organochlorine pesticides remain on the market. Pyrethroids and carbamates for the most part have avoided regulatory action. The toxic effects are similar between these different chemicals and most of these chemical are in the bodies of most Americans so harms that are detected including autism may be the result of multiple, cumulative, or synergistic effects. Chemical makers spend heavily on lobbying and campaign contributions to keep in place a regulatory system that protects their profits and imposes few burdens or restrictions on their products. In the next chapter I will review the regulatory history of selective serotonin reuptake inhibitors.

Chapter 8

The failure to effectively regulate SSRIs

8.0 Introduction

In chapter 1, I showed that selective serotonin reuptake inhibitors (SSRIs) are designed to cross the blood brain barrier and they also cross the placental barrier at a high rate (Hendrick et al., 2003; Rampono et al. 2009). Eight major studies (Croen et al. 2011; Eriksson et al. 2012; Rai et al., 2013; Sørensen et al. 2013; Gidaya et al. 2014; Harrington et al. 2014; El Marroun et al. 2014; Boukhris et al. 2016) have found a statistically significant association between SSRI use by women during pregnancy and subsequent autism in their children. Hviid, Melbey, and Pasternak (2013) found an association between SSRI use by women before conception and autism in their offspring but did not find an association between SSRI use during pregnancy and autism. Clements et al. (2015) found a statistically significant association between SSRI use during pregnancy and autism and then created a second model (that controlled for maternal major depression in spite of the lack of evidence supporting a link between depression in the absence of chemical interventions and autism) that rendered their results insignificant; the study was also characterised by financial conflicts of interest. Of all of the possible factors associated with autism in this thesis, the connection between SSRI use during pregnancy and autism is the clearest. And yet in the U.S. doctors are still prescribing these drugs to pregnant women and there are no black box warnings in connection with autism risk and no bans on their use during pregnancy.

In this chapter I will review the scientific history of SSRIs (8.1) and show that the serotonin theory of depression that is used to sell these drugs is not supported by the evidence. Next, I will review the regulatory history of SSRIs and show that drug makers used ethically dubious methods to gain approval for these drugs in spite of a lack of evidence of their effectiveness and safety (8.2). Then I will discuss the relationship and differences between medicalisation and iatrogenic injury (8.3). Finally I will review lobbying expenditures by SSRI manufacturers (8.4) and offer some criticisms of the existing literature on SSRIs and autism (8.5).

8.1 The scientific history of SSRIs

Whitaker (2010) notes that the modern psychopharmaceutical revolution began shortly after World War II. After the breakthroughs of sulfa drugs and penicillin during the war, scientists came to expect that other breakthroughs would soon follow (Whitaker, 2010, p. 46). Researchers at Rhône-Poulenc in France tested chemical dyes called phenothiazines against malaria, Frank Berger in Britain tested a disinfectant called phenylglycerol ether against respiratory disease, and chemists at Hoffmann-La Roche in Switzerland tested a former German rocket fuel called hydrazine against tuberculosis (Whitaker, 2010, pp. 48–54). In tests on animals and (after later refinements) in people, in addition to the antibiotic properties, these chemicals also produced changes in the central nervous system (Whitaker, 2010). The research at Rhône-Poulenc led to chlorpromazine, the first major tranquilizer (for mental disturbances like schizophrenia); Berger's research led to meprobamate, the first minor tranquilliser (for treatment of anxiety in otherwise healthy people); and the research at Hoffmann-La Roche led to iproniazid, an 'energizer' that seemed to help patients with depression (Whitaker, 2010,

p. 54). These drugs proved wildly popular and favourable accounts in newspapers and magazines made these discoveries appear safer, more targeted, and more effective than they actually were (Whitaker, 2010, p. 58).

Initially these drugs were viewed as tonics, things that could change mood or behaviour, but not as medicines per se (Whitaker, 2010, p. 54). Over the course of the 1950s, however, the discourse about these drugs changed as a result of what Whitaker calls an 'unholy alliance' of the American Medical Association looking to increase the power and prestige of doctors, pharmaceutical companies looking to increase profits, and media outlets looking for stories of big breakthroughs (Whitaker, 2010, pp. 54–57). In an earlier era, the AMA was a gatekeeper, screening drugs for purity via their Council on Pharmacy and Chemistry (Whitaker, 2010, p. 55). In the 1950s, those efforts were abandoned and the AMA, pharmaceutical companies, and doctors started working together to market drugs to the public; one notable example was the television show, *The March of Medicine*, that touted the benefits of these new psychopharmaceuticals and other drugs (Whitaker, 2010, p. 57). A report for the *New York Times* coined the word 'antidepressants' in an article in 1959 (Whitaker, 2010, p. 60) and increasingly these drugs were described as medicines with the implication that they cured a known underlying condition.

Yet, there was still no evidence to explain why they worked as they did. In animal studies in the 1950s, scientists were able to isolate several chemical messengers in the brain including acetylcholine (which was discussed above in connection with pesticides), serotonin, norepinephrine, and dopamine (Whitaker, 2010, p. 61). In 1955, David Brodie at NIMH found that if he gave reserpine, an herbal drug from India used to treat

psychosis, to rabbits, that it lowered their levels of serotonin and made them lethargic and apathetic (Whitaker, 2010, p. 62). Arvid Carlsson discovered that reserpine also depleted norepinephrine and dopamine (Whitaker, 2010, p. 62). These findings fit neatly with the emerging narrative that depression, schizophrenia, and other mental health problems were caused by chemical deficiencies or imbalances in the brain that could be corrected with these new medicines (Whitaker, 2010).

But when scientists went looking for lower levels of serotonin in humans with depression, their studies produced conflicting findings.[13] 5-HIAA is the main metabolite of serotonin and it is used to estimate serotonin levels in the body. Bowers, Heninger, and Gerbode (1969), Papeschi and McClure (1971), and Bowers (1974) did not find an association between 5-HIAA levels and depression. Mendels and Frazer (1974) reviewed eight studies on the relationship between use of reserpine (which lowers serotonin) and depression in hypertension patients and did not find an association (p. 447). Mendels, Stinnett, Burns, and Frazier (1975) found that large increases in serotonin as a result of administering high doses of L-tryptophan did not relieve depression.

The (low) serotonin theory of depression was given a temporary reprieve as a result of two studies led by Åsberg. Åsberg, Thorén, Träskman, Bertilsson, and Ringberger (1976) found that 29% of 68 patients had low levels (defined as below 15 nanograms) of 5-HIAA in cerebrospinal fluid (CSF). Åsberg, Träskman, and Thorén (1976) found that patients with low 5-HIAA ‘attempted suicide significantly more often... and they used more violent means’ (p. 1193). But a closer examination of this data showed flaws

[13] I am indebted to Whitaker (2010) for pointing me to most of the sources in the literature review in this section.

in study design — what these studies reported as novel findings were in fact the regular distribution curves of 5-HIAA in the general population (Whitaker, 2010, p. 73). Maas et al. (1984) in a study for the National Institute of Mental Health found that ‘contrary to expectations, no relationships between CSF 5-HIAA and response to amitriptyline were found in the depressed patients...’ (p. 1167).

When the SSRI, Prozac, first hit the market in 1988, pharmaceutical marketing executives needed a story to explain the mechanism of action so they went with the serotonin theory of depression in spite of the fact that the scientific evidence did not and still does not support it (Lacasse & Leo, 2005). Doctors liked these drugs because they were perceived to have fewer side effects than existing tricyclic antidepressants and consumers demanded these drugs in part, due to direct-to-consumer advertising of prescription pharmaceuticals — which is only allowed in two countries worldwide (U.S. and New Zealand) and which increased following a 1985 FDA decision that lifted a moratorium on TV advertisements for these drugs (Greene & Herzberg, 2010).

This created the extraordinary situation whereby the scientific consensus is that depression is not a result of a serotonin deficiency even as this now discredited theory of the case is used to sell these pills to an eager public. Lacasse and Leo (2005) write, ‘there is not a single peer reviewed article that can be accurately cited to directly support claims of serotonin deficiency in any mental disorder, while there are many articles that present counterevidence’ (p. 1213). Even as one leading scholar after another came forward to debunk the serotonin deficiency theory of depression [Valenstein, 1998; Horgan, 1999; Glenmullen, 2000; Delgado & Moreno, 2000; Kramer, 2002, David Burns interviewed in Lacasse & Gomery, 2003; Healy, 2004, Kendler,

2005] drug makers, in direct-to-consumer advertising, continued to promote the idea (Lacasse & Leo, 2005).

As sales of Prozac and other SSRIs continued to grow, the efficacy of these drugs was called into question. Kirsch, Moore, Scoboria, and Nicholls (2002) 'examined the efficacy data submitted to the FDA for the six most widely prescribed SSRIs approved between 1987 and 1999' (p. 2). They found that about '80% of the response to medication was duplicated in placebo control groups, and the mean difference between drug and placebo was approximately 2 points on the 17-item (50-point) and 21-item (62-point) Hamilton Depression Scale' (Kirsch et al. 2002, p. 1). Overall they concluded that the 'the pharmacological effects of antidepressants are clinically negligible' (Kirsch et al., 2002). Those were conclusions based on the data submitted to the FDA — but as I showed in chapter 5, when contract research organisations generate unfavourable data, it often just disappears. So if one included the unpublished data, the differences between treatment and control (placebo) could possibly be smaller or non-existent. Indeed that is what happened when Kirsch et al. (2008) did a meta-analysis of all of the published and some of the unpublished data on four new antidepressants (GlaxoSmithKline had participated in a clinical trial registry program and so four previously unpublished studies were available) (Kirsch et al., 2008, p. 261). They found that 'the differences between drug and placebo were not clinically significant in clinical trials involving either moderately or very severely depressed patients' and were only statistically significant for 'the upper end of the very severe' patients (Kirsch et al., 2008, p. 260).

So why do psychiatrists continue to write scripts for toxic drugs that do not outperform a placebo for the vast majority of patients? Consumer demand is likely a factor.

Conflicts of interest also may play a role. The best available evidence shows that psychiatrists receive more money from pharmaceutical companies than doctors in any other specialty (Harris, Carey, & Roberts, 2007; Insel, 2010). Direct payment to physicians for prescribing a particular drug is prohibited but drug companies can sidestep these rules by hiring doctors to give lectures, serve as consultants, participate in a study, or write practice guidelines (Harris, et al., 2007).

8.2 Regulatory history of SSRIs

The regulatory history of SSRIs is a case study in how business interests in medicine manipulate scientific data and capture regulatory institutions to generate profits at the expense of public health.

Fluoxetine (brand name Prozac) was the first SSRI licensed for clinical use in the U.S. Its regulatory history was complicated by the fact that it did not work very well. Fluoxetine was developed by the Eli Lilly & Co. in the early 1970s; Wong, Horng, Bymaster, Hauser, and Molloy (1974) wrote the first peer reviewed journal article on it. In animal tests, fluoxetine did not seem to have an antidepressant effect and it increased aggression in rats (Healy, 2004, p. 30). Lilly explored using it as an antihypertensive but it did not seem to lower blood pressure (Healy, 2004, p. 31). Lilly also explored using it as a weight loss drug and, conversely, as a treatment for eating disorders (Healy, 2004, p. 31). Herbert Meltzer conducted the first tests of fluoxetine on humans and found that it had a negligible effect on depression and caused a side effect called akathisia (which is characterised by constant restlessness and need for motion) in many of his patients (Healy, 2004, p. 32). So Lilly started paring fluoxetine with benzodiazepines (minor

tranquillisers) in drugs trials — meaning that all of the effect in the treatment group may have come from the tranquillisers not fluoxetine (Healy, 2004, p. 32). Fluoxetine also failed in trials with patients hospitalised for depression and with atypical psychotic disorders (Healy, 2004, p. 32).

Lilly shook up its clinical trial program and brought in Irwin Slater to direct it (Healy, 2004, p. 32). Slater hired Louis Fabre to run a trial of fluoxetine with five mildly depressed patients; all responded favourably (Healy, 2004, p. 32). Fabre was later investigated by Upjohn in connection with a different clinical trial for pushing the ethical boundaries of patient recruitment (Abraham & Sheppard, [2000], p. 84 in Healy, 2004, p. 32).

Efforts to gain regulatory approval for fluoxetine in Europe experienced a setback in 1984 when German regulators concluded, ‘Considering the benefit and the risk, we think this preparation totally unsuitable for treatment of depression’ (Healy 2004, p. 39). Lilly turned its attentions to the regulatory process in Sweden instead. There is an unusually detailed record of what happened behind the scenes because John Virapen, the managing director for Lilly in Sweden, became a whistle-blower and wrote a tell-all memoir about everything he did to get the drug approved (Gøtzsche, 2013, p. 203). Among the claims in Virapen (2010) — he flew doctors to the Caribbean for a week and plied them with ‘diving, surfing, sailing, pretty girls, and hot nights’ (p. 84). He also figured out who the independent expert was who had been hired to review the clinical trial data and, after some negotiation, paid him a $20,000 bribe (100,000 Swedish crowns) and arranged for a research grant for his institution (Virapen, 2010, p. 94).

Fluoxetine was later approved in Germany following ‘unorthodox lobbying methods’ as well (Healy, 2004, p. 248).

A change in how drugs were approved at the FDA also helped Lilly to secure approval for fluoxetine in the U.S. (Healy, 2004, p. 35). In 1981, Paul Leber became head of the FDA’s neuropharmacology branch (Shorter, 2009, p. 179). He instituted a series of reforms in the approval process for new psychopharmaceuticals (Healy, 2004, p. 35). ‘Leber’s reforms required that a new drug show evidence from two pivotal [understood to mean placebo controlled] studies that it worked and the majority of studies performed should go the same way’ (Healy, 2004, p. 35). Two of three placebo controlled studies of fluoxetine showed mixed results but some marginal benefits — including a study by Louis Fabre with just 11 patients who completed the four week trial — and that was enough to get it approved by the FDA in 1987 (Healy, 2004, p. 35).

Lilly also revolutionised the way psychopharmaceuticals were sold. Up until this point, drugs had usually been named after their chemical ingredients (Healy, 2004, p. 32). Lilly hired Interbrand to come up with a name for fluoxetine and it came up with Prozac to imply professionalism (pro-) and targeting (-zac) (Healy, 2004, p. 33). Combined with direct-to-consumer marketing, by the time Prozac was launched in 1988 ‘patients were lining up asking for Prozac by name, an experience new to American psychiatrists’ (Healy, 2004, p. 38).

Within four years of launch, Prozac became Lilly’s first billion dollar drug (Whitaker, 2010, p. 321) and a wave of competing SSRIs soon followed. Lilly’s market capitalisation increased from $10 billion when Prozac first launched in 1987 to $90

billion in 2000, the last full year that Prozac was still under patent (Lilly also brought the antipsychotic, Zyprexa, to market during this period and it too became a billion dollar drug) (Whitaker, 2010, p. 321). Lilly senior executives gained $3.1 billion from cashing out stock options during this period as well (Whitaker, 2010, p. 321).

8.3 Understanding the relationship and differences between medicalisation and iatrogenic injury

This review of the political economy of SSRIs would be incomplete without a discussion of medicalisation which is a massive problem in psychiatry and is often discussed, incorrectly in my view, in connection with autism. Medicalisation is defined by Conrad (1992) as ‘a process by which nonmedical problems become defined and treated as medical problems, usually in terms of illnesses or disorders’ (p. 209). There is a vast body of literature on medicalisation — particularly amongst critics of capitalist health care (e.g., Illich, 1976; Ehrenreich & English, 1979; Navarro, 1980).

Medicalisation is especially problematic in psychiatry, where the number of mental disorders grows with each new edition of the *Diagnostic and Statistical Manual* (Gøtzsche, 2013, p. 191). Financial conflicts of interest are rife amongst the authors of the *DSM* and the fear is that the pharmaceutical industry is using these definitions to prescribe ever greater numbers of pills to people who do not actually need them or benefit from them. Cosgrove, Krisky, Vijayaraghavan, and Schneider (2006) conducted a study of the authors of the *DSM-IV* and found that 57% of panel members had financial conflicts of interest; and that some panels had 100% conflicted members including the panel for mood disorders. Following criticism, the American Psychiatric

Association (APA) instituted a new policy that required financial conflicts of interest statements for panel members involved with drafting the *DSM-5* (Cosgrove & Krimsky, 2012). However, COI subsequently increased — 69% of the *DSM-5* task force members reported having ties to the pharmaceutical industry — a 21% increase over the previous edition (Cosgrove & Krimsky, 2012).

In many cases there is an additional step to medicalisation that is often overlooked — particularly in psychiatry, medicalisation often leads to treatment with toxic medical interventions which then cause iatrogenic injury (Gøtzsche, 2013). When medicalisation is discussed in the literature, authors sometimes are referring to medicalisation in the first sense as defined by Conrad (1992) (‘nonmedical problems come to be treated as medical problems’) but in other cases they are referring to the whole process of disease mongering followed by toxic treatments that cause material harms (including chronic illness, disability, and death).

So is autism perhaps partially the result of medicalisation and, if so, is it the result of medicalisation in the first sense (an invented disorder) or in the second sense (misdiagnosis of some sort that then leads to toxic treatments that produce iatrogenic injury)?

Frances (2010) and Gøtzsche (2013) think autism is an example of medicalisation in the first sense (not an actual increase in prevalence, rather, a changing of diagnostic criteria to label more people as autistic). Frances chaired the task force that wrote the *DSM-IV* but by the *DSM-5* he had become a fierce critic of the entire process. Frances (2010) argues that the *DSM-IV* created ‘three false positive “epidemics”’ — ADHD, autism,

and childhood bipolar disorder. Gøtzsche (2013) quotes Frances favourably and seems to concur that autism is the result of medicalisation. If Frances (2010) and Gøtzsche (2013) are correct then all of the epidemiological evidence that I have cited so far in this thesis is likely wrong.

Neither Frances nor Gøtzsche have conducted research nor published journal articles on autism. Frances (2010) and Gøtzsche (2013) also seem unaware of the fact that Byrd et al. (2002) and Hertz-Picciotto and Delwiche (2009) have already studied this matter at length and concluded that only a small fraction of the increase in autism prevalence was a result of changes in diagnostic criteria. Even though Frances (2010) and Gøtzsche (2013) are well-versed in the problem of medicalisation, they miss all of the ways that autism could be the result of iatrogenic injury.

As I showed above, SSRIs do not outperform a placebo for the vast majority of people who are using them in the U.S. (Kirsch et al., 2008). But because doctors and a willing public bought the now discredited story of the serotonin imbalance theory of depression, SSRI use in the American population is at astonishing levels. Today 12.7% of Americans (8.6% of males and 16.5% of females) 12 and older are on antidepressants the vast majority of which are SSRIs (Pratt, Brody, & Gu, 2017); a quarter of all antidepressant users have been on them for a decade or longer (Pratt et al., 2017); antidepressants are the drug most prescribed to Americans age 18 to 44 — people of reproductive age (National Center for Health Statistics, 2016); and 6.5% of all women enrolled in private health insurance and 8.1% of women on public health insurance use these drugs during pregnancy (Dawson et al., 2016). The evidence from the eight studies I have cited shows that taking SSRIs before or during pregnancy significantly

increases the risk of autism in the offspring. So a strong case can be made that autism is not a false positive epidemic, as Frances (2010) asserts, but rather has a material basis as a result of iatrogenic injury resulting from the use of SSRIs by women who are pregnant or may soon become pregnant.

8.4 Lobbying and campaign contributions

The top four most prescribed SSRIs in the U.S. (and their manufacturers) are: Zoloft (Pfizer), Celexa (Forest Laboratories), Prozac (Eli Lilly), and Lexapro (Forest Laboratories) (Moore & Mattison, 2017, p. 275). Pfizer and Eli Lilly spend heavily on lobbying and their interests go well beyond SSRIs to cover the full range of pharmaceutical products that they produce. From 1999 through 2018, Pfizer spent $191.42 million on lobbying; in 2018, 49 out of 64 Pfizer lobbyists had previously held government jobs; and 34 members of Congress owned Pfizer shares (Center for Responsive Politics, 2018, ‘Pfizer’). From 1999 through 2018, Eli Lilly spent $141.65 million on lobbying; in 2018, 49 out of 62 Eli Lilly & Co. lobbyists previously held government jobs; and 9 members of Congress owned shares in Eli Lilly (CRP, 2018, ‘Eli Lilly’). For much of its history Forest Laboratories maintained a lower profile in Washington D.C. (it also had a much smaller portfolio of products than either Pfizer or Eli Lilly). From 2005 to 2014, Forest Laboratories spent a total of $2.4 million on lobbying (CRP, 2018, ‘Forest Laboratories’). In July 2014, Forest Laboratories was acquired by Actavis which later merged with Warner Chilcott to create the pharmaceutical giant Allergan which spends heavily on lobbying ($14 million from 2015 through 2018) (CRP, 2018, ‘Allergan’). GlaxoSmithKline is the producer of another bestselling SSRI, Paxil, and a range of other pharmaceutical products; I write

about their lobbying expenditures in the next chapter. Many of these pharmaceutical companies also fund lobbying and campaign contributions through political action committees including the Pharmaceutical Research and Manufacturers of America. The critics of SSRIs are not well organised nor well funded and seem to consist of a handful of doctors, academics, and journalists who have no ongoing lobbying presence in Washington D.C.

8.5 Criticisms and rejoinders

There may be confounding factors that are clouding the data about a possible association between SSRI use during pregnancy and autism. Greater use of SSRIs during pregnancy might be an indicator of increased pharmacological use overall (such as analgesics) or greater compliance with all directives from doctors including obstetric interventions (such as Pitocin and anesthesia) and vaccines. Any study on SSRIs and autism that does not control for these additional factors could contain unacknowledged confounding factors in their results. Controlling for these additional factors would be relatively easy in the Scandinavian studies and with health maintenance organisations such as Kaiser Permanente because they have complete medical records in their databases. But in the current political climate, exploring the dangers of obstetric interventions or vaccines is seen as politically risky, so that might explain why researchers often fail to control for these factors.

8.6 Conclusion

In this chapter, I showed that the early research that led to SSRIs was focused on the serotonin deficiency hypothesis and that the serotonin deficiency narrative was central to marketing campaigns even though scientific evidence in support of the theory never materialised. I showed that the first SSRI, Prozac, was approved in Sweden and then Germany following numerous breaches of scientific ethics including bribes and that approval in the U.S. was based on limited evidence including a study with just 11 people that lasted one month. I pointed out that medicalisation has two different meanings — medicalisation can refer to pathologising aspects of everyday life or medicalisation can refer to pathologising aspects of everyday life and then treating said condition with toxic medical interventions that produce real and lasting harm. I argued that autism is often incorrectly understood as medicalisation in the first sense described here whereas it might properly be understood in the second sense — SSRIs are widely prescribed to those experiencing the normal ups and downs of life but by consuming SSRIs, women who are pregnant or about to become pregnant expose their future offspring to a teratogen that increases the risk of autism. The tragedy is made all the worse by the fact that for most people, SSRIs do not outperform a placebo. The FDA and CDC have done nothing in response to the growing evidence about the links between SSRIs and autism. Pharmaceutical companies are among the most prolific spenders on lobbying in Washington, D.C. and organised opposition to SSRIs is limited to a few doctors, academics, and journalists. In the next chapter I will explore the political economy of the regulation of vaccines.

Chapter 9

The political economy of the regulation of vaccines

9.0 Introduction to the vaccines and autism debate

One of the things that makes vaccines different from every other possible environmental trigger described thus far is the presence of thousands of parents who claim that they personally witnessed autistic regression — their child was healthy, the child was vaccinated pursuant to the U.S. schedule at a ‘well baby’ visit, and within hours, minutes, days, or weeks the child lost speech, motor coordination, eye contact, and/or developed a host of other symptoms associated with autism. With the other toxicants on the list, the possible damage is invisible — cells and systems are harmed during critical developmental periods in utero or slowly over time and this damage is only flagged later when the child misses key developmental milestones. With vaccines there are parents who say that they witnessed with their own eyes what happened to their previously healthy child. Recent scholarship suggests that autistic regression may be the rule rather than the exception (Ozonoff et al., 2018). The debate over vaccines is the most contentious facet of the autism debate and it is one of the most polarised debates in American society today. As a result, I devote more pages to the research in connection with vaccines than any other facet of the autism debate.

The vaccines and autism debate is also one of the strangest debates I have ever seen in political economy so I want to foreground the discussion in this chapter by highlighting some of the internal contradictions and paradoxes that swirl around this topic:

1. All parties to the debate acknowledge that the current vaccine schedule could not exist in the absence of liability protection. Vaccines, according to their producers, cannot compete in the normal capitalist marketplace because class action lawsuits from those injured by their products would drive them out of business. Many state governments then require citizens to have this product injected into their bodies as a condition of entry to school, day care, and some jobs. So there is a paradox at the heart of this debate which is that this product is required in the name of public safety, even while its producers acknowledge that the product does not meet the usual product liability norms of the capitalist marketplace.

2. We know that vaccines cause injury sometimes — there is an entire separate branch of the U.S. Court of Federal Claims to compensate those injured by vaccines and the U.S. Supreme Court, in *Bruesewitz v. Wyeth* (2011), ruled that vaccines are 'unavoidably unsafe'. So the question is not do vaccines sometimes cause harm but rather, what is the rate of harm? However, the official government position is that to measure the likely rate of harm, via a comparison with an unvaccinated control group, would be unethical (see #5 below).

3. We know that the Vaccine Adverse Event Reporting System (VAERS), because it is voluntary, undercounts the actual number of vaccine injuries. The former FDA commissioner David Kessler (1993) stated that adverse events in connection with pharmaceutical products are underreported by a factor of 100. So the question is not whether VAERS undercounts, but the degree of undercounting.

4. Many of the ingredients in vaccines — in particular ethylmercury and aluminium — are known neurotoxins (Grandjean & Landrigan, 2014). Defenders of the current paradigm argue that ‘the dose makes the poison’ (see Offit & Jew, 2003), but that idea has been challenged in recent years as toxicologists have discovered non-linear dose response curves and concluded that some substances, such as lead, have no safe dose (Grandjean & Landrigan, 2014, p. 331). The debate is not over whether ethylmercury and aluminium are neurotoxins, the debate is over their dose response curves which are not well understood.

5. All parties to the debate admit that there are no studies with an unvaccinated control group that show that the national vaccine schedule is safe. Defenders of the status quo admit this as a point of pride, arguing that a proper double blind RCT would be unethical because they already know (based on experience) that vaccines are safe. But at the same time they argue that RCTs are the gold standard and should guide all other decisions in medicine. It creates an unusual spectacle whereby autism advocacy groups are demanding double blind RCTs while mainstream figures in science and medicine are violating their own preferred epistemology by blocking the sorts of studies that could resolve this debate.

6. Even though the facts mentioned here are not in dispute, if one publicly points out these troubling contradictions and paradoxes in connection with the national vaccine program, one is risking one’s career and one will likely be ostracised by colleagues, friends, and family and labelled crazy and a conspiracy theorist (see: Martin, 2018). If one responds to the uncertainty created by undone science by refusing to vaccinate one’s children, most states then mandate that they cannot go to publicly funded day care

or school. Even more troubling, doctors ‘may report the parent to Child Protective Services’ for ‘medical negligence’ if the parent refuses to vaccinate his/her child (Rosenberg, 2012, p. 242).

The debate regarding vaccines and autism is fraught. Yet, this is a conversation one must have if one is to understand the political economy of autism. This chapter has two main sections — the regulatory history of vaccines in the U.S. (9.1.0) and the scientific debate about vaccines and autism (9.2.0). Each section has numerous subsections that I will introduce at the start of each section. In this chapter I will attempt to show that capitalism shapes every aspect of the national vaccine schedule. Policies, procedures, bureaucratic infrastructure, and regulatory decisions are focused narrowly on the product and getting the product approved and into the marketplace without ever assessing the health of the whole system.

9.1.0 Introduction to the political economy of vaccines

In this section I will provide an overview of the size of the vaccine market (9.1.1); document the growth in the U.S. vaccine schedule (9.1.2); review the vaccine approval process (9.1.3); argue that clinical trials as part of the FDA licensure process are too short, too small, and use toxic placebos (9.1.4); discuss COI at the FDA’s Vaccines and Related Biological Products Advisory Committee (VRBPAC), the CDC’s Advisory Committee on Immunization Practices (ACIP), and the National Vaccine Advisory Committee (NVAC) (9.1.5); show that post-market surveillance of vaccine adverse events is inadequate (9.1.6); document the revolving door between CDC and vaccine

makers (9.1.7); discuss the lobbying at the state level to make vaccines compulsory (9.1.8); and show COI in science and medical journals associated with vaccines (9.1.9).

9.1.1 The size of the vaccine market

Vaccine manufacturers reported $28.3 billion in global sales in 2015 (Transparency Market Research, 2016). The vaccine market is characterised by oligopoly as just four firms — GSK, Merck, Pfizer, and Sanofi — generated 86% of total global vaccine revenue in 2015 (EvaluatePharma, 2016). Several market research companies project robust growth in vaccine sales over the coming years: Markets to Markets projects the global vaccine market to reach $48 billion by 2021; Zion Market Research projects the vaccine market to reach $59.2 billion by 2020; and Mordor Intelligence projects a global vaccine market of $55 billion by 2021 (La Vigne, 2016). Just over one-third of global sales are projected to come from North America by 2024 ($28 billion out of $72.5 billion in vaccine sales in 2024) (Transparency Market Research, 2016). Paediatric vaccines currently account for 57.5% of the vaccine market but adult vaccines sales are expected to outpace paediatric vaccines sales in the coming years (Transparency Market Research, 2016).

Johnson (2009) writing in the *Wall Street Journal* observes that the 1986 NCVIA and the Vaccine Injury Compensation Program ‘is an important reason why the vaccine business has been transformed from a risky, low-profit venture in the 1970s to one of the pharmaceutical industry’s most attractive product lines today’ (para. 2). More recently, ‘Old vaccines have been reformulated with higher costs. New ones have entered the market at once-unthinkable prices. Together, since 1986, they have pushed

up the average cost to fully vaccinate a child with private insurance to the age of 18 to $2,192 from $100, according to data from the Centers for Disease Control and Prevention' (Rosenthal, 2014, para. 4). 'The federal government... buys half of all vaccines' administered to children, and even with bulk discounts, its costs have increased 15-fold since 1986 (Rosenthal, 2014, para. 5). Just as there are billion dollar drugs, there are now billion dollar vaccines. So for example, Prevnar 'is priced at $136 [per shot], and most states require children to get four doses before entering day care or school' (Rosenthal, 2014, para. 6). 'Pfizer, the sole manufacturer, had revenues of nearly $4 billion from its Prevnar vaccine line last year, about double what it made from high-profit drugs like Lipitor and Viagra, which now face generic competitors' (Rosenthal, 2014, para. 6). With liability protection, a guaranteed market of 4 million new children born into the U.S. each year, and guarantors in the form of the federal government footing half of the bill and insurance companies also picking up a large share, vaccines are a product unlike any other in the marketplace. The profits that one can earn from this unique product are largely dependent upon a pharmaceutical company's ability to get additional vaccines added to the schedule. Yet as an indicator of just how vast the pharmaceutical industry is at this point, 'even though the dollar figure is large and growing, vaccines still only account for 3 percent of the market share within the global pharmaceutical industry' (La Vigne, 2016).

9.1.2 The growth in the U.S. vaccine schedule

In 1983, the official U.S. vaccine schedule could be explained in half a page and consisted of the following vaccines: DTP (diphtheria, tetanus, and pertussis) (2 months), OPV (oral polio vaccine) (2 months), DTP (4 months), OPV (4 months), DTP (6

months), MMR (measles, mumps, and rubella) (15 months), DTP (18 months), OPV (18 months), DTP (4 years), OPV (4 years), and Td (tetanus and diphtheria without pertussis) (15 years) (CDC, 1983). So, counting each component of the conjugate vaccines separately, the schedule contained 24 doses total consisting of 7 injected vaccines and 4 oral vaccines. In 1985 the autism rate in the U.S. was calculated at 1 in 2,500 (Autism Speaks, 2010). The current vaccine schedule (CDC, 2017) takes eight pages to explain and consists of the following:

Centers for Disease Control and Prevention Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger, United States (2017)	
Influenza (pregnancy)	DTaP (18 months)
Tdap (pregnancy)	Influenza (18 months)
Hep B (birth)	Hep A (18 months)
Hep B (2 months)	Influenza (30 months)
rotavirus (2 months)	Influenza (42 months)
DTaP (2 months)	DTaP (4 years)
Hib (2 months)	IPV (4 years)
PCV (2 months)	MMR (4 years)
IPV (2 months)	Varicella (4 years)
rotavirus (4 months)	Influenza (5 years)
DTaP (4 months)	Influenza (5 years)
Hib (4 months)	Influenza (6 years)
PCV (4 months)	Influenza (7 years)
IPV (4 months)	Influenza (8 years)
Hep B (6 months)	Influenza (9 years)
rotavirus (6 months)	HPV (11 years)
DTaP (6 months)	Tdap (12 years)
Hib (6 months)	Influenza (12 years)
PCV (6 months)	Meningococcal (12 years)
IPV (6 months)	Influenza (13 years)
Influenza (6 months)	Influenza (14 years),
Influenza (7 months)	Influenza (15 years)
Hib (12 months)	Influenza (16 years)
PCV (12 months)	Meningococcal (16 years)
MMR (12 months)	Influenza (17 years)
Varicella (12 months)	Influenza (18 years)
Hep A (12 months)	

DTaP (diphtheria, tetanus, and acellular pertussis); Hib (haemophilus influenzae type b); HPV (human papillomavirus); IPV (inactivated poliovirus); MMR (measles, mumps, rubella); PCV (pneumococcal conjugate vaccine); Tdap (tetanus, diphtheria, and acellular pertussis) — which is different than DTaP.

As one can see the schedule is heavily front-loaded into the first two years of life with as many as seven injections at the six month paediatric ‘well baby’ visit. In total, counting each component of the conjugate vaccines separately, the current schedule has 74 doses of 53 injected vaccines and three oral vaccines. Presently the autism rate is estimated at 1 in 36 (Zablotsky et al., 2017). This simply shows temporal association, but the association is troubling and that is one of the cases to answer here.

9.1.3 The vaccine approval process in the U.S.

Vaccine development goes through four clinical stages (Pickering & Orenstein, 2002). ‘Phase 1 trials in humans include the smallest number of volunteers and are primarily designed to identify problems of acute safety’ (Pickering & Orenstein, 2002, p. 148). As I will show below (9.1.4) there are concerns that this phase may be too short and too small to detect iatrogenic events such as autism. Phase 2 looks at ‘dose range and immunogenicity’ and involves 100–1,000 human participants (Pickering & Orenstein, 2002, p. 148). Phase 3 looks at ‘vaccine efficacy’ and involves 500 to 20,000 participants (Pickering & Orenstein, 2002, p. 148). Phase 4 trials happen after the vaccine is already on the market and may involve 10,000 to 100,000 participants; postmarketing surveillance ostensibly includes millions of participations (Pickering & Orenstein, 2002, p. 148).

The vaccine approval process in the U.S. is unusual because no less than 4 committees of political appointees sit above the FDA licensure process. The charter for each of these committees is focused first and foremost on the product, vaccines, rather than on health or wellness per se. The federal government uses a stakeholder model of decision

making where all of the relevant parties, including the vaccine maker, are usually at the table. The stakeholder model stands in contrast to Mertonian norms of science that emphasise disinterestedness and organised scepticism as well as the literature on the funding effect that shows that COI change research outcomes.

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) consists of 15 members appointed by the FDA commissioner (FDA, 2017b). The charter states that the VRBPAC 'advises the Commissioner or designee in discharging responsibilities as they relate to helping to ensure safe and effective vaccines and related biological products for human use...' (FDA, 2017b). In 2017, Leonard Friedland, Vice President of GlaxoSmithKline (GSK) and David Greenberg, Associate Vice President of Sanofi Pasteur both sat on the VRBPAC (FDA, 2017a). The VRBPAC often offers their recommendations regarding a new vaccine *before* FDA staff have made a determination whether the vaccine is safe and effective (Pickering & Orenstein, 2002, p. 149). Putting the political (stakeholder) process ahead of the scientific review process raises troubling questions about the objectivity of the FDA.

The American Academy of Pediatrics (AAP) also has a Committee on Infectious Diseases (COID) that studies new vaccines in the pipeline and makes recommendations on which vaccines should be added to the schedule. Since 2001, the APA's COID vaccine schedule is 'intentionally harmonized' with the CDC's ACIP schedule so that they are the same. Like the VRBPAC, the COID weighs in with their opinions before the FDA decides whether a vaccine is safe (Pickering & Orenstein, 2002, p. 150). The membership of COID is not publicly posted online, meetings are not public, and

minutes are not published. I wrote to the AAP in 2017 to request a list of COID members and the AAP never responded.

The National Vaccine Advisory Committee (NVAC) at the Department of Health and Human Services 'consists of 15 members appointed by the director of the national Vaccine Program in consultation with the National Academy of Sciences' (Pickering & Orenstein, 2002, p. 149). The charter of the NVAC states that it is to 'study and recommend ways to encourage the availability of an adequate supply of safe and effective vaccination products in the United States' (NVAC, 2015). The assumption here, which is echoed in the charters of the other three advisory groups as well, is that vaccines are a permanent part of the health landscape. As of February 2016, both Timothy Cooke, CEO of NovaDigm (vaccine producer), and Philip Hosbach, Vice President of Sanofi Pasteur, are members of NVAC.

The most important committee of all is the Advisory Committee on Immunization Practices (ACIP) at the CDC. Walton, Orenstein, & Pickering (2015) provide a history of ACIP. In 1938, the American Academy of Pediatrics — Committee on Immunization Procedures (now the Committee on Infectious Diseases) published an eight page pamphlet that came to be known as the Red Book that gave recommendations on the treatment of eighteen diseases (Walton et al., 2015, p. 406). Guidance was provided on six vaccines for children — diphtheria, pertussis, tuberculosis, typhoid fever, varicella, and smallpox (variola) (Walton et al., 2015, p. 406). In 1964, the Surgeon General of the U.S. Public Health Service created the Advisory Committee on Immunization Practices (ACIP) — prior to that vaccine policy was ad hoc or left to the states (Smith, 2010, p. 68).

ACIP has become a virtual policy factory for adding vaccines to the national schedule. The ACIP contains 15 regular members and a quorum of 8 is enough to approve a recommendation (Smith, 2010, A73). ACIP also has 8 ex officio non-voting members made up of representatives from the various federal agencies that are involved with implementing vaccine policy and 31 non-voting liaison representatives from most of the major professional health associations in the country including the AAP, AMA, and America's Health Insurance Plans (the trade association of the health insurance industry) (Smith, 2010, p. A69). ACIP meets three times a year; and *14 working groups meet at least once a month to prepare draft policy recommendations* (Smith, 2010, p. A70).

> Four ACIP working groups are permanent: (1) Adult Immunization Schedule; (2) Influenza Vaccines; 3) General Recommendations on Immunization; and (4) Harmonized Schedule for Children and Adolescents, which works to ensure that vaccine schedules for children and adolescents are harmonized among ACIP, the American Academy of Pediatrics and the American Academy of Family Physicians, all of whom participate together in this working group (Smith, 2010, A72).

The result of this extraordinary policy infrastructure is astonishing speed in adding new vaccines to the schedule. A few recent examples illustrate the point. The FDA approved the rotavirus vaccine, RotaTeq on 3 February 2006 and ACIP voted to add it to the schedule on 21 February 2006 (Smith, 2010, p. A73). Rotarix, also for the prevention of rotavirus, was approved by the FDA in April 2008 and added as an approved option to the routine infant immunisation schedule in June 2008 (Smith, 2010, p. A74). An earlier

rotavirus vaccine, Rotashield, was approved by ACIP and that recommendation was later withdrawn because it caused intussusception (an intestinal disorder) and fatalities in some children. So too with the HPV vaccine: Gardasil was approved by the FDA on 8 June 2006 (FDA, 2009b); the ACIP working group had been working on HPV policy since 2004 and ACIP recommended ‘a routine 3-dose vaccination series for girls 11 and 12 years of age’ three weeks later on 29 June 2006 (CDC, 2007).

Officially, ACIP recommendations are not law; but in practice they are ‘generally regarded as national policy’ and adopted by most private health insurance companies and most states (Smith, 2010, p. A71). Furthermore, an ACIP recommendation gets a vaccine added to the federal Vaccines for Children Program that ‘pays for vaccine administration to almost 50% of American children under 6 years of age’ (Smith, 2010, p. A71). Most states then mandate that children must be immunised according to the national schedule in order to attend public day care or public schools.

The eight to fifteen people who effectively decide what is injected into more than 90% of the population are not elected officials so they are not directly answerable to voters. In theory the CDC or HHS director could overrule ACIP but in practice that has only happened once (in 2003 when ACIP recommended a small pox vaccine for bioterrorism response teams and HHS overrode their decision) (Smith, 2010, p. A73). Also, it is striking how much more effective and efficient ACIP is compared with their counterparts in pesticide policy at the EPA for example — where it can take decades to develop a policy in connection with a single chemical substance. One key difference is that ACIP is recommending medical interventions that generate profits whereas the EPA is making recommendations that hurt corporate profits.

9.1.4 Vaccine licensure process at the FDA is characterised by studies that are short, small, and often use toxic placebos

Vaccine safety studies used in the licensure process are conducted by the manufacturers which presents a clear conflict of interest. In this subsection I will present evidence that vaccine safety studies are too short and often use toxic placebos instead of saline in order to hide adverse reactions.

If hypothetically, iatrogenic injury from vaccines had a long latency period — because of the toxicokinetics of the vaccine or the dynamics of autoimmune disease or the difficulties created by the fact that the target market are infants who are unable to narrate their own internal experience — many of the vaccine safety studies that have been approved by the FDA would not have been able to identify them because the trials were so short. For example, there are two hepatitis B vaccines licensed for use in the U.S. — one made by Merck and one made by GlaxoSmithKline. The evidence suggests neither of them has been adequately tested for safety in the target population. Holland (2012) notes that the package insert for Merck's Recombivax HB states: 'In three clinical studies, 434 doses of Recombivax HB, 5 mcg, were administered to 147 healthy infants and children (up to 10 years of age) who were monitored for 5 days after each dose' (p. 70). Holland (2012) points out that 'the insert does not state the ages of the children or the proportion of the 147 subjects who were infants. It makes no mention of newborns' even though it is now given to almost all newborns (p. 70). By the same token, the package insert for GlaxoSmithKline's (GSK) Engerix-B states: 'In 36 clinical studies, a total of 13,495 doses of Engerix-B were administered to 5,071 healthy adults

and children who were initially seronegative for hepatitis B markers, and healthy neonates. All subjects were monitored for 4 days post-administration' (Holland, 2012, p. 70). There is no mention of how many neonates were in the study and the study results were not broken out separately for this population either (Holland, 2012, p. 70).

But it is not just the hepatitis B vaccine. Relatively short safety studies are the norm in the licensing of vaccines. The package insert for the Hib (haemophilus influenzae type b) vaccine manufactured by Merck shows that it was licensed based on a trial that monitored adverse reactions for three days; the package insert of the Hib vaccine manufactured by GSK shows that it was licensed based on a trial that monitored adverse reactions for four days; and 'the only stand-alone polio vaccine was licensed after a mere 48-hour follow-up period' (Informed Consent Action Network, 2017b, p. 2).

In addition to short safety studies, vaccines are almost always tested against toxic placebos rather than saline in order to hide adverse events. As I showed in chapter 5, Contract Research Organisations (CROs) have a number of ways that they can produce the outcomes desired by their pharmaceutical company clients. CROs are under enormous pressure to maximise the evidence of efficacy and minimise the evidence of harms. One way that many vaccine studies are manipulated is that instead of using a saline placebo as part of an RCT, another vaccine is used as the comparator instead. Alternatively, CROs put the toxic adjuvants (ethylmercury, aluminium) in the placebo and the only difference between the drug and placebo is the biological agent. None of this is prohibited by law. Beatrice Golomb (1995) then at the Department of Medicine at UCLA drew attention to problems with placebos in a letter to *Nature*:

> The U.S. Food and Drug Administration sets no regulation on the constituents of placebos, and any guidelines are at best informal. Astonishingly, no systematic efforts are made to ensure the inertness of placebos: there is nothing validating the placebo standard against which other agents are measured. Further, the drug companies funding the trials control the placebo ingredients. The identity of the placebo and fillers used with the experimental drug are rarely stated in scientific studies (p. 530).

Fifteen years later, Golomb et al. (2010) showed that there are still no regulations concerning the contents of placebos in the U.S. In a review of all RCTs published in the four highest impact medical journals in 2008 and 2009, only 34% of studies of injectable treatments fully disclosed the contents of the placebo (Golomb et al., 2010, p. W-189). Jacobson, Ovsyannikova, and Poland (2009) reviewed four recent vaccine trials involving children and none of them used a saline placebo. ICAN (2018) reviewed the FDA applications for all of the vaccines currently on the national schedule and discovered that none of them used saline placebos (with the exception of Gardasil-9 [HPV vaccine] where Merck ran a small subtrial using a saline placebo — but all of the study participants had previously received three doses of the original Gardasil vaccine and were in good health) (p. 6).

9.1.5 Conflicts of interest at the VRBPAC and ACIP

Getting a vaccine added to the schedule can be worth a billion dollars or more to a vaccine maker so the potential for conflicts of interest are extraordinary. The FDA's

Vaccines and Related Biological Products Advisory Committee (VRBPAC) and the CDC's Advisory Committee on Immunization Practices (ACIP) have been characterised by extraordinary conflicts of interest (Krimsky, 2004).

Following a high profile debacle in connection with the approval of the Rotashield rotavirus vaccine, the U.S. House of Representatives, Committee on Government Reform in August 1999 started an investigation into 'conflicts of interest in federal vaccine policy making' (Committee on Government Reform, 2000). The committee studied financial disclosure forms, examined minutes of meetings, and interviewed advisory committee members (Committee on Government Reform, 2000, p. 1). The majority staff report was released on June 15, 2000. It concluded that, 'conflict of interest rules employed the FDA and the CDC have been weak, enforcement has been lax, and committee members with substantial ties to pharmaceutical companies have been given waivers to participate in committee proceedings' (Committee on Government Reform, 2000, p. 1). Among other problems, the committee found that:

- The CDC routinely grants waivers from conflict of interest rules to every member of its advisory committee [ACIP].
- The Chairman of the CDC's advisory committee [ACIP]... owned 600 shares of stock in Merck, a pharmaceutical company with an active vaccine division.
- Four out of eight CDC advisory committee members who voted to approve guidelines for the rotavirus vaccine in June 1998 had financial ties to pharmaceutical companies that were developing different versions of the vaccine.

- Three out of five FDA advisory committee members who voted to approve the rotavirus vaccine in December 1997 had financial ties to pharmaceutical companies that were developing different versions of the vaccine (Committee on Government Reform, 2000, p. 1).

The actions of both ACIP and VRBPAC appear contrary to federal law that 'requires that advisory committee members disclose their financial interests and recuse themselves from matters in which they have an interest' (Committee on Government Reform, 2000, p. 2). Paul Offit, who will be cited often in this chapter, was named in the report as having voted in favour of Rotashield three times as part of his membership in ACIP in spite of the fact that he had a COI as a result of holding patents on a rival rotavirus vaccine; Offit is also the Maurice R. Hilleman Professor of Vaccinology at the University of Pennsylvania, a chair endowed by Merck; and Offit only recused himself for the vote as to whether to withdraw Rotashield from the market (Committee on Government Reform, 2000, p. 18). The VRBPAC and ACIP both approved Rotashield unanimously, in spite of concerns about safety expressed by several committee members, *prior to* the vaccine receiving FDA approval. On August 10, 2000, Dan Burton, chairman of the Committee on Government Reform wrote to the Secretary of the Department of Health and Human Services in connection with the report stating, 'It has become clear over the course of this investigation that the VRBPAC and the ACIP are dominated by individuals with close working relationships with the vaccine producers' (Krimsky, 2004, p. 97). The final report contained 17 proposed reforms including, 'individuals who serve on advisory committees involving vaccines should have no financial ties to vaccine manufacturers' (Committee on Government Reform, 2000, p. 22). As of January 2018, a Vice President from Merck and an Associate Vice

President from Sanofi Pasteur were serving as voting members on the VRBPAC and the ACIP still does not disclose the names of the members of its working groups nor publish minutes from working group meetings.

Financial conflicts of interest at the CDC go well beyond ACIP. While the CDC repeatedly claims on its website that it 'does not accept commercial support' the evidence proves otherwise (ICAN, 2017a, p. 26). As I showed in chapter 5, the CDC Foundation accepts millions of dollars in corporate donations every year (see also Lenzer, 2015). The moment the CDC accepts any outside funding it becomes a conflicted party subject to the funding effect and such funding raises doubts as to the scientific integrity of their work.

9.1.6 Post-market surveillance of vaccine adverse events is inadequate

The 1986 National Childhood Vaccine Injury Act established the Vaccine Adverse Event Reporting System (VAERS) administered by the Department of Health and Human Services to track injuries from vaccination (in ICAN, 2017a, p. 2). 'In 2016, VAERS received 59,117 reports of adverse reactions following vaccination including 432 deaths, 1,091 permanent disabilities, 4,132 hospitalizations, and 10,284 emergency room visits' (ICAN, 2017a). As discussed in the introduction to this chapter, former FDA Commissioner David Kessler (1993) noted that only a small percentage of adverse events are ever reported. He cites Scott et al. [1987], in a study of physicians in Rhode Island, who found that 'only about 1% of serious adverse events are reported to the FDA' (Kessler, 1993, p. 2765). Because VAERS reports are voluntary, it is impossible to know the true number of adverse events in connection with vaccines every year.

The Department of Health and Human Services provided a nearly $1 million grant to Harvard Pilgrim Health Care (affiliated with Harvard Medical School) to measure vaccine adverse events in a large not-for-profit health services company (Lazarus & Klompas, 2011). In their final report, Lazarus and Klompas (2011) write,

> Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions (2.6 percent of vaccinations) were identified. This is an average of 890 possible events, an average of 1.3 events per clinician, per month (p. 6).

These are alarming numbers — an adverse event rate of 2.6% is much higher than the '1 in a million' figure so often mentioned by the CDC and clinicians.

The Harvard Pilgrim Health Care team also reported that it would be feasible to move from a voluntary to an automatic electronic system of reporting vaccine injury that would vastly improve the accuracy of the data submitted to VAERS (Lazarus & Klompas, 2011). However that system was never implemented because after the Harvard Pilgrim team presented their preliminary data, the CDC ceased all contact with the researchers (Lazarus & Klompas, 2011). 'Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed...' (Lazarus &

Klompas, 2011, p. 6). Below I will also show that Harvard Pilgrim faced bankruptcy and other problems in 1999, but there is no evidence that these problems interfered with the HHS study led by Lazarus and Klompas.

9.1.7 Revolving door between CDC and vaccine makers

There is a revolving door between the CDC branch responsible for vaccine safety and the vaccine makers they are charged with regulating. Thomas Verstraeten was a senior research scientist at the CDC who led perhaps the most important study of vaccines and autism to date (Verstraeten et al., 2003). He was hired by vaccine maker GlaxoSmithKline on the morning he was scheduled to present his findings to the Institute of Medicine and moved to their offices in Belgium (Kirby, 2005). Julie Gerberding was director of the CDC and administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) from 2002 to 2009 during which time the CDC produced several reports that concluded there was no link between vaccines and autism. ‘A year after leaving as director of CDC in 2009, Dr. Julie Gerberding took a position as president of Merck Vaccines’ (DeLong, 2012, p. 70). SEC filings show that Gerberding sold over 38,000 shares of Merck stock in 2015 for just over $2.3 million dollars and that following the sale she still owned just under 32,000 shares of Merck stock valued at about $2 million (U.S. Securities and Exchange Commission, 2015).

Elias Zerhouni served as director of the National Institutes of Health from 2002 to 2008. After leaving government he became an advisor to Christopher Viehbacher, Chief Executive of the pharmaceutical giant Sanofi-Aventis (Herper, 2010, para. 2). In 2010,

Zerhouni was named to head the research labs at the Sanofi-Aventis in spite of the fact that he had little background in drug development (Herper, 2010, para. 4).

The revolving door also happens at the state level where legislative mandates are key to expanding the market for vaccines. Eddy Bresnitz served as New Jersey's deputy commissioner of health and state immunologist where he helped usher in a requirement that all children in the state must get annual flu vaccinations in order to attend preschool or day care in spite of the flu vaccine's low efficacy rate (Capuzzo, 2007). Shortly thereafter he was hired as Medical Director at Merck where he oversees Global Adult Vaccines (Belkin, 2011, p. 163).

9.1.8 Lobbying at the state level to make vaccines compulsory

Even though vaccines are licensed and approved at the federal level, in the U.S. system, vaccine policy is ultimately at the discretion of the states. In spite of the potential for that to lead to widely varying policies, vaccination law is remarkably similar between states. Mello, Abiola, and Colgrove (2012) document the fact that 'school entry mandates' (state requirements that children cannot attend school unless they have been vaccinated according to state recommendations) are largely driven by pharmaceutical company campaigns that include everything from providing information, lobbying, drafting the legislation, mobilising physicians' organisations, and conducting consumer marketing campaigns (p. 893). So for example, within a year of the approval of the HPV vaccine by the FDA and ACIP, 'legislation relating to the vaccine was introduced in 41 states and the District of Columbia, including bills in 24 states that would mandate HPV vaccination for 6th-grade girls' (Mello et al., 2012, p. 893).

More recently, vaccine makers have pushed states to repeal religious and personal belief exemptions to vaccine mandates. Perhaps the most noteworthy example is California's SB277 that eliminated 'all personal and religious belief exemptions to the state's childhood vaccine requirements for entry into public and private schools, as well as day care centers' (Parpia, 2015, para. 1). An investigation by the *Sacramento Bee* revealed that 'pharmaceutical companies and their trade groups gave more than $2 million to current members of the Legislature in 2013–2014'; the top recipient of this largesse was Senator Richard Pan who received $95,150 from drug makers and was the sponsor of SB277 (Miller, 2015, para. 5). Leading pharmaceutical companies spent another $3 million during that session on 'lobbying the Legislature, the governor, state pharmacists' boards, and other agencies' (Miller, 2015, para. 7).

Peter Doshi, editor of *BMJ* notes that Every Child by Two (ECBT), the American Academy of Pediatrics, and the Immunization Action Coalition (IAC) also lobby for state vaccine mandates and removal of personal belief exemptions (Doshi, 2017, p. 1). Ostensibly these are non-profit organisations, but they all receive substantial funding from pharmaceutical companies that stand to profit from these recommendations (Doshi, 2017, p. 1). These organisations are also funded by the CDC even though 'U.S. federal law prohibits use of CDC award money for lobbying' (Doshi, 2017, p. 2).

9.1.9 COI in scientific journals associated with vaccines

DeLong (2012) shows that COI are endemic to scientific publishing in connection with vaccine research. DeLong (2012) searched for the terms 'vaccine' and 'safety' during

the years 2006 to 2010 in the six medical journals with the highest impact factors (*Archives of Internal Medicine*, *AIM*, *BMJ*, *JAMA*, the *Lancet*, and the *NEJM*) and *Pediatrics*. Her search returned 39 articles that contained both terms — of those, 'thirty-one studies (79.5%) included at least one author who declared a COI with a vaccine manufacturer, and 24 studies (61.5%), included at least three authors with COIs' (DeLong, 2012, p. 72).

9.2.0 Introduction to the scientific debate on vaccine safety

The conflict over the safety of individual vaccines and the vaccine schedule has become so fierce that many people refer to it as the 'vaccine war(s)' (see, e.g., Public Broadcasting Service, 2010; Wadman & You, 2017). The combatants in the vaccine wars are the medical, pharmaceutical, and public health establishment (with some exceptions) versus a range of vaccine safety and autism advocacy groups often made up of the parents of vaccine injured children. The sites of struggle include print media, film, TV, radio, the internet, social media, doctors offices, hospitals, playgroups, day care facilities, and schools to name a few. And the ammunition in the vaccine wars is a wide range of studies and testimonials that opposing sides use to make their case.

Healthychildren.org (2017), a project of the American Academy of Pediatrics, has a webpage titled 'Vaccine Safety: Examine the Evidence' that provides brief descriptions and links to 43 studies, one court case, and one investigative journalism report. Since the 1970s, Institute of Medicine (IOM, now called the National Academy of Medicine) committees have issued 60 reports on vaccine safety. IOM (1991) reviewed the literature on 22 common adverse reactions to the DTP vaccine, IOM (1994) examined

the scientific literature on 54 commonly reported adverse events associated with seven of the vaccines on the schedule, and IOM [2012] reviewed the literature on 158 injuries associated with six vaccines on the schedule (ICAN, 2017a). In each case the IOM found a causal relationship between some vaccines and some adverse outcomes, but it did not find a causal association between any vaccine and autism (ICAN, 2017a). Paul Offit, Professor at the University of Pennsylvania and Chief of the Division of Infectious Diseases at the Children's Hospital of Philadelphia has become the de facto face of the national vaccine schedule in the U.S in part through putting out books every few years on some aspect of the vaccine debate (Offit & Bell, 1999; Offit, 2005, 2007, 2008, 2010). Science bloggers including Skeptical Raptor, Respectful Insolence, and Just the Vax link to a wide range of articles and studies that show that vaccines are safe.

By contrast, the relatively new, anonymous website, Vaccine Safety Commission (n.d.), links to 50 studies that show a link between vaccines and a range of adverse outcomes including autism. Miller (2016a) reviews 400 critical vaccine safety studies, that he argues collectively make the case that vaccines are unsafe and cause autism amongst other iatrogenic injuries. Skyhorse Publishing has produced at least 16 books on the association between vaccines and autism including Conte and Lyons (2014); Habakus, Holland, and Rosenberg (2012); Kennedy (2014)*;* and Lyons-Weiler (2016). SafeMinds, an autism advocacy group, contributed to 55 studies in their first 14 years of existence (SafeMinds, 2013). Ginger Taylor (2016) became an activist after her son regressed into autism after his 18 month shots. Her website, *Adventures in Autism* links to 142 studies on the links between vaccines and autism (Taylor, 2007). There are also websites that collect testimonials from parents who claim that vaccines caused autism and/or other disorders in their children. Vaxxed.com (n.d) has collected 6,736 vaccine injury

testimonials on video; Following Vaccinations (n.d) has collected 1,400 vaccine injury testimonials; and Vaccineinjury.info (n.d.) has 858 testimonials (as of 16 October 2017). It is not clear if there is any overlap between these testimonial sites.

The sheer number of studies cited by various camps tells us little about the contents — other than to say that these factions live in separate universes, each of which is relatively stable; there are more than enough studies, performed by parties respected within these respective knowledge communities, to support each step in the logic claimed by each camp. These separate universes are a mirror image of each other — for every study cited by the mainstream camp, there is an opposite study cited by the sceptics camp on the same topic, sometimes even using the same data, and vice versa. The mainstream position that vaccines are safe and effective still dominates all of the leading journals, academic institutions, and government agencies. But vaccine safety and autism advocacy groups have closed the credibility gap somewhat over the last seventeen years. When the first study came out from an autism advocacy group, Bernard, Enayati, Redwood, Roger, and Binstock (2001), it was a medical hypothesis backed by a literature review. But vaccine safety and autism advocacy groups have become increasingly sophisticated and now fund their own animal (Hewitson et al., 2010) and epidemiological studies (e.g. Mawson et al. 2017a and 2017b), and can point to research from elite institutions to back their claims (e.g. Leslie, Kobre, Richmand, Guloksuz, & Leckman, 2017, that shows an association between vaccines and a range of adverse mental health outcomes, includes four researchers from the Yale Child Studies Center). It is not possible to work through every study on vaccine safety and the safety of individual ingredients. Instead I will focus on eleven key facets of the conflict that illustrate the logic of the opposing camps and the differences between them. I will begin

this section by covering five key debates: What are the net benefits to society from widescale vaccination programs (9.2.1)? How important is herd immunity (9.2.2)? Is ethylmercury toxic at the doses contained in the vaccine schedule (9.2.3)? Is aluminium toxic at the doses contained in the vaccine schedule (9.2.4)? Are other ingredients in vaccines toxic at the doses contained in the vaccine schedule (9.2.5)? Then I will review studies showing no association between vaccines and autism (9.2.6), vaccinated vs. unvaccinated studies (9.2.7), studies on the safety of the hepatitis B vaccine (9.2.8), recent studies on the flu vaccine (9.2.9), allegations of fraud in vaccine safety research (9.2.10), and evidence that vaccines do not work very well in the first year of life (9.2.11).

9.2.1 What are the net benefits to society from widescale vaccination campaigns?

There are two radically different ways of seeing the net benefits to society from widescale vaccination programs. Public health officials often cite vaccination programs and the invention of antibiotics as two of the most important health breakthroughs in human history (Offit, 2010). Whitney, Zhou, Singleton, and Schuchat (2014) estimate that, ‘among children born during 1994–2013, vaccination will prevent an estimated 322 million illnesses, 21 million hospitalizations, and 732,000 deaths over the course of their lifetimes, at a net savings of $295 billion in direct costs and $1.38 trillion in total society costs’ (p. 352). Zhou et al. (2014) in a study of the 2009 birth cohort estimated that every dollar spent on vaccination results in $3 in direct benefits and $10 in societal benefits (p. 577). However, Rozenbaum, Van Hoek, Hak, and Postma (2010) point out that cost benefit analyses of vaccine impact are often highly dependent on assumptions about indirect effects and produce widely ranging estimates (p. 2367).

Many of those who study the history of science and medicine take a different view. They argue that changes in the political economy of states, not mass vaccination campaigns, are responsible for the large gains in life expectancy over the last 100 years (Guyer, Freedman, Strobino, & Sondik, 2000; Wootton, 2006). Over the course of the 20th century, life expectancy in the U.S. increased by 56% (Guyer et al., 2000, p. 1307). 'Between 1900 and 1998, the percentage of child deaths attributable to infectious diseases declined from 61.6% to 2%' (Guyer et al., 2000, pp. 1307 and 1314). But when Guyer et al. (2000) looked at the data from 99 years worth of annual vital statistics for the U.S. they found that the evidence does not support the intuition that the increase in life expectancy and decline in child deaths stemmed from the introduction of antibiotics and vaccines. They write, 'nearly 90% of the decline in infectious disease mortality among U.S. children occurred before 1940 when few antibiotics or vaccines were available' (p. 1314). Later they underscore this point when they write,

> Vaccination, while first used in the 18th century, became more widely implemented in the middle part of the [20th] century. Vaccines against diphtheria, tetanus, and pertussis became available during the late 1920s but only widely used in routine pediatric practice after World War II. Thus vaccination does not account for the impressive declines in mortality seen in the first half of the century (Guyer et al. 2000, p. 1315).

That is not to say that vaccines had no part in the health gains over the last century — the declines in rates of infectious disease have been impressive following widespread national vaccination campaigns (Guyer et al. 2000, p. 1315). Breyer (1993) points out

that the last few percentage points of any remedy are the most expensive and most difficult to achieve. But the fact remains that the declines in fatalities from infectious disease are largely the result of political and economic factors including ‘improved socioeconomic conditions’, ‘water treatment, food safety, organized solid waste disposal, and public education about hygienic practices’, along with ‘improvements in housing and decreased crowding in U.S. cities’ (Guyer et al. 2000, p. 1315). In the debate over vaccines the two sides are often talking past each other with supporters of the current scheme citing estimates of morbidity (disease incidence) while critics point out that changes in political economy have made a greater contribution than vaccines to declines in mortality over the last hundred years.

9.2.2 How important is herd immunity?

A common refrain in articles and studies in defence of the current vaccine schedule is that ‘maintaining high immunization rates’ is essential to creating ‘herd immunity’ (Offit, 2010). Even though the term was coined almost 100 years ago, it was not widely used until recently (Fine, Eames, & Heymann, 2011, p. 911). Today, ‘herd immunity’ carries a variety of different meanings; the common thread that connects the different definitions is the idea that the more people who are vaccinated in a population, the lower the risk of infection among susceptible individuals (Fine et al., 2011, p. 911). Widescale vaccination programs are thus said to provide ‘indirect protection’ to those who are immunocompromised or otherwise unable to receive vaccines (Fine et al., 2011, p. 911). Herd immunity has become the ‘central rationale for compulsory vaccination’ (Holland & Zachary, 2014, p. 4).

Critics of the current vaccine schedule argue that herd immunity is a myth promoted by pharmaceutical companies to sell more vaccines. They point out that the ‘herd immunity threshold’ (also called the ‘vaccine critical level’) — the proportion of the population who need to be vaccinated to provide herd immunity — keeps rising (Solomon, 2014). In the 1960s the U.S. Public Health Service claimed that it could eradicate measles by 1967 by vaccinating 55% of the population (Sencer, Dull, & Langmuir, 1967). Later the herd immunity threshold was revised upward to 70%, then 80%, 83%, 85%, and 90%, (Solomon, 2014). Now it is routine to see public health officials use 95% vaccination rates as essential for maintaining herd immunity (Offit, 2010). Fine et al. (2011) go one step further and recommend 100% immunisation rates which means that the size of the ‘herd’ that is protected through passive immunity approaches zero.

A second criticism is that the theory of herd immunity is based on observations of natural immunity even though vaccine induced immunity does not function in the same way. Natural exposure to and recovery from viruses such as measles provides lifetime immunity. Immunity from vaccines wanes over time — usually in about 2 to 10 years (Blaylock, 2009). So the argument is that models based on herd immunity from natural infections do not explain herd immunity thresholds from vaccine-induced immunity (Blaylock, 2009). At any given time over the last 50 years, upwards of 50% of the adult population did not have immunity to the various diseases for which they were vaccinated against as children (Blaylock, 2009). In a widely circulated article in *The Hill*, Dubeau (2016) asks, if most of the population does not have immunity to the various viruses that one vaccinates against (because the effectiveness has waned over time), then where are all the epidemics (that proponents of herd immunity claim would break out if the vaccination rate fell below 95%)?

Resolving this question as to the value of herd immunity potentially has important implications for autism. If herd immunity does not work as claimed, it changes all of the cost benefit analyses on which vaccine decisions are made and undermines the rationale for mandatory vaccination policies as well.

9.2.3 Is ethylmercury toxic (at the doses contained in the vaccine schedule)?

Morris Kharasch, a chemist at the University of Maryland, invented thimerosal (also spelled thiomersal) in 1927 and his patent was granted in 1928 (Kharasch, 1928). 'Thimerosal is 49% mercury by weight, in the form of ethylmercury attached to thiosalicylate' (Hertz-Picciotto, 2011, p. 847) and it has been used as an antibacterial and preservative. Eli Lilly began marketing thimerosal under the trade name Merthiolate in the 1930s and it was added to a wide range of products including antiseptic ointments, nasal sprays, topical creams, and vaccines (Baker, 2008). Antibiotics were not yet in widespread use and an antibacterial agent that could be used in a range of products was in high demand (Subcommittee on Human Rights and Wellness, 2003, p. 10). Early safety studies were primitive by modern standards. Smithburn, Kempf, Zerfas, and Gilman (1930) administered high doses of thimerosal (up to 500 mg of thimerosal which = 248 mg ethylmercury) to 22 human patients during a meningitis outbreak. Thimerosal in this case was used as the treatment itself — not as an additive or preservative. The patients did not appear to display 'anaphylactoid or shock symptoms' so later commentaries declared 'the toleration of such intravenous doses indicates a very low order of toxicity of Merthiolate for man' (Powell & Jamieson, 1931, p. 306). Geier, Sykes, and Geier (2007) note that seven of the patients were only monitored for one day

and speculate that the short observation period may have been because these seven patients died of meningitis. Only one patient was observed for 62 days but that also may be too short to measure the long term effects of ethylmercury (Geier et al., 2007, p. 577).

Powell and Jamieson (1931) divided 200 rabbits into 6 groups and injected them with different amounts of thimerosal — 15, 20, 25, 30, 35, and 40 mg per kilogram of body weight. Seven days later all of the rabbits injected with 15 mg/kg had survived and 29 of the rabbits injected with 25 mg/kg survived and 12 died; so 15 parts per million became the no observed adverse effect level (NOAEL). No behavioural changes were included and the rabbits were only studied for seven days. As I will show below, more recent studies suggest that Powell and Jamieson (1931) dramatically underestimated the toxicity of thimerosal. Later, as the approval process at the FDA became more stringent, thimerosal was grandfathered in without further safety studies because it was 'generally considered safe' as a result of its widespread use (Kirby, 2005, p. 48).

Geier et al. (2007) cite 62 studies published between 1935 and 1998 that show thimerosal is toxic to plants, animals, and people. Kennedy (2014) cites five studies that show that ethylmercury may be more toxic than methylmercury. Kennedy (2014) also points out that California's Office of Environmental Health Hazard Assessment (OEHHA) designated thimerosal a human reproductive toxin in 1990 (p. 83). In 2003, Bayer Corporation petitioned to reconsider this designation and in response the OEHHA (2004) reaffirmed its earlier ruling.

The regulatory history of thimerosal fits with the pattern of almost every other chemical reviewed in this thesis — even when there is good epidemiological data on health risks,

it can take decades or longer to get effective regulatory action. Geier et al. (2007) provide a helpful literature review of attempts to regulate thimerosal (and I am grateful to them for alerting me to the sources in this paragraph). Concerns about the toxicity of thimerosal date back to Salle and Lazarus [1935] and a sizeable literature on health harms developed over the ensuing years (Geier et al., 2007, p. 578). The FDA became concerned about the safety of over the counter drugs containing mercury in 1974 and convened an advisory panel to conduct a formal review in 1975 (Geier et al., 2007, p. 589). The Veteran's Administration and NIH funded a study by van Horn et al. [1977] that concluded that thimerosal is toxic in ophthalmic drugs (Geier et al., 2007, p. 589). The National Institute of Environmental Health Sciences funded a study by Fagan et al. [1977] that found that thimerosal is 'highly toxic' and that 'equally effective and far less toxic broad-spectrum antifungal and antibacterial antiseptics are currently available' (in Geier et al., 2007, p. 589). The FDA's advisory panel issued its report in 1980 and declared that all 18 of the products containing mercury that it reviewed were either unsafe or ineffective (Geier et al., 2007, p. 589). The panel also noted that thimerosal causes an allergic reaction in anywhere from 10 to 26% of those studied (Geier et al., 2007, p. 589). The FDA published an Advance Notice of Proposed Rules or Notice of Proposed Rules to regulate or restrict mercury content in '1980, 1982, 1990, 1991, 1994, and 1995. No action was taken on any of these occasions' (Geier et al., 2007, p. 590).

The catalyst for the current debate about mercury in vaccines and autism was an amendment by Representative Pallone (Democrat, New Jersey, 6th District) to the Food and Drug Modernization Act in 1997 that required the FDA to produce a list of 'drugs and foods that contain intentionally introduced mercury compounds' and to provide a 'quantitative and qualitative analysis of the mercury compounds on the list' (Offit &

Jew, 2003, p. 1394). This was more than a decade after the passage of the NCVIA of 1986 and the vaccine schedule had already doubled by this time. At the time three vaccines on the schedule contained thimerosal — DTaP, Hib, and hepatitis B — and all of those vaccines required multiple doses. So American children were being 'exposed to a cumulative dose of mercury as high as 187.5 µg by 6 months of age' (Offit & Jew, 2003, p. 1394). Over the years, federal agencies had set different limits for the maximum safe daily exposure of mercury — the EPA set the limit at 0.1 micrograms per kilogram of body weight; 'the Agency for Toxic Substances and Disease Registry (ATSDR) calculated the safety limit at 0.3 micrograms per kilogram per day, and the FDA officials set the limit at 0.4 micrograms per kilogram per day' (Kirby, 2005, p. 49). Prior to Representative Pallone's amendment, no one at the CDC, EPA, ATSDR, or FDA had actually done the math to figure out how much mercury American children were receiving through the expanded vaccine schedule (Kirby, 2005, p. 49). Prompted by the FDA Modernization Act, the FDA finally did the calculations and discovered that 'most American children were being exposed to levels [of mercury] in excess of federal limits' (Kirby, 2005, p. 49). 'A two-month-old child weighing 5 kilograms could have been exposed to 62.5 micrograms of mercury in a single day. This would have been 125 times more than the EPA limit for that child (0.5 micrograms per day), 42 times more than the ATSDR limit (1.5 micrograms per day), and 31 time more than the FDA limit (2.0 micrograms per day)' (Kirby, 2005, p. 49). The various federal limits were set based on ingested mercury, but injected mercury is considerably more dangerous because it bypasses the entero-hepatic pathway that the body usually uses to filter and remove toxicants (Thomas & Margulis, 2016, p. 13).

Documents turned over in a lawsuit against the pharmaceutical industry revealed that Merck was aware of the increased mercury levels in the vaccine schedule, was concerned about the possible health effects, and failed to notify regulators about it (Kennedy, 2005 and 2014). A 27 March 1991 memo by renowned vaccine inventor and Merck scientist Maurice Hilleman, 'warned Gordon Douglas, then-president of the company's vaccine division, that six-month-old children administered the shots on schedule would suffer mercury exposures 87 times the daily Swedish safety standards' (Kennedy, 2014, p. 89). 'Hilleman recommended that thimerosal use be discontinued, "especially where use in infants and young children is anticipated"' (Kennedy, 2014, p. 90). 'Hilleman also noted that the drug industry knew of non-toxic alternatives to thimerosal' while also expressing concerns about cost (Kennedy, 2005, p. 7). Douglas, and by extension Merck, ignored Hilleman's warning and between 1991 (when the memo was written) and 1999 (when thimerosal was eventually removed from some vaccines) ACIP added seven additional shots containing thimerosal to the national childhood vaccine schedule (Kennedy, 2005, p. 8).

So how does anyone justify the continued use of mercury in vaccines more than 80 years after safety concerns were first raised and more than four decades after the FDA expressed concerns about mercury in medications? Those who support the current schedule argue that it has been taken out of most childhood vaccines and that the toxicokinetics of ethylmercury are different than the toxicokinetics of methylmercury and therefore ethylmercury is safer than methylmercury (Offit & Jew 2003).

There are reasons to be sceptical about these arguments. Yes, thimerosal has been removed from most vaccines on the U.S. schedule for children (and replaced with

increased aluminium) but thimerosal is still in three different brands of multidose flu vaccines (Fluvirin, Flulaval, Fluzone), one meningococcal vaccine, and three tetanus-diphtheria vaccines (Thomas & Margulis, 2016, p. 14). The CDC and its defenders want to have it both ways — they want credit for proceeding from an abundance of caution in removing thimerosal from many vaccines on the childhood schedule but then inexplicably, they added it even earlier in the developmental window when the fetus is most vulnerable to toxicants. The toxicokinetics of ethylmercury (and the similarities and differences between methylmercury and ethylmercury) are not well understood (Clarkson & Magos, 2006; Clarkson, Vyas, & Ballatori, 2007). IOM (2001) estimates that 'methylmercury has a whole-body half-life in the range of 70 to 80 days' (p. 39). IOM (2001) does not venture a guess for the half-life of ethylmercury, saying simply that it is 'not known' (p. 39). Dórea, Farina, and Rocha (2013) argue that *in vitro* studies show remarkable similarities between ethylmercury and methylmercury but that *in vivo* studies suggest distinct toxicokinetics (p. 700) But then they go on to write, 'a simultaneous exposure to both etHg and meHg might result in enhanced neurotoxic effects in developing mammals' (Dórea et al., p. 700). Given that methylmercury (meHG) is already in the bodies of most Americans, simultaneous exposure (when ethylmercury is injected) is more than just a hypothetical scenario.

Jafari, Rostampou, Fallah, and Hesami (2017) performed a meta analysis of 44 studies on 'the association between mercury levels and autism spectrum disorders' and found that the 'mercury level in whole blood (Hedges' [g] = 0.43; CI: 0.12, 0.74), red blood cells (Hedges' [g] = 1.61; CI: 0.83, 2.38), and brain (0.61ng/g; CI: 0.02, 1.19) was

significantly higher in ASD patients than healthy subjects' (p. 289).[14] In section 9.2.9, I will discuss in more detail a study showing an association between the flu shot during pregnancy and ASD.

9.2.4 Is aluminium toxic (at the doses contained in the vaccine schedule)?

Nearly 100 years ago, scientists discovered that simply injecting killed viruses into people usually did not produce a robust immune response. So they started experimenting with adjuvants — substances that shock the body into producing a greater immune response. Ramon [1925] pioneered the use of adjuvants including 'starch, plant extracts, or fish oils combined with the diphtheria toxoid administered to horses' (Garçon, Hem, & Friede, 2018, p. 61). Glenny, Pope, and Waddington [1926], in experiments for the Pasteur Institute observed that if they combined aluminium potassium sulphate (also known as alum) with diphtheria toxoid that it improved the immune response to the vaccine (Garçon et al., 2018, p. 61). Over time various aluminium compounds were added to many vaccines, 'aluminum salts, in the form of aluminum oxyhydroxide or hydroxyphosphate, are the most widely used adjuvants in human vaccines' (Garçon et al., 2018, p. 61). However, 'there is still no consensus regarding the mechanisms by which aluminium-containing adjuvants potentiate the immune response' (Garçon et al., 2018, p. 66). Aluminium adjuvants have been injected 3 billion times into human bodies (Garçon et al., 2018, p. 66) and yet scientists are still not sure how they work.

[14] 'A Hedges' *g* is a measure of effect size... a *g* of 1 indicates the two groups differ by 1 standard deviation, a *g* of 2 indicates they differ by 2 standard deviations' (Glen, 2016).

The recent history of thimerosal and aluminium adjuvants are intertwined in important ways. Thimerosal was removed from many vaccines starting in 1999; manufacturing of many thimerosal containing vaccines stopped in 2001, but vaccines that were not past their expiration date were allowed to remain on the market until January 2003 (CDC, 2015a). The removal of thimerosal from vaccines was an extremely important natural experiment that would reveal whether in fact ethylmercury was responsible for the autism epidemic. But the CDC took actions during this period that introduced confounding factors that muddied the waters (Miller, 2016b). In February 2000, ACIP added 4 doses of the pneumococcus vaccine to the childhood schedule and each dose contains 125 µg of aluminium (Miller, 2016b, p. 109). In 2002, ACIP added two doses of influenza vaccine to the schedule for all children 6 to 23 months of age even though the majority of doses contain thimerosal (Miller, 2016b, p. 109). In 2004, ACIP recommended adding the flu vaccine for pregnant women even though thimerosal has been shown to cross the placenta barrier and the blood brain barrier in the fetus is not yet developed at that stage (Miller, 2016b, p. 109). In 2005, ACIP added two doses of hepatitis A vaccine to the childhood schedule and each dose contains 250 µg of aluminium (Miller, 2016b, p. 109). In 2011, ACIP added DTaP to the schedule for pregnant women which contains 625 µg of aluminium (Miller, 2016b, p. 109) even though aluminium has been shown in animal studies to cross the placenta barrier and foetal blood brain barrier (Yumoto et al. 2001). In all during this period, ACIP added to the schedule as much 25 µg of thimerosal and 625 µg of aluminium for pregnant women along with up to 50 µg of thimerosal and 1,000 additional µg of aluminium for children in the first two years of life (Miller, 2016b, p. 109). Offit, Reiss, and others routinely claim that the ‘removal of thimerosal from the schedule’ proves that vaccines are safe which is disingenuous because thimerosal was not completely removed from the

children's schedule, it was also added to the schedule for pregnant women, and the aluminium content increased for both pregnant women and young children and all of those are confounding factors. Regarding thimerosal, the actions of ACIP members during this period give lie to the notion that they are committed to proceeding out of an abundance of caution. Regarding aluminium, ACIP's actions appear to be guided by the belief that such adjuvants are safe. However, I will show below that the evidence used to demonstrate the safety of injected aluminium is weak.

Unlike metals such as copper or iron, 'aluminium has no known beneficial physiological action in the human body' (Morris, Puri, & Frye, 2017, p. 1347). The FDA, CDC, and vaccine spokespeople like Offit and Jew (2003) all tend to refer to aluminium adjuvants as 'aluminium salts' whereas critics point out that these are metals and often refer to 'aluminium nanoparticles'. Proponents tend to express units of adjuvants in milligrams whereas critics tend to write the units in micrograms both of which appear to be discursive choices to minimise or maximise the perception of the quantity. The technical names of the three aluminium adjuvants used in vaccines are crystalline aluminium oxyhydroxide (AlOOH), aluminium phosphate (made up of both Al-OH and Al-OPO_3), and potassium aluminium sulphate (alum) Al$K(SO_4)$ (Garçon et al., 2018, pp. 63–64). Proponents point out that 'aluminium is the most abundant metal' on the surface of the earth; they also argue that aluminium adjuvants have been used in vaccines for over 80 years and then conclude that therefore it is safe (Offit & Jew, 2003; Garçon et al., 2018). Critics argue that the 80 year history of aluminium adjuvants fits their narrative just as well if not better (it is unclear whether Sukhareva's patients were exposed to aluminium adjuvants but Kanner's and Asperger's independent discoveries of autism occurred after the introduction of aluminium adjuvants in vaccines). The

scientific case in support of the safety of aluminium adjuvant is based mainly on experiments by Priest, Newton, Day, Talbot, and Warner (1995), and Flarend et al. (1997), and toxicokinetic models developed by Keith, Jones, and Chou (2002) for the ATSDR and Mitkus, King, Hess, Forshee, and Walderhaug (2011) for the FDA. Taking each of these studies in turn:

Priest et al. (1995) injected 0.7 µg of the radioactive isotope ^{26}Al into a healthy 41-year old Caucasian male (p. 287). Blood samples were taken regularly for 880 days, urine and faeces were collected for 14 days, and whole-body radioactivity was measured daily for the first 10 days and then less frequently over a period of 1,178 days (Priest et al., 1995, p. 289). They found that 65% of the ^{26}Al was excreted in the first 24 hours, that elimination continued but at a slower rate after that, and that 4% of the ^{26}Al was still in the body after three years (Priest et al., 1995, p. 289). They speculated but were not able to confirm that the 4% of the ^{26}Al that remained was deposited in the bone and that further depletion depended on bone turnover (Priest et al. 1995, p. 292). Two of the largest aluminium trade associations in the world funded the study — 'the Aluminum Association, Washington D.C. and the International Primary Aluminium Institute, London' (Priest et al., 1995, p. 292).

Flarend et al. (1997) injected intramuscularly 850 µg of aluminium hydroxide adjuvant (labeled with radioactive ^{26}Al), into each of two New Zealand White rabbits and 850 µg of aluminium phosphate adjuvant (also labeled with radioactive ^{26}Al) into each of two other New Zealand White rabbits. Blood and urine were collected before the start of the experiment and regularly for 28 days after injection (Flarend et al., 1997). The rabbits were killed on day 28 and tissues samples were taken from the 'brain, heart, left kidney,

liver, mesenteric lymph node, and spleen'; bone samples from the femur were taken but lost and the brain sample of one of the rabbits was lost as well (Flarend et al., 1997, p. 1315).

Over the course of 28 days, 6% of the aluminium hydroxide adjuvant and 22% of the aluminium phosphate was eliminated via urine (Flarend et al., 1997, p. 1316). The adjuvant that remained in the tissues was distributed as follows: 'kidney > spleen > liver > heart > lymph node > brain' (Flarend et al., 1997, p. 1317). In the discussion section, Flarend et al. (1997) declared that since the increase of aluminium in the blood of these rabbits was relatively small, the corresponding increase in plasma aluminium concentration in adult humans could be projected at 0.8% and that therefore aluminium adjuvants are safe (Flarend et al., 1997, p. 1318). This conclusion rests on two leaps of logic — that the conversion from rabbits to people is correct and that low levels in the blood cause no harms. No evidence is supplied to support either assertion. Furthermore, Flarend et al., (1997) performed no behavioral tests on the rabbits and they have no measure of what the long term effects of the aluminium deposits in the brain and other tissues would have been. It is also clear from the discussion section (and the small sample size and the fact they did not bother to fix problems like losing the brain tissue of 25% of their sample) that they saw this study as just a preliminary experiment and that other studies on aluminium adjuvant safety would surely follow. However, further studies of this type have not been done and public health officials have used Flarend et al. (1997) when they attempt to model the toxicity of aluminium in the vaccine schedule. Flarend et al. (1997) 'was supported in part by the Showalter Trust' (p. 1318); Robert E. Showalter was a former Vice-President and Board Member of Eli Lily and Company — one of the largest vaccine producers in the world.

Keith, Jones, and Chou (2002) at ATSDR built a model to estimate ‘infant body burdens during the first year of life for breast milk and formula diets and for a standard vaccination schedule’ (p. S13). They wanted to see whether infant body burdens exceeded the minimal risk level (MRL) of 2 mg Al/kg of body weight per day previously established by ATSDR (1999) for *ingested* aluminium (Keith et al., 2002). They rely on Priest et al. (1995) for the transfer rate from blood, the elimination rates, and retention functions and rely on Flarend et al. (1997) for the distribution pattern of aluminium in the body. They calculate that the body burden from aluminium in vaccines ‘exceeds that from dietary sources’ but is below the MRL except on the day of birth as a result of the hepatitis B vaccine and at the two-month vaccinations; the four month and six month vaccinations also reach the MRL but do not exceed it (Keith et al., 2002, p. S15).

The Keith et al. (2002) model was problematic for a number of reasons. The 1999 ATSDR MRL was based on ingested aluminium which is not comparable to injected aluminium. The Priest et al. (1995) and Flarend et al. (1997) studies on which Keith et al. (2002) depends are both characterised by a financial conflict of interest and their sample sizes are too small to be statistically valid. Keith et al. (2002) takes no account of differences in the blood brain barrier or renal function between adults and infants. Even with an MRL that was arguably too high, the standard vaccine schedule exceeded it. Then ACIP added even more aluminium containing vaccines to the schedule pushing the exposure levels even further above the MRL. ATSDR (2008) lowered the MRL to 1 mg Al/kg of body weight per day based on new animal studies on the dangers of

ingested aluminium. The federal government, rather than changing the vaccine schedule, decided to create a new toxicokinetic model to show that the vaccine schedule was safe.

Mitkus et al. (2011) was written by five employees of the FDA, Center for Biologics Evaluation and Research and it updates the model from Keith et al. (2002) in light of ACIP increasing aluminum content in the schedule even as ATSDR was showing harms from ever-lower doses. As I showed in chapter 5, the FDA is a conflicted party because it relies on fees from companies they regulate and because they accept corporate donations through the Reagan-Udall Foundation for the FDA, Inc. Given the stakes, it is problematic, to say the least, that this paper was not written by an independent body. Mitkus et al. (2011) change a number of assumptions about aluminium disposition and toxicity and conclude that 'the body burden of aluminum from vaccines and diet through an infant's first year of life is significantly less than the corresponding safe body burden of aluminum modeled using the [ATSDR (2008)] regulatory minimum risk level' (p. 9538). But that is not what their data show. Their data shows that the aluminium in the birth dose of hepatitis B vaccine and the vaccines in the 2 month visit exceed the MRL, the 4 month vaccines meets the MRL, and the 6 month vaccines nearly reach the MRL (Mitkus et al. 2011, p. 9541). They call these periods that exceed the MRL, 'brief excursions' without providing any discussion of the potential toxicological risks of those 'excursions' (Mitkus et al. 2011, p. 9541). Later in the paper they relax one of the assumptions (about the rate of release of aluminium from the injection site) and the 'brief excursions' then fall below the MRL and they thus declare the schedule safe (Mitkus et al., 2011, pp. 9541–9542).

Mitkus et al. (2011) acknowledge that there are reasons to question some of the assumptions in their model. The retention rate of aluminum that they use ‘is based on results for only one person’ — the adult male volunteer described above in Priest (1995) (Mitkus et al., 2011, p. 9542). They go on to say that ‘pharmacokinetic data in infants or in more than one adult’ would have been desirable and then quickly close the door to that possibility by writing, ‘an expansion of this study is unlikely’ (Mitkus et al., 2011, p. 9542). Then they acknowledge that their ‘estimate of the rate and extent of absorption of aluminum hydroxide and [aluminium] phosphate following intramuscular injection [that comes from Flarend et al., 1997], are based on data from only two rabbits for each of the two adjuvants tested’ — however they failed to acknowledge that all of the bone samples were lost as was the brain sample of one of the rabbits (Mitkus et al., 2011, p. 9542). So by their own admission, the safety of the vaccine schedule, administered to more than 90% of all children in the U.S., comes down to a model based on estimates of the toxicokinetics of aluminium from one adult male human and three rabbits.

Criticisms of Mitkus et al. (2011) have been withering. Masson, Crépeaux, Authier, Exley, and Gherardi (2017) point out that Mitkus et al. (2011) once again used an ingested MRL that is not comparable to injected aluminium toxicity, failed to distinguish between different types of aluminium adjuvants, misunderstood or misrepresented aluminium transport in the body, ignored animal studies that show that the ATSDR MRL is too high (by a factor of 17), and overestimated the rate of elimination of aluminium from the body, amongst other concerns. Masson et al. (2017) was funded by an interesting mix of institutions — ANSM (roughly the French equivalent of the FDA), the Ile-de-France Region of the PICRI Program (Institutions

and Citizens for Research and Innovation), and well known vaccine safety critics, the Children's Medical Safety Research Institute (CMSRI).

Critics of vaccine safety have created a large body of research on the toxicity of aluminium and the dangers of aluminium in vaccines.

Christopher Exley, perhaps the world's leading expert on aluminium toxicity, has authored 98 journal articles on the toxicity of aluminium beginning with toxicokinetics in animals, then studying the possible role of aluminium in Alzheimer's Disease, and more recently looking at whether aluminium in vaccines might be a factor in causing autism. Christopher Shaw and Lucija Tomljenovic, both at the University of British Columbia, have produced more than 20 studies on aluminium toxicity and many of them have focused on the possible role of aluminium in ASD. The volume of critical literature is so large that it is not possible to cover it all in this section so I will highlight a few key studies.

Miller (2016b) provides a brief historical literature review of critical aluminium studies including a case of industrial aluminium poisoning [Spofforth, 1921] and animal experiments that showed harm when aluminium hydroxide cream was applied to the brains of monkeys [Chusid, Pacella, Kopeloff, & Kopeloff, 1951; Driver, Ettlinger, Moffett, & St. John-Loe, 1968]. Baylor, Egan, and Richman (2002) note that 'the British Ministry of Health recommended aluminium-free vaccines in 1957' (p. S20).

Bishop, Morley, Day, and Lucas (1997) randomly assigned 227 premature infants who required intravenous feeding to receive either standard feeding solution (that contained

25 µg of aluminium per decilitre) or a special feeding solution (that contained 2.2 µg of aluminium per decilitre); the neurodevelopment of the surviving infants (*n* = 182) was then assessed at 18 months of age (p. 1557). They found that the 'aluminum exposure from the standard intravenous solutions was... associated with a mean loss of one point on the Bayley Mental Development Index per day of full intravenous feeding, after adjustment for potentially confounding factors' (Bishop et al., 1997, p. 1561). Long-term exposures were associated with even more severe outcomes. 'In infants fed intravenously for 10 or more days, those receiving the standard solution had a major (10 point) deficit in their Mental Development Index and were twice as likely to have a Mental Development Index below 85' which is a key threshold that indicates the risk of later learning problems (Bishop et al., 1997, p. 1561).

Zheng (2001) shows that, in animal studies, aluminium exposure increases the permeability of the blood-brain barrier. Tomljenovic and Shaw (2011a), ran a correlation analysis between rising amounts of aluminium in national vaccine schedules around the world and rising prevalence rates of autism. They found that

> (i) children from countries with the highest ASD prevalence appear to have the highest exposure to Al from vaccines; (ii) the increase in exposure to Al adjuvants significantly correlates with the increase in ASD prevalence in the United States observed over the last two decades (Pearson $r=0.92$, $p<0.0001$); and (iii) a significant correlation exists between the amounts of Al administered to preschool children and the current prevalence of ASD in seven Western countries, particularly at 3–

> 4 months of age (Pearson r=0.89–0.94, p=0.0018–0.0248)' (Tomljenovic and Shaw, 2011a, p. 1489).

What is more, they argue that their results satisfy eight out of nine of Hill's (1965) criteria for establishing causality. Tomljenovic and Shaw (2011a) was supported by the Katlyn Fox Foundation founded by a mother who lost her daughter to Sudden Infant Death Syndrome following vaccination and the Dwoskin Family Foundation that funds vaccine safety research among other areas. Christopher Shaw is also the chair of the Scientific Advisory Board for the CMSRI that was founded by Claire Dwoskin.

The Global Advisory Committee on Vaccine Safety (GACVS) at the World Health Organization (WHO) in their meeting of 6–7 June 2012 felt compelled to respond to Tomljenovic and Shaw (2011a and 2011b). The GACVS called the two papers 'seriously flawed'; they pointed out that Tomljenovic and Shaw (2011a and 2011b) are ecological studies that are best used for generating hypotheses rather than drawing causal comparisons (WHO, 2012). Then GAVCS went one step further and held up Mitkus et al. (2011) as 'a comprehensive risk assessment that further supports the clinical trial and epidemiological evidence of the safety of aluminium in vaccines' (WHO, 2012). Given everything that is known about the limitations of Mitkus et al. (2011) to call it 'comprehensive' is not credible and raises troubling questions about the objectivity of the GACVS and WHO.

Khan et al. (2013) injected intramuscularly three different mice strains with 18 μg of aluminium oxyhydroxide adjuvant — a dose designed (via allometric conversion) to match the aluminium dose given to children via the U.S. vaccine schedule. They found

that aluminium oxyhydroxide adjuvant was well tolerated in normal mice but that aluminium nanoparticles ended up in the brains of mice specifically bred with a weak blood brain barrier or high tissues levels of what is called CCL2 — a key protein in the immune system (Khan et al. 2013, p. 16). The authors concluded that 'continuously escalating doses of this poorly biodegradable adjuvant in the population may become insidiously unsafe...' (Khan et al., 2013, p. 1). The research was supported by funding from two French patients' associations representing those suffering from muscle diseases (Khan et al., 2013, p. 16).

Crépeaux et al. (2017) injected aluminium oxyhydroxide (known as Alhydrogel) adjuvant into mice at 200, 400 and 800 µg/kg of body weight. They found that Alhydrogel does not follow a linear dose response curve and that the group exposed to lower doses (200 µg/kg) exhibited more neurobehavioral changes and had higher levels of cerebral Al levels than groups exposed to higher doses (Crépeaux et al. 2017, p. 48). Further testing revealed that the 200 µg dose was composed exclusively of 'small aluminium nanoparticles' that they speculated may travel into the brain more easily. One of the important takeaways from their study is that the classic 'the dose makes the poison' rule of toxicology does not appear to apply to Alhydrogel — the most used adjuvant in vaccines today (Crépeaux et al. 2017, p. 48).

Mold, Umar, King, and Exley (2017) examined the post-mortem brain tissue of four men and one woman who had received a diagnosis of autism during their lives. House, Esiri, Forster, Ince, and Exley (2012) had previously conducted a study of aluminium in the brain tissue of 60 donors; based on that study, Mold et al. (2017) established baselines of ≤1 µg/g dry weight as 'pathologically benign', ≥2.0 µg/g dry weight as

‘pathologically concerning’, and ≥3.0 µg/g dry weight as ‘pathologically significant’ (p. 78). ‘The brains of all 5 donors had at least one tissue sample with a pathologically-significant content of aluminium’ (Mold et al., 2017, p. 78). They commented, ‘We recorded some of the highest values for brain aluminium ever measured in healthy or diseased tissues in these male ASD donors including values of 17.10, 18.57, and 22.11 µg/g dry weight’ (Mold et al., 2017, p. 81) with the only similar comparator being ‘a 42 year old male with familial Alzheimer’s disease’ (Mirza, King, Troakes, & Exley, 2017). Mold et al. (2017) has been criticised for small sample size (n = 5), not having a control group, and the fact that it was funded by the CMSRI — a well-known vaccine safety advocacy group (Gorski, 2017).

9.2.5 Are other vaccine ingredients toxic (at the doses contained in the vaccine schedule)?

Thimerosal and the three types of aluminium adjuvants are just four out of hundreds of vaccine ingredients. The CDC (2015b) ‘Pink Book’ provides a complete list of what it calls ‘excipients and media’ gathered from vaccine product inserts developed as part of the FDA approval process. Many of these other ingredients including polysorbate 80, neomycin, monosodium glutamate, the use of human and animal cell cultures, and borax are also subject to fierce debate regarding safety. The presence of formaldehyde has divided vaccine safety groups with some raising concerns (Raines, 2015) and others arguing that ‘there is no clear evidence it is harmful and there are good theoretical and evidence-based reasons why it is not likely to cause harm other than local inflammation at the injection site’ (Vaccine Papers, 2015). The FDA (2014b) and CDC (2015b) maintain that these additional ingredients are safe at the doses contained in the schedule.

However, there is little research on long-term effects of many of these ingredients and there is almost no research on synergistic effects between these ingredients and between these ingredients and other chemicals (hormones, toxicants) already in the body.

9.2.6 Studies showing no association between vaccines and autism

In chapter 1, I showed that more than 20 scientific studies have looked at the association between vaccines and autism and concluded that there does not appear to be an association (Fombonne & Chakrabarti, 2001; Madsen et al., 2002; Mäkelä, Nuorti, & Peltola, 2002; Pichichero, Cernichiari, Lopreiato, & Treanor, 2002; Hviid, Stellfeld, Wohlfahrt, & Melbye, 2003; Madsen et al., 2003; Nelson & Bauman, 2003; Stehr-Green, Tull, Stellfeld, Mortenson, & Simpson, 2003; Verstraeten et al. 2003; Wilson, Mills, Ross, McGowan, & Jadad, 2003; Andrews et al., 2004; Heron & Golding, 2004; Smeeth et al., 2004; Honda, Shimizu, & Rutter, 2005; Fombonne et al., 2006; Miles & Takahashi, 2007; Thompson et al., 2007; Baird et al., 2008; Hornig et al. 2008; Schechter & Grether, 2008; and Tozzi et al., 2009). Handley (n.d.) has created a website that provides detailed descriptions of the flaws in study design and the conflicts of interest of the authors in connection with most of these studies. Even though randomised double blind controlled trials are widely recognised as the gold standard in medicine, none of these studies has a proper control group of unvaccinated children. Supporters of the status quo openly acknowledge that this research remains undone. Gerber and Offit (2009) write ‘No studies have compared the incidence of autism in vaccinated, unvaccinated, or alternatively vaccine children...’ (p. 460). Then they go on to argue, ‘These studies would be difficult to perform because of the likely differences among these 3 groups in health care seeking behavior and the ethics of experimentally

studying children who have not received vaccines' (Gerber & Offit 2009, p. 460). Offit (2010) writes, 'It would be, of course, an entirely unethical experiment. No investigator could prospectively study children who are denied a potentially lifesaving medical product. And no university's or hospital's institutional review board worth its salt would ever approve such a study' (p. 162). Gerber and Offit are not outliers here, IOM (2013) also acknowledged that this research has not been done and argued that 'it would be unethical to conduct such a study'.

Regarding the practical claim that a vaccinated vs. unvaccinated study would be difficult to perform, the evidence suggests that this is untrue. In spite of widespread vaccine mandates in almost all 50 states there are still pockets of unvaccinated children including some religious groups (the Amish), clients of Homefirst Health Services in metropolitan Chicago, and homeschooled populations (although such comparisons would not be an RCT). Smith, Chu, and Barker (2004) even produced a study for the CDC, called 'Children who have received no vaccines: who are they and where do they live?' Furthermore, the challenge of limiting confounding variables is not impossible. Indeed, the Institute of Medicine (2013) concluded, 'It is possible to make this comparison through analysis of patient information contained in large databases such as the VSD [Vaccine Safety Datalink]' (p. 17) before going on to claim that a true RCT would be unethical.

But the claim that a true RCT of the vaccine schedule (or even individual vaccines against a placebo, more on that below) would be unethical appears to be an example of begging the question, the fallacy in which the writer or speaker assumes the statement under examination to be true. There are valid reasons to question whether the vaccine

schedule is safe — additives like thimerosal in the flu shot were initially grandfathered in and not subject to rigorous modern safety testing, there is more aluminium in the schedule than ever before, the schedule is larger than at any point in history, the U.S. schedule contains more doses of more vaccines than any other country, the schedule contains genetically modified vaccines that did not exist when the NCVIA was passed — to name just a few examples. The logic of Gerber, Offit, and the IOM is that because the vaccine schedule is safe, it would be unethical to study whether it is safe. They simply assume away the question.

Because vaccines are required for almost all U.S. children (in order to access day care and schools) the stakes are higher and because injection bypasses the body's usual filtering mechanisms in the alimentary canal the potential risks are higher, making the need for proper RCTs greater than with any other pharmaceutical product. It is also not true that no vaccinated vs. unvaccinated studies exist which I explain in detail below.

9.2.7 Vaccinated vs. unvaccinated studies

In the absence of government funded double blind RCTs on the safety of the vaccine schedule (or even prospective or retrospective comparisons between vaccinated and unvaccinated groups), many vaccine safety and autism advocacy groups have funded their own surveys and studies. As I pointed out in chapter 1, this is an example of what Moore (2006) calls Activist-Initiated Participatory Science and in some cases these surveys and studies might be considered part of what Rose (2017) calls the 'Autism Literary Underground'.

Are these studies valid? It is hard to know. The same issues of the funding effect apply in these cases as with the corporate and government funded studies — any COI no matter how small has been shown to change research outcomes. Most of these are conflicted studies so there is reason for scepticism. The situation is made considerably more complicated by the fact that mainstream public health institutions refuse to conduct vaccines safety studies with an unvaccinated control group — so there are no studies that contradict these findings. It makes for an untenable situation — on the one hand a number of studies by advocacy groups show startling results; on the other hand mainstream actors claim that these results are unlikely to be true and then refuse to conduct the sort of studies that would resolve the matter. But there are two studies that are not characterised by a financial conflict of interest (Gallagher & Goodman, 2008 and 2010) and their results are in line with the findings of the other vaccinated vs. unvaccinated studies reviewed in this section.

The NVKP (Nederlandse Vereniging Kritisch Prikken) (Dutch Association of Critical Diseases) is a volunteer organisation in Holland founded by ‘a group of people who had experience with negative consequences of vaccination’ (NVKP, 2006). In 2004, the NVKP conducted a survey of parents of 635 children that included both members of NVKP as well as non-members (NVKP, 2006). After filling out a questionnaire, the survey team followed up to request supplementary information and ask control questions (not specified) (NVKP, 2006). Partially vaccinated results were excluded as were incomplete questionnaires (NVKP, 2006). The final sample included 312 fully vaccinated children and 231 completely unvaccinated children (NVKP, 2006). The fully vaccinated had lower incidence of German measles, whooping cough, and heart rhythm disorder/heart murmur (NVKP, 2006). On every other measure — from allergies to

asthma to diabetes and febrile convulsions — the unvaccinated children were healthier (NVKP, 2006). Furthermore, there were 8 autism cases in the fully vaccinated population and none in the unvaccinated population (NVKP, 2006). Problems with this study include recall bias, selection bias, excluding the partially vaccinated results, source of funding bias, not peer reviewed, and not published in a medical journal.

Generation Rescue (2007) contracted with the polling firm Survey USA to conduct a telephone survey to measure health outcomes between vaccinated and unvaccinated children. Generation Rescue noted that phone surveys are also used by the CDC to estimate prevalence of autism nationwide and that the CDC has previously defended telephone surveys as highly reliable (Generation Rescue, 2007). Survey USA collected data on 9,175 boys and 8,499 girls in five counties in California and four counties in Oregon (Generation Rescue, 2007). They found that 'vaccinated boys were 155% more likely to have a neurological disorder (RR = 2.55), 224% more likely to have ADHD (RR = 3.24), and 61% more likely to have autism' (RR = 1.61) (Generation Rescue, 2007). One of the things that is intriguing about this survey is that there was *negative* correlation between vaccination status and autism in girls — unvaccinated girls in the survey had an autism rate of 3% while fully vaccinated girls in the survey had an autism rate of 1% (Generation Rescue, 2007). Gorski (2007) and others raised concerns about study design including possible reporting bias (as it was an automated phone poll, parents of neurotypical children may have hung up before completing the survey at a higher rate than parents of children on the spectrum). The study was never published in an academic journal and has since disappeared from the Generation Rescue website; old links to the study are broken and no explanation has been posted for its removal (I located cached versions of the study available through the Internet Archive).

More recently, Generation Rescue and the CMSRI funded two ambitious vaccinated vs. unvaccinated studies led by Anthony Mawson, a visiting professor of epidemiology at the Jackson State University School of Public Health (Mawson, Ray, Bhuiyan, & Jacob, 2017a; and Mawson, Bhuiyan, Jacob, & Ray, 2017b). Mawson has a thirty year career in epidemiology and a long publishing track record including two publications in *The Lancet* (Jackson State University, n.d.) so he brings more credibility to the debate than some prior efforts by autism advocacy groups.

Mawson and his co-authors acknowledged the financial conflict of interest and took pains to point out their editorial independence, stating, 'The funders had no role or influence on the design and conduct of the research or the preparation of reports' (Mawson et al., 2017a, p. 10). Mawson and his co-authors designed 'a cross-sectional survey of homeschooling mothers on their vaccinated and unvaccinated biological children ages 6 to 12' and they worked with the National Home Education Research Institute (NHERI), a homeschool think tank, to implement the study (Mawson et al., 2017a, p. 3). They obtained results for 666 children of which 405 (61%) were vaccinated and 261 (39%) were unvaccinated (Mawson et al., 2017a, p. 1). The study controlled for race, gender, adverse environment (not defined), antibiotic use during pregnancy, preterm birth, and ultrasound during pregnancy (Mawson et al., 2017a, p. 8). As one would expect, they found that vaccinated children 'were significantly less likely than the unvaccinated to have had chickenpox (7.9% vs. 25.3%; OR = 0.26; CI: 0.2, 0.4) and whooping cough (pertussis) (2.5% vs. 8.4%; OR = 0.3; CI: 0.1, 0.6), and less likely, but not significantly so, to have had rubella (0.3% vs. 1.9%; OR = 0.1; CI: 0.01, 1.1)' (Mawson et al., 2017a, p. 4).

The results for chronic illness were a different story. ‘Vaccinated children were significantly more likely than the unvaccinated to have been diagnosed with the following: allergic rhinitis (10.4% vs. 0.4%; OR = 30.1; CI: 4.1, 219.3), other allergies (22.2% vs. 6.9%; OR = 3.9; CI: 2.3, 6.6), eczema/atopic dermatitis (9.5% vs. 3.6%; OR = 2.9; CI: 1.4, 6.1), a learning disability (5.7% vs. 1.2%; OR = 5.2; CI: 1.6, 17.4), ADHD (4.7% vs. 1.0%; OR = 4.2; CI: 1.2, 14.5), ASD (4.7% vs. 1.0%; OR = 4.2; CI: 1.2, 14.5), any neurodevelopmental disorder (i.e., learning disability, ADHD or ASD) (10.5% vs. 3.1%; OR = 3.7; CI: 1.7, 7.9), and any chronic illness (44.0% vs. 25.0%; OR = 2.4; CI: 1.7, 3.3)’ (Mawson et al., 2017a, p.4).

Mawson, Bhuiyan, Jacob, and Ray (2017b) conducted a separate analysis of the data on preterm children, vaccination status, and health outcomes. Preterm in this case is ‘defined as birth occurring before 37 completed weeks of gestation’ (Mawson et al., 2017b). The preterm population in the U.S. is large: ‘in 2012, 450,000 babies (11%) were born preterm in the United States, resulting in 35% of all infant deaths in that year’ (Mawson et al., 2017b, p. 1). Autism rates are higher in extremely preterm infants: Johnson et al. [2010] found that 8% of extremely preterm infants were later diagnosed with autism; Padilla et al. [2017] found 27.4% of their sample of 84 extremely preterm (<27 weeks of gestation) infants were later diagnosed with autism (Mawson et al., 2017b, p. 2). The CDC’s vaccine schedule makes no exceptions for preterm births. ‘Preterm infants receive the same doses of the recommended vaccines and on the same schedule as term infants’ — even though vaccine safety studies conducted by manufacturers specifically exclude preterm infants and clinical practice shows that

vaccine adverse events in this population are significantly higher than in the population of children born at full term (Mawson et al., 2017b, p. 2).

Mawson et al. (2017b) found ‘no association... between preterm birth and neurodevelopmental disability [NDD defined as learning disability, ADHD, and/or ASD] in the absence of vaccination’ (Mawson et al., 2017b, p. 1). Preterm birth coupled with vaccination increased the odds of NDD by more than five-fold as compared to non-preterm children who were vaccinated (48% vs. 8.9%; OR = 5.4; CI: 2.5, 11.9) (Mawson et al., 2017b, p. 5). Preterm birth coupled with vaccination increased the odds of NDD by more than twelve-fold compared to preterm birth without vaccination (48% vs. 0%; OR = 12.3; CI: 0.67, 224.2, p=.024; but ‘not technically significant because no child in the sample with an NDD was both preterm and unvaccinated’) (Mawson et al., 2017b, p. 5). Preterm birth coupled with vaccination increased the risk of NDD by more than fourteen-fold ‘compared to children who were neither preterm nor vaccinated’ (48% vs. 3.3%; OR = 14.5; CI: 5.4, 38.7) (Mawson et al., 2017b, p. 5). If Mawson et al. (2017b) are correct, then the high rates of NDD amongst children born preterm may be due almost entirely to the effect of vaccination, rather than the early arrival. Acknowledged limitations of the study include small sample size, health outcomes were not validated by clinical records, and possibility of under-estimating morbidity in unvaccinated children because they are less likely to see a doctor (Mawson et al., 2017b, p. 6). It is also problematic to lump learning disabilities, ADHD, and ASD together and Mawson et al. (2017b) acknowledge that they did this because the sample sizes were so small (p. 3). They cite Surén et al. [2012] as showing a high degree of overlap between these three diagnoses and yet it would have been better to present the results separately

as well (Mawson et al., 2017b, p. 3). The Mawson et al. (2017a, 2017b) results highlight the need for immediate further study with larger sample sizes.

The journey to publication for the two Mawson et al. articles was winding. The two articles were submitted to major journals without success. Eventually abstracts of the two studies were published online in *Frontiers in Public Health*, however following a behind the scenes lobbying effort, the studies disappeared from the website without explanation; they were not retracted, they just vanished (Handley, 2017). Then they were published in the obscure, *Journal of Translational Science*. Once again pressure behind the scenes resulted in the studies disappearing without explanation, and then, after a period of about two weeks, they suddenly reappeared (Handley, 2017).

Paul Thomas is a pediatrician in Portland, Oregon who is an outspoken critic of the CDC's vaccine schedule. In 2016 he co-authored, *The Vaccine Friendly Plan* with Jennifer Margulis. Based on his reading of the scientific data, Thomas developed an alternative schedule with no vaccines during pregnancy or at birth, no more than one aluminium containing vaccine at any one visit, and he delays administering the MMR vaccine until after age 3 (Thomas & Margulis, 2016, p. 339). Thomas vaccinates according to the wishes of the parents and so his patients fall into one of three groups — those who follow his alternative schedule, those who do not vaccinate at all, and those who follow the CDC schedule. Researchers (unnamed) reviewed 'the health outcomes of 2,230 children over age two and under age seven who were patients at... Integrative Pediatrics [Thomas's clinic] from June 2008 [which is when the clinic first opened] to February 2015' to examine the relationship between vaccination status and health

outcomes (Thomas & Margulis, 2016, p. 326). The results are presented in the table below:

Table 9.1: Clinical Data from Integrative Pediatrics

Group	Total	Autism/ASD	Rate
Alternative schedule	1,098	0	0
Unvaccinated	238	0	0
CDC schedule	894	15	1/60

Source: Thomas and Margulis (2016), p. 326.

Given current estimates of 1 in 36 children with ASD, one would expect to see about 30 cases in the group of children vaccinated according to the alternative schedule and about seven cases in the unvaccinated population — instead there were none; while the 1/60 autism cases for children vaccinated according to the CDC schedule is just slightly lower than the national average (Thomas & Margulis, 2016, p. 327). Are these figures valid? Thomas has a financial conflict of interest so scepticism is warranted and these results have not been published in a peer reviewed journal. But if the figures are correct, it would mean that a big piece of the autism puzzle may have been found. Given the stakes, one would think public health officials and media outlets would take an immediate interest in following up to verify whether the data are correct. As of this writing (September 2018), there was no sign of follow up from the CDC or any other federal agency and none of the top 10 (by circulation) newspapers in the country have reviewed the book.

Gallagher and Goodman (2008 and 2010) are also vaccinated vs. unvaccinated studies and I will review them in the subsection below.

9.2.8 Hepatitis B vaccine

Given word limits it is not possible to go over every vaccine on the schedule. But I want to take a moment to focus on the birth dose of the hepatitis B vaccine because it is perhaps the most unusual addition to the national vaccine schedule and four studies have linked it with autism. In this subsection I will review medical knowledge about hepatitis B, the regulatory history of the hepatitis B vaccine, and recent studies that raise questions about the safety of the hepatitis B vaccine administered to newborns.

According to the CDC (2015c):

> Hepatitis B is a liver infection caused by the Hepatitis B virus (HBV). Hepatitis B is transmitted when blood, semen, or another body fluid from a person infected with the Hepatitis B virus enters the body of someone who is not infected. This can happen through sexual contact; sharing needles, syringes, or other drug-injection equipment; or from mother to baby at birth.

The CDC (2015c) notes that ‘Risk for chronic infection [with hepatitis B virus] is related to age at infection: approximately 90% of infected infants become chronically infected, compared with 2%–6% of adults’. So that would recommend earlier age of administration. But given its routes of transmission, the at-risk population for chronic

hepatitis B infection is drug addicts, prostitutes, prisoners, health workers, and men who have unprotected sex with many men (WHO, 2009, p. 413). Holland (2012) points out that, 'while the ACIP [Mast et al., 2006] notes that transmission through saliva is possible, it suggests that nonsexual interpersonal contact must occur over an extended period, such as living with a chronic hepatitis B infected person in the same household' (p. 68). The important takeaway is that children are not likely to be infected by casual contact (unlike measles for example).

Conis (2011) and Holland (2012) document the regulatory history of the hepatitis B vaccine and I summarise their work below. Maurice Hilleman developed the first hepatitis B vaccine; it was produced by Merck Sharp & Dohme under the brand name Heptavax and approved by the FDA in 1981 (Schmeck, [1981], in Conis, 2011, p. 160). When ACIP first reviewed Heptavax in 1982, it noted that the U.S. is 'an area of low HBV prevalence' and that only 5% of the population is at risk over the course of their lifetimes (Holland, 2012, p. 68). So 'ACIP recommended the vaccine only for "higher risk groups": health-care workers, infants born to mothers infected with hepatitis B, and people likely to be in sexual or "needle stick" contact with those infected with hepatitis B' (CDC, [1982], in Holland, 2012, p. 68).

In 1986, the FDA approved a second hepatitis B vaccine, Recombivax HB, also from Merck Sharp & Dohme (Boffey, [1986] in Conis, 2011). Recombivax was the first genetically engineered vaccine and it is made by inserting a gene from the hepatitis B virus into yeast cells (*Saccharomyces cerevisiae*), causing those cells to produce hepatitis B surface antigen (HBsAg) which then was combined with an aluminum

adjuvant and thimerosal preservative to produce an immune response when injected (FDA, 1988).

In 1988, ACIP called for screening all pregnant women in the U.S. to identify those who were positive for hepatitis B and recommended that children of mothers who test positive be vaccinated against hepatitis B (CDC, [1988], in Holland, 2012, p. 68). It estimated the population of pregnant women infected with hepatitis B at 16,500 and calculated that without vaccination, 3,500 infants would develop chronic hepatitis B infection (CDC, [1988], in Holland, 2012, p. 68).

In 1989, a second genetically engineered hepatitis B vaccine was approved by the FDA — Engerix-B manufactured by SmithKlineBeecham (Associated Press, [1989], in Conis, 2011). By 1990, CDC officials had noticed that the full three-dose course was rarely completed by high-risk populations (Holland, 2012). In 1991, ACIP reclassified hepatitis B as a 'major health problem' in the U.S. and 'recommended hepatitis B vaccination for all infants regardless of the mother's infection status' (CDC, [1991], in Holland, 2012, p. 69). Overnight, the action of ACIP increased the market for hepatitis B vaccines for children from the 16,500 infants born to infected mothers to the four million children born in the U.S. each year times three doses. 'By 1999, 42 states had mandated the hepatitis B vaccine for students, and over 25,000 reports of adverse events linked to the vaccine had been reported to VAERS [the Vaccine Adverse Event Reporting System]' (Conis, 2011, pp. 164–165).

'In January 1999, ACIP expanded its hepatitis B vaccination recommendation to include "all unvaccinated children aged 0–18 years and made hepatitis B vaccine available

through the Vaccines for Children program (VFC)"' for families who could not afford the vaccine (CDC, [1999], in Holland, 2012, p. 72). This expanded the market to 76 million children at three doses each for a total of 228 million doses, about half of which would be paid for by the federal government (Holland, 2012, p. 73). Amidst rising VAERS reports of injuries from the hepatitis B vaccine, the 106th Congress held hearings on the vaccine (Holland, 2012, p. 73). Michael Belkin, whose daughter died 15 hours after receiving a hepatitis B vaccine, testified that in 1996, 'there were 54 cases of hepatitis B in the 0–1 age group' (Committee on Government Reform, [1999], in Holland, 2012, p. 75). But that 'same year there were 1,080 reports of adverse events in the 0–1 age group and 47 deaths' (Holland, 2012, p. 75). 'Total VAERS hepatitis B [vaccine] reports for the 0–1 age group outnumbered reported cases of the disease 20 to 1' (Committee on Government Reform, [1999], in Holland, 2012, p. 76). As noted above, VAERS may undercount actual injuries by a factor of 100 (Kessler, 1993).

Undeterred, in 2005, ACIP further expanded its hepatitis B recommendations by declaring that 'all delivery hospitals should implement standing orders for administration of hepatitis B vaccination as part of routine medical care of all medically stable infants weighing greater than or equal to 2000 g at birth' (CDC, [2005], in Holland, 2012, p. 73). This is an extremely aggressive medical intervention for a virus that is not transmitted through casual or airborne contact, a virus that by the CDC's own admission has very low incidence in the U.S. population, a virus that 90–94% of healthy people are able to clear on their own if they do come in contact with it, and given that since 1988 hospitals have screened all pregnant mothers for HBV so that children of infected mothers could be vaccinated against the disease.

How long does the hepatitis B vaccine provide immunity? It is a crucial question because the vaccine is given to children just hours after birth but given the routes of transmission, exposure to HBV usually does not happen until adulthood if at all. ACIP estimated that 15–50% of children do not have immunity 5 to 15 years after vaccination with the full three dose series (CDC, [2005], in Holland, 2012, p. 74). There are reasons to believe that ACIP was overly optimistic in its assessment. Petersen et al. (2004) in a study of low risk children found that 'Anti-HBs disappeared by 5 years of age in most children who were vaccinated with hepatitis B vaccine from birth' (p. 650). Brands were not disclosed but 100% of children vaccinated with one hepatitis B vaccine and 87.5% of children vaccinated with a second brand had no antibodies against hepatitis B at seven years of age (Petersen et al., 2004, p. 650). Wu, Lin, Wang (2013) in a survey of 8,733 senior high school students in Taiwan born after 1987 found that only 48.3% had antibodies to HBsAg (hepatitis B surface antigen). The study is limited by the fact that it did not make a distinction between those with HBsAG of ≥10 mIU/mL (which is generally considered protective against hepatitis B infection) and those with less than 10 mIU/mL. Middleman et al. (2014) writing in *Pediatrics* acknowledges that 'little is known about duration of protection after the infant primary series of hepatitis B (HB) vaccine in settings of low HB endemicity' (p. e1500). They studied 420, 16- through 19-year-olds who had received the full three shot series of hepatitis B vaccine as young children and found that only '24% had protective anti-HBs levels of ≥10 mIU/mL' (Middleman et al., 2014, p. e1500). The authors were pleased by the fact that 92% of subjects achieved protective anti-HBs after receiving another booster dose (Middleman et al., 2014, p. e1500). But it is not clear how long that booster dose lasts and why it is an improvement over the 90+% of the population who are able to clear the virus naturally even in the absence of vaccination.

The epidemiological research on the safety of the hepatitis B vaccine is mixed but there are several studies that have generated cause for concern. Lewis et al. [2001], Marques et al. [2007], Demirjian and Levy [2009], and Price et al. [2010] did not find an association between hepatitis B vaccination and adverse events (Gallagher & Goodman, 2010, p. 1665). By contrast, Fisher and Eklund [1999], Fisher et al. [2001], and Mikaeloff et al. [2009] found an association between hepatitis B vaccination and a range of serious health problems but did not look at autism (Gallagher & Goodman, 2008, pp. 1665–1666).

Gallagher and Goodman (2008) using data from the National Health and Nutrition Examination Survey 1999–2000 found that boys who received all three doses of the hepatitis B vaccine (*n* = 46) were 8.63 times more likely (OR) to have a developmental disability than boys who did not receive all three doses (*n* = 7) (CI: 3.24, 22.98) (p. 1002). The study has been criticised for small sample size and not sufficiently controlling for confounding factors (Left Brain/Right Brain, 2009). Gallagher and Goodman (2010) using data from the National Health Interview Survey 1997–2002 found that boys:

> who received the first dose of hepatitis B vaccine during the first month of life had 3-fold greater odds for autism diagnosis (n = 30 with autism diagnosis and 7044 without autism diagnosis; OR = 3.002; 95% CI = 1.109, 8.126), relative to boys either vaccinated later or not at all, adjusted for race, family structure, and maternal education (p. 1669).

In this study the authors obtained shot records for the children which addresses the problem of recall bias (Gallagher & Goodman, 2010, p. 1670). Perhaps most importantly, Gallagher and Goodman had no financial conflicts of interest (Gallagher & Goodman, 2010, p. 1665) — these studies were not funded by pharmaceutical companies, the CDC, nor autism advocacy groups.

Given that the scientific case is so weak for requiring the birth dose of hepatitis B vaccine for all newborns, what motivated ACIP's multiple decisions to expand its use (and why did AAP and NVAC go along with those decisions)? One possibility is cultural capture — the members appear to view vaccines as an unalloyed good so the more, the earlier, the better. But adding 228 million arguably unnecessary doses of a vaccine to the national schedule without a strong scientific justification raises the troubling possibility of financial capture — that profit interests may have been the motivating factor. Or perhaps it is a combination of both. In any event, one is hard pressed to make the case that ACIP's decisions in connection with the hepatitis B vaccine are in children's or the nation's best interests.

9.2.9 Troubling recent data on the benefits and safety of the flu vaccine

As described in section 9.2.3 above, after thimerosal was removed from most vaccines in the early 2000s, it still remained in the some versions of the flu vaccine. Furthermore, as thimerosal was being phased out of most vaccines, the CDC added the flu vaccine to the schedule for children and pregnant women (Harper, Fukuda, Uyeki, Cox, & Bridges, 2004) which nullified the natural experiment of removing it from the other vaccines. ACIP's actions in connection with the flu vaccine are troubling on many levels. Green

(1996) writes, ‘the single greatest area of risk and uncertainty in the pharmaceutical context is in the field of drugs for pregnant women’ (p. 340). Most clinical trials do not include pregnant women because of the risks involved so data on the safety of administering vaccines during pregnancy are usually lacking. In this subsection I will review studies that show that the flu vaccine is not very effective in adults or children and that administering the flu vaccine during pregnancy increases the risk of autism. Collectively these studies will once again raise questions about the degree of cultural and financial capture at ACIP (and by extension, the CDC, HHS, AAP, NVAC, etc.)

The scientific case for recommending the flu vaccine for either adults or children is dubious. In 2014, Cochrane (formerly the Cochrane Collaboration) published a systematic review of the literature on the effectiveness of the influenza vaccine among adults (Demicheli et al., 2014). They noted that ‘over 200 viruses cause influenza and influenza like illness (ILI), producing the same symptoms (fever, headache, aches, pains, cough and runny noses)... At best, vaccines may only be effective against influenza A and B, which represent about 10% of all circulating viruses’ (Demicheli et al., 2014). Furthermore, they found that ‘vaccination shows no appreciable effect on working days lost or hospitalisation’ (Demicheli et al., 2014). In 2012, Cochrane conducted a systematic review of influenza vaccine in children. They noted that the CDC recommends the flu vaccine for children in the U.S. at 6 months of age, but their own findings showed, ‘in children under the age of two, the efficacy of inactivated vaccine was similar to placebo’ (Jefferson, Rivetti, Di Pietrantonj, Demicheli, & Ferroni, 2012). Furthermore, they found that ‘that reliable evidence on influenza vaccines is thin but there is evidence of widespread manipulation of conclusions and spurious notoriety of the studies’ (Jefferson et al., 2012).

Zerbo et al. (2017) in a cohort study using in-house data from Kaiser Permanente (private health maintenance organisation) of 196,929 children, of whom 3,103 had autism spectrum disorder, found that maternal influenza *infection* (actually getting the flu) during pregnancy was not associated with increased autism risk (p. 1). But they found that maternal vaccination with the flu shot during the first trimester was associated with a 20% increased risk of autism '(adjusted hazard ratio = 1.20; CI: 1.04, 1.39)' (Zerbo et al. 2017, p. 1). Then they applied a Bonferroni adjustment and the result was no longer statistically significant and so they concluded, 'These findings do not call for changes in vaccine policy or practice' (Zerbo et al. 2017, p. 1). As I pointed out earlier in the chapter on phthalates, BPA, and flame retardants, Bonferroni adjustments are controversial (Perneger, 1998; Moran, 2003; Nakagawa, 2004) and 'there is no formal consensus for when Bonferroni procedures should be used' (Nakagawa, 2004, p. 1044). The most cited paper in the medical literature, Perneger (1998), states that 'Bonferroni adjustments are, at best, unnecessary and, at worst, deleterious to sound statistical inference' (Perneger, 1998, p. 1236). *JAMA Pediatrics* published letters by Hooker (2017) and Donzelli, Schivalocchi, and Battaggia (2017) that argued that the use of a Bonferroni adjustment in Zerbo et al. (2017) was not supported by sound statistical reasoning.

Zerbo et al. (2017) appears to demonstrate an extraordinary degree of cultural capture. Kaiser Permanente is an enclosed healthcare system — all doctors, specialists, hospitals, and pharmacy services are delivered through the Kaiser network. So the healthier their patients, the more money they make (because the patients are not using services). Patients with autism are expensive because they require lots of specialists and often

have a host of co-morbid conditions including seizures (Tuchman & Rapin, 2002), gut issues (Erickson et al., 2005), sleep issues (Malow et al., 2012), anxiety (White, Oswald, Ollendick, & Scahill, 2009), and OCD (Russell, Mataix-Cols, Anson, & Murphy, 2005). Kaiser Permanente has everything to gain — from higher profits to greater market share to prestigious prizes in medicine — from figuring out the causes of autism. And yet even when their own data shows an association between the flu shot (that they recommend for all of their pregnant patients) and autism they dismiss it. They are betting the financial viability of the company and the health of millions of children and the nation itself on a Bonferroni adjustment being correct in this instance, even though that decision rests on dubious theoretical and empirical grounds. Zerbo et al. (2017) appear to have placed an ideological commitment to vaccination ahead of their commitment to sound scientific practices.

9.2.10 Allegations of fraud in vaccine safety research

In this subsection I will briefly review allegations of scientific misconduct against Andrew Wakefield who is a well known critic of vaccine safety as well as allegations of scientific misconduct against Thomas Verstraeten, Poul Thorsen, and William Thompson who conducted research on vaccines and autism for the CDC.

Allegations of ethical misconduct against Andrew Wakefield are well known (see, e.g., Deer, 2011a, 2011b, 2011c; Godlee, Smith, & Marcovitch, 2011) and often brought up in discussions of vaccine safety (Offit, 2010). However, the story is much more complex than is usually portrayed in the popular debate. Wakefield et al. (1998) published in *The Lancet* a case series of 11 children with autism that hypothesised that

the MMR vaccine may have led to ileal-lymphoid-nodular hyperplasia and non-specific colitis which led to their autism. Following the publication of the article, the Royal Free Hospital held a press conference in February 1998 in which Wakefield called for the MMR vaccine to be withdrawn and replaced with single virus vaccines. *The Sunday Times*, hired Brian Deer, a freelance journalist, to investigate Wakefield's research. Wakefield's study was eventually retracted by *The Lancet* (The Editors of *The Lancet*, 2010), and he was struck from the UK medical registry (GMC, 2010) following the longest investigation in the history of the General Medical Council (Dyer, 2010, p.1). Godlee et al. (2011) in *BMJ* argued that Wakefield falsified data — but that was based on their understanding of *Deer's* investigation — the GMC did not investigate whether Wakefield's data were correct; he was struck for violating ethics rules (Triggle, 2010). Godlee et al. (2011) was itself problematic. It relied on the work of Deer — but Deer's investigation was initially funded by *The Sunday Times* which is owned by Rupert Murdoch's News Corp and Murdoch's son James sat on the board of GSK — one of the makers of the MMR vaccine (Sharav, 2016). Three months after publishing their condemnation of Wakefield, the *BMJ* had to issue an *errata* to disclose that it had a financial conflict of interest because it was backed by the two pharmaceutical companies that manufacture the MMR vaccine — Merck and GSK (*BMJ*, 2011). One of Wakefield's co-authors, the Australian paediatric gastroenterologist John Walker-Smith was also struck from the register by the GMC. But, unlike Wakefield, Walker-Smith appealed the decision to the Court of Queen's bench which concluded that the GMC's conclusions were 'based on inadequate and superficial reasoning' and declared, 'the finding of serious professional misconduct and the sanction of erasure are both quashed' (*Walker-Smith v. GMC*, 2012). Many autism advocacy groups argue that the logic of the high court's decision likely extends to Wakefield's case as well (Elizabeth Birt Center

for Autism Law and Advocacy, n.d.) while supporters of the current vaccine schedule argue that it does not (Reiss, 2016b).

What is less well known is that there are allegations of fraud against three researchers at the CDC or under contract with the CDC in connection with studies that concluded there is no link between vaccines and autism.

In the 1990s as autism rates began to skyrocket in the United States, a group of parents came up with the hypothesis that thimerosal in vaccines might be the culprit (Kirby, 2005). It was plausible enough to merit investigation — as described above, thimerosal is 49.6% ethylmercury, ethylmercury is a known neurotoxin, and the expansion of the vaccine schedule beginning in 1987 meant that children were being exposed to more ethylmercury in the vaccine schedule than ever before. Even more troubling, the cumulative levels of ethylmercury in the CDC's schedule vastly exceeded the safe levels of methylmercury established by the ATSDR, EPA, and FDA (Kirby, 2005, p. 49). The CDC decided to investigate this hypothesis and the task fell to one of its senior research scientists, Thomas Verstraeten. For his study, Verstraeten turned to the Vaccine Safety Datalink (VSD) which the CDC set up in 1991 and included health records from four health maintenance organisations ('Group Health Cooperative of Puget Sound in Washington, Northwest Kaiser Permanente in Oregon, Northern California Kaiser, and Southern California Kaiser Permanente') (Chen et al., 1997). Using the Freedom of Information Act, autism advocacy groups such as SafeMinds (2003 and 2004) discovered that Verstraeten produced five different generations of the analysis. There is no evidence that he initially planned five phases of research — rather, e-mails and other documents turned over to SafeMinds reveal that early drafts of the

analysis produced large statistically significant dose dependent associations between thimerosal exposures and neurodevelopmental disorders including autism and with each subsequent draft Verstraeten, after extensive consultation with colleagues, found various ways to re-organise the analysis to reduce the effect (SafeMinds, 2004, p. 2). Taking each phase in turn:[15]

Generation Zero. (This was the earliest analysis but only discovered in a later document dump and it is the only analysis with a zero exposure group, hence the Generation Zero label). Verstraeten, Davies, Gu, and DeStefano, (1999) submitted an abstract, to the annual Epidemic Intelligence Service conference, on their initial work examining the relationship between thimerosal in vaccines and developmental neurological impairment. Their initial sample consisted of immunisation records from 400,000 infants born between 1991 and 1997 available through the VSD (Verstraeten et al., 1999). Importantly, their analysis included a zero exposure group (at one month of age) that they could compare against the highest ethylmercury exposure group (>25 µg) in examining 'subsequent risk of degenerative and developmental neurologic disorders and renal disorders before age 6' (Verstraeten et al., 1999). They write,

> The relative risk (RR) of developing a neurologic development disorder was 1.8 (95% confidence intervals [CI] = 1.1–2.8) when comparing the highest exposure group at 1 month of age (cumulative dose >25 µg) to the unexposed group. Within this group we also found an elevated risk for the following disorders: autism (RR 7.6, 95% CI=1.8–31.5), nonorganic sleep

[15] SafeMinds (2003, 2004) provides the outline of this critique of the Verstraeten et al. (2003) research project and I use Verstraeten et al. (1999) and Kirby (2005) to fill in critical details.

> disorders (RR 5.0, 95% CI = 1.6–15.9), and speech disorders (RR 2.1, 95% CI = 1.1–4.0) (Verstraeten et al., 1999).

The authenticity of this abstract is not disputed (Willingham, 2014). Those who question vaccine safety see this document as the only CDC funded vaccinated vs. unvaccinated study, a smoking gun, and evidence of a CDC cover up (SafeMinds, 2003, 2004). Those who accept the status quo position see this document as an example of how 'preliminary results change over time as data collection and analysis are completed' (Willingham, 2014).

Generation 1. In an e-mail dated 17 December 1999, Verstraeten wrote to Robert Davis and copied Frank DeStefano with the subject line, 'It just won't go away'; in the body of the e-mail he wrote that 'all the harm is done in the first month' (Kirby, 2005, p. 192). Just over two months later, Verstraeten had produced a new draft of the analysis — a thirty page report titled 'Thimerosal VSD Study, Phase 1— update 2/29/00' (Kirby, 2005, p. 191). Verstraeten made a number of questionable judgement calls, such as excluding all children who did not receive 2 polio vaccines (which reduced the number of zero exposure patients), combining the zero exposure group with the <25 µg group, and introducing 'stop dates' that reduced the number of children in the sample with a diagnosis of autism (SafeMinds, 2004, p. 19). Even then, the relative risk of autism for the highest exposure group (>62.5 µg) was 2.48 (Kirby, 2005, p. 191). On 19 March 2000, Verstraeten e-mailed DeStefano to explain that he had run a separate analysis on 10 premature infants from Northern California Kaiser and found that the highest exposure group had a relative risk of developing autism of 5.0 (Kirby, 2005, p. 193) [which is in line with the Mawson et al. (2017b) finding of an OR of 5.4 for premature

infants]. Verstraeten wrote that the findings were ‘very extreme’ and said that ‘It warranted closer examination of these diagnoses’ (Kirby, 2005, p. 193).

Generation 2. By June 2000, Verstraeten had produced another draft of the analysis, and now the relative risk of autism was 1.69 — still troubling but no longer statistically significant. CDC officials organised a gathering of leading epidemiologists at the Simpsonwood Conference Center in Georgia on 7–8 June 2000, to review Verstraeten’s latest findings (Kirby, 2005, p. 130; SafeMinds, 2003). As a result of the deliberations at Simpsonwood, Verstraeten and his team re-organised the study. Among the changes, Verstraeten added data from another HMO (Harvard Pilgrim which had previously filed for bankruptcy, used a different reporting system than the other two HMOs, and had been fined for record keeping failures) (Kirby, 2005, p. 148).

Generation 3. By 1 July 2001, Verstraeten had produced a new analysis that he was scheduled to present to the Institute of Medicine; he opened his remarks by announcing that he had just been hired by vaccine maker GSK and would be relocating to work at their offices in Belgium (Kirby, 2005, p. 176). In spite of this clear conflict of interest, Verstraeten presented his findings as scheduled. In the new analysis, Verstraeten broke out each HMO separately and further subdivided the disability categories which shrank the statistical power of each of his findings (SafeMinds, 2003, p. 13).

Generation 4. The final paper, Verstraeten et al. (2003) was published in *Pediatrics*; even though Verstraeten was now living in Belgium and working for GSK this was not disclosed in the journal article. Verstraeten et al. (2003) was highly influential in shaping IOM (2004) that concluded that there was no association between thimerosal

and autism and IOM (2004) was influential in shaping the Omnibus Autism Proceedings that denied the claims of 5,000 families. When autism advocacy groups later requested the VSD data used by Verstraeten et al. (2003) so that it could be re-analysed, the CDC claimed that the data had been lost; a contractor testified that he had been ordered to destroy data and the CDC announced that as of 2000 it would no longer monitor thimerosal exposures via the VSD (Kirby, 2005, p. 396).

Poul Thorsen is a Danish doctor and researcher who has a long publishing track record of studies investigating the causes of autism. He was the data manager for Madsen et al. (2002) that found no evidence of an association between the MMR vaccine and autism and the data manager for Madsen et al. (2003) that found no evidence of an association between thimerosal containing vaccines and autism. In the 1990s, Denmark represented a potentially interesting natural experiment because it manufactures many of its vaccines via a state agency, and it removed thimerosal from vaccines in 1993. Poul Thorsen was a rising star in epidemiological research because he was adept at using big data to examine health questions (Grundvig, 2016, pp. 12–13). Thorsen figured out that he could use the Danish Health Registries — ‘more than 200 healthcare databases that store virtually all disease, disorders, and ailments of Danish citizens after 1968’ to perform a range of retrospective studies for government agencies including the CDC (Grundvig, 2016, pp. 12–13). Madsen et al. (2003) was instrumental in shaping the IOM (2004) decision that vaccines do not cause autism and the Omnibus Autism Proceedings decisions as well. But a closer look at the study revealed there were important flaws in study design. Kennedy (2016) observed:

> In 1993, the same year Denmark removed thimerosal-containing vaccines from distribution, it coincidentally required, for the first time, that outpatient autism cases be reported on the government's national disease registry. Prior to 1993, only inpatient cases were reported. These represented less than 10 percent of the total. Denmark's new reporting protocols increased the reported autism incidence cases by nearly 1300 percent. Dr. Thorsen and his pals took advantage of that artificial rise to suggest that real autism incidence had increased following thimerosal's ban. The authors violated established peer-review scientific protocols by deleting the entire 2001-year class of seven-year-olds from the final published version. That deletion was flagrant research fraud. The 2001 cohort was the first to be entirely free from thimerosal exposure in their vaccines (p. xiii).

Similar flaws characterised Madsen et al. (2002) (Kennedy, 2016, p. xv). Grønborg et al. [2013] later reanalysed the data from that period and showed a decline in autism rates following the removal of thimerosal (Kennedy, 2016, p. xv).

On 13 April 2011, Thorsen was indicted by a federal grand jury and 'charged with 13 counts of wire fraud and 9 counts of money laundering' in connection with the theft of '$1 million in CDC grant money earmarked for autism research' (Crosby, 2011). As of 2017, Thorsen was still on the [U.S.] Office of the Inspector General's Most Wanted list (OIG, n.d.). Even after his indictment, the CDC's Coleen Boyle stayed in contact with Thorsen; Diana Schendel at the CDC and Rosemary Higgins at NIH continued to publish with Thorsen (Clay, 2017, p. 3).

Reiss (2016a) makes a three-fold argument as to why accounts of Thorsen's alleged crimes are overstated. 1.) 'Thorsen was one of several authors, and not a lead one...'; 2.) 'there's nothing to suggest any data manipulation....'; and 3.) 'If Thorsen is accused of stealing from the CDC, how can he at the same time be an accomplice of the CDC in hiding data?' (Reiss, 2016a). Responding to each argument in turn: 1.) Thorsen was the data manager for the project, that is not incidental; 2.) the data *was* manipulated by changes in how autism was recorded in Denmark and the deletion of key data that changed research outcomes (Kennedy, 2016); and 3.) data manipulation and stealing from the CDC are not mutually exclusive.

William Thompson is one of the scientists at the CDC tasked with investigating a possible association between the MMR vaccine and autism following publication of Wakefield et al. (1998). Thompson is the third author on a key study, DeStefano, Bhasin, Thompson, Yeargin-Allsopp, and Boyle (2004) that said there is no association between the MMR vaccine and autism. Brian Hooker is the father of a child who regressed into autism two weeks after being vaccinated at 15-months of age (Barry, 2015). Hooker has become adept at using the Freedom of Information Act to request key government documents from the CDC about autism research (Barry, 2015). Hooker has sometimes found allies within the CDC who help him to ask the right questions and ask for the right documents (Barry, 2015). Hooker and Thompson spoke on the phone several times between 2002 and 2003 but then Hooker was blocked from further contact when he filed suit in the vaccine court as part of what became the Omnibus Autism Proceedings (Barry, 2015). Then in 2013, Thompson called Hooker (Barry, 2015). Thompson and Hooker spoke on the phone more than 30 times over the period November 2013 to

August 2014 (Barry, 2015). Hooker secretly recorded four of those phone conversations and transcripts of the calls are contained in the book, *Vaccine Whistleblower* (Barry, 2015) and recordings of the calls are featured in the documentary film *Vaxxed* (Bigtree et al., 2016). Among the highlights of those calls, Thompson stated that 'I've basically decided to stop lying'; that 'thimerosal-containing vaccines should never be given to pregnant women'; and that the CDC was 'sitting on' a database of about 1,200 children with autism called the SEED study that had never been made public (Barry, 2015). Thompson has never denied the veracity of those recordings and in (2014) he issued a statement via his attorney saying,

> I regret that my co-authors [DeStefano, Bhasin, Yeargin-Allsopp, and Boyle] and I omitted statistically significant information in our 2004 article published in the journal *Pediatrics*. The omitted data suggested that African American males who received the MMR vaccine before age 36 months were at increased risk for autism. Decisions were made regarding which findings to report after the data were collected, and I believe that the final study protocol was not followed.

Thompson also contacted U.S. Representative Bill Posey and turned over 100,000 pages of documents to him. Posey took to the House floor to enter Thompson's testimony into the Congressional record including Thompson's statement that,

> All the authors [DeStefano, Bhasin, Yeargin-Allsopp, and Boyle] and I met and decided sometime between August and September 2002 not to report any race effects for the paper. Sometime soon after the meeting,

> where we decided to exclude reporting any race effects, the coauthors scheduled a meeting to destroy documents related to the study. The remaining four coauthors all met and brought a big garbage can into the meeting room and reviewed and went through all the hard copy documents that we had thought we should discard and put them in a huge garbage can (Congressional Record, 2015, p. H5602).

Reportedly, Thompson was granted whistle-blower protection by President Obama in 2015 (Howley, 2015) but thus far he has not been called to testify before Congress. Willingham (2015) writing in *Forbes* questions Thompson's account of destruction of data arguing that electronic copies would have survived because CDC is a 'multilevel bureaucracy with multiple levels of data backup, archiving, and storage' (para. 9). As evidence to support that claim she cites the work of Frost (2014) writing on the Minitab blog who reviewed DeStefano et al. (2004) and concluded that it was 'a careful observational study that assessed the role of potential confounders' before acknowledging that it lacked an unvaccinated control group.

It is standard practice at scientific journals for articles to be retracted if there is any evidence of fraud or scientific misconduct. To date, none of the studies co-authored by Verstraeten, Thorsen, or Thompson described above has been retracted (although *Pediatrics* in 2004 attached an *errata* to Verstraeten et al. [2003] to correct an error and simultaneously noted that 'he is currently employed by GlaxoSmithKline'). Furthermore, it is standard practice in systematic reviews to exclude studies where there is evidence of bias. Yet at no point have the IOM (now the National Academy of Medicine) nor the wider scientific community taken steps to exclude Verstraeten et al.

(2003), Madsen et al. (2002 and 2003), and DeStefano et al. (2004) from meta analyses nor systematic reviews.

9.2.11 Vaccines do not work very well in the first year of life

Mainstream immunologists acknowledge that vaccines do not work very well in the first year of life. *Vaccines* (Plotkin, Orenstein, Offit, & Edwards, 2018) is a standard medical textbook. Chapter 2, Vaccine Immunology, is authored by Claire-Anne Siegrist (2018) who wears a number of different hats — 'Professor of Vaccinology at the University of Geneva, Switzerland; attending physician for paediatric infectious diseases, vaccinology and immunology at the University Hospitals of Geneva; Director of the Pediatric Department of the University of Geneva; and Head of the WHO collaborating Center for Neonatal Vaccinology' (WHO, 2010). Siegrist (2018) writes that 'currently available vaccines have largely been developed empirically, with little or no understanding of how they activate the immune system' (p. 16). Empirically, in this case means through trial and error and subsequent observation.

Later in a section on 'The challenges of neonatal and early life immunization' Siegrist (2018) writes,

> Early life responses markedly differ from those elicited in mature hosts. The blunting of neonatal immune responses has been regarded for many years as resulting from 'neonatal tolerance', reflecting the antigen naïveté of the immune system and, subsequently, its immaturity. Recent work has prompted a change of perspective, leading to the recognition

> that the neonatal and early life immune system is, in contrast, specifically adapted to the unique challenges of early postnatal life and develops over time through poorly defined but tightly regulated processes (p. 32).

Offit (2010) characterises unvaccinated children as uniquely vulnerable, however Siegrist (2018) sees it the opposite way — that children come into the world uniquely well-suited to the surrounding environment.

Siegrist (2018) presents a table (2-10) with seven reasons why vaccine responses in early life may be limited including the, 'influence of maternal antibodies' (p. 32). Infants receive immune protection from the mother through breast milk — so when a child is vaccinated, the immune response is often driven by the mother's antibodies, not necessarily those produced by the infant. This realisation — that maternal antibodies interfere with immune response to vaccines in infants — led Moon et al. (2010) to suggest that 'strategies to overcome this negative effect, such as delaying breast-feeding at the time of immunization, should be evaluated' (p. 919). Moon and three of her co-authors are at the CDC and another co-author was at NIH. Moon and her team were widely criticised for this proposal and the CDC later distanced itself from this recommendation (Johnson, 2017).

Siegrist's (2018) initial response to the failures of vaccines in the early years of life is to recommend upping the number of antigens before acknowledging that this strategy also fails as a result of 'higher titers of maternal antibodies elicited by maternal immunization' (p. 34). Both Siegrist and the CDC then appear to fall back on simply

upping the number of vaccine doses in early years. Siegrist (2018) writes, ‘Maternal antibodies usually allow a certain degree of priming (i.e., of induction of memory B cells) through yet undefined mechanisms. As a rule, the blunting of infant antibody responses by maternal antibodies disappears after boosting’ (p. 34). It is interesting to note that neither of those assertions have citations in the text. But one can see how both the WHO and CDC have gotten themselves into a sort of arms race against maternal antibodies, recommending ever more potent vaccines and ever more doses to overcome the fact that vaccines during early life do not work very well. But given the data on the risks of mercury and aluminium and other adjuvants presented earlier in this chapter, one can also see how this arms race against maternal antibodies might also produce catastrophic iatrogenic outcomes for infants for whom the blood-brain barrier is not fully developed. Furthermore, it does not take a lot of imagination to come up with alternatives to this sort of arms race. Since vaccines do not work well during the first years of life, encouraging more breast feeding (maternal antibodies for free), providing more paid leave, and postponing vaccines until the child is older and more suited to an effective immune response would seem like promising science-based alternatives. However, none of those alternatives is profitable and the ideological commitment to vaccination is so strong that such alternatives are usually not even contemplated in the mainstream scientific community.

9.3 Lobbying and campaign contributions by vaccine makers

In the last chapter I wrote about lobbying expenditures by Pfizer ($191.42 million from 1999 through 2018). The other three major vaccine makers — GSK, Merck, and Sanofi — also spend heavily on lobbying. From 1999 through 2018, GSK spent $92.84 million

on lobbying (CRP, 2018, ‘GSK’). From 1999 through 2018, Merck spent $119.83 million on lobbying (CRP, 2018, ‘Merck’). From 1999 through 2018, Sanofi spent $109.78 million on lobbying (CRP, 2018, ‘Sanofi’). Combined, the four pharmaceutical companies that control 86% of the vaccine market spent a reported $513.87 million on lobbying over that twenty year period.

Autism Speaks is the largest autism advocacy group in the U.S. but is no longer seeking a cure for autism and it does not support the vaccine autism hypothesis. From 2005 when it started through 2018, Autism Speaks spent a total of $6.2 million on lobbying — primarily on issues of services and support for people with autism. The Coalition for Safe Minds spent $45,000 on lobbying in 2012 and again in 2013 but does not appear to have spent money on lobbying before or since. Neither Generation Rescue nor Children’s Health Defense appears to have a lobbying presence in Washington, D.C.

9.4 Conclusion

In this chapter I showed that the vaccine market is large, profitable, and growing rapidly (9.1.1); documented that the U.S. vaccine schedule tripled following the passage of the NCVIA of 1986 (9.1.2); reviewed the vaccine approval process (9.1.3); argued that clinical trials as part of the FDA licensure process are too short and too small and use toxic placebos (9.1.4); provided evidence of COI at the FDA’s Vaccines and Related Biological product Advisory Committee (VRBPAC), the CDC’s Advisory Committee on Immunization Practices (ACIP), and the National Vaccine Advisory Committee (NVAC) (9.1.5); showed that post-market surveillance of vaccine adverse events is inadequate (9.1.6); highlighted the revolving door between CDC and vaccine makers

(9.1.7); discussed the lobbying at the state level to make vaccines compulsory (9.1.8); and showed COI in science and medical journals associated with vaccines (9.1.9). I also showed that there are two very different ways of looking at the net benefits to society from widescale vaccination programs (9.2.1), reviewed the debate over herd immunity (9.2.2), discussed the toxicity of ethylmercury (9.2.3) and aluminium (9.2.4); noted that little is known about the toxicity or interaction effects of other ingredients in the vaccine schedule (9.2.5); reviewed studies showing no association between vaccines and autism (9.2.6); uncovered a wealth of vaccinated vs. unvaccinated studies (9.2.7); discussed studies on the safety of the hepatitis B vaccine (9.2.8), reviewed recent studies on the flu vaccine (9.2.9); documented allegations of fraud in vaccine safety research (9.2.10); and noted that vaccines do not work very well in the first year of life (9.2.11). Finally I showed that the four largest vaccine makers spent heavily on lobbying ($513.8 million combined over the last 20 years) while the Coalition for Safe Minds (the only autism advocacy group opposed to vaccines that used a registered lobbyist during that period) spent $90,000 (9.3). Given the stakes, it is essential for government to be able to prove the safety of the U.S. vaccine schedule. Yet over the last three decades, as the schedule has tripled and moved earlier into key developmental windows, public health authorities have responded to legitimate questions and concerns with obfuscation, self-dealing behaviour, and legislative strategies based on coercion.

Chapter 10

Conclusion

10.0 Introduction

In this chapter I will review the main findings of my research (10.1), discuss the implications of my findings (10.2), highlight the limitations of the research (10.3), and suggest some possibilities for future research (10.4).

10.1 Main findings of my research

In chapter 1, I presented evidence that autism prevalence rates are high and rising. One in 36 children in the U.S. are now diagnosed as being on the autism spectrum (Zablotsky et al., 2017); this is a 27,000% increase from the first autism prevalence estimate of less than 1 per 10,000 people in the population (Treffert, 1970). In 2015, ASD cost the U.S. an estimated $268 billion a year in direct costs and lost productivity; given current rates of increase, costs could reach $1 trillion a year within 10 years (Leigh & Du, 2015). In the U.S. on average, 'the cost of supporting an individual with an ASD and intellectual disability during his or her lifespan was $2.4 million... The cost of supporting an individual with an ASD without intellectual disability was $1.4 million' (Buescher et al., 2014, p. 721). Mothers often experience sharp declines in earnings as many become the principle care giver (Cidav et al., 2012).

While the federal government through its various health agencies has devoted the bulk of research funding toward exploring theories of genetic causation, 'there is no such

thing as a genetic epidemic' (Kirby, 2005; Barclay, 2005; Hertz-Picciotto in Cone, 2009). The most comprehensive study of twins and autism to date estimates that genetic heritability explains at most 38% of ASD cases and this is likely an overestimate (Hallmayer et al., 2011). The CDC also promotes the idea that the rise in autism prevalence may be the result of diagnostic expansion and substitution. Yet, several studies have concluded that diagnostic expansion and substitution, while a factor, represent a small fraction (somewhere around 26.9% to 31.3%) of the total increase (Byrd et al. 2002; Hertz-Picciotto & Delwiche, 2009; Nevison & Blaxill, 2017).

There are many large, well-conducted studies that suggest that a range of toxicants may be driving the increased prevalence of autism. Possible environmental triggers include mercury from coal fired power plants (Palmer et al. 2006 and 2009), hazardous air pollutants (Windham et al., 2006), and emissions from motor vehicles (Hoyer et al., 2004; Volk et al., 2011); phthalates (Ejaredar et al., 2015), BPA (Kardas et al., 2016), and flame retardants (Bennett et al., 2016); Roundup (Swanson et al., 2014); organophosphates, chlorpyrifos, pyrethroids, and carbamates (Shelton et. al., 2014); SSRIs (Croen et al., 2011; Eriksson et al., 2012; Rai et al., 2013; Sørensen et al., 2013; Gidaya et al., 2014; Harrington et al., 2014; El Marroun et al., 2014; Boukhris et al., 2016), acetaminophen (Avella-Garcia et al., 2016; Liew, Ritz, Virk, & Olsen, 2016) and vaccines (Gallagher & Goodman, 2008 and 2010; Thomas & Margulis, 2016; Mawson et al., 2017a and 2017b). Other environmental factors that have been associated with autism are the age of parents at conception (Croen et al., 2002; Glasson, 2002; Bhasin & Schendel, 2007; and Durkin et al., 2008) as well as maternal obesity combined with maternal diabetes (Li et al., 2016). It is unclear whether those two additional environmental factors are also related to toxicants (e.g. different outcomes for older

parents could be the result of the natural aging process or the result of longer lifetime exposure to toxicants and rising obesity and diabetes rates could stem in part from environmental triggers). While noting that correlation is not causation, all of the possible environmental triggers have a plausible causal pathway by which they might cause autism. All of the toxicants in this list have higher odds ratios or relative risks for autism than other products that have been withdrawn from the market (Vioxx, Zicam) or discontinued (hormone replacement therapy) due to their side effects.

In the midst of this crisis, the CDC does not use the word epidemic, the NIH devotes only a tiny fraction of research funding toward studying environmental factors, and no federal agency in the U.S. is engaged in trying to prevent autism via more proactive regulation of toxicants. The question then becomes, given rising prevalence rates and the extraordinary impacts of ASD on individuals, families, and communities, what explains why public health authorities, thus far, have failed to ban or restrict toxicants that have been shown to increase autism risk?

This is an interesting historical moment for studying issues of science and medicine because by most accounts positivism is dead (its demise possibly hastened by Kuhn, 1962) and yet it is not entirely clear what replaces it (e.g. poststructuralism does not offer a solid foundation for making science-based policy decisions). So it is important to be clear about the theoretical lenses I use to approach the material (chapter 2). My ontology and epistemology are shaped by Longino's (1990) contextual empiricism — scientific knowledge is socially constructed and always subject to change but within the range of what is 'known' now, there are relatively better and worse choices available to policymakers. My methodology is influenced by the critical public health work of

Navarro (2008) and the descriptive political epidemiology of Pega et al. (2013). My research offers an elaboration on Lukes (1974) by showing: 1.) the battle of ideas in connection with autism; 2.) how the producers of toxicants are able to keep issues off the table; and 3.) how power also distorts the interests, preferences, and ideation of dominant (*advantaged*) groups (who seem to build defences to protect profitable turf rather than pursuing knowledge wherever it leads them). Finally, this thesis is an application of Wendell's (1996) research on the social construction of disability — particularly the political economy factors that can create material changes in human bodies — while challenging the exclusively poststructural approaches to the social construction of disability as represented by Haraway (1991).

Kuhn (1962) presents an idealised vision for how science changes its mind from immature science with competing paradigms to the emergence of a dominant paradigm which leads to a period of normal science followed by anomalies that produce crises that can lead to a paradigm shift (chapter 3). Wootton (2006) shows that the history of medicine does not resemble Kuhn's model at all. Galenic medicine decreased one's odds of survival. The 19th century saw some important breakthroughs that moved medicine toward a replicable empirical foundation but many of the early innovators (Horace Wells, Alexander Gordon, and Ignaz Semmelweis) were bullied, harassed, and ostracised by their peers and driven to an early grave. Medicine seemed to enjoy a golden age in the mid 20th century following the invention of antibiotics along with randomised controlled trials to confirm their effectiveness. The fact that in the developed world chronic conditions (including autism) have now surpassed illness from viruses and/or bacteria suggests that the golden age has passed and that a new uncertain future has emerged (Bethell et al., 2011).

The history of toxic chemical disasters and long term toxic chemical exposures possibly offers some important lessons for the autism epidemic (chapter 4). Toxic chemical disasters go through stages — from a private issue to a public issue to a political issue (Reich, 1991). Even after 30 years of rising prevalence rates, autism is still mostly a private issue and it is just beginning to become a public issue. Case studies in long term toxic chemical exposures such as asbestos, lead, and tobacco also reveal common patterns. Because many of these toxic industries use the same PR firms for product defence, they tend to follow a similar playbook that moves through stages including denial, insisting that harms only happen at high levels of exposure, and blaming other factors (such as genetic predisposition or lifestyle characteristics) (Sass & Rosenberg, 2011). I also showed that victim blaming is common in the early stages, legal discovery is essential in unearthing key documents, and often some new technology is developed that enables earlier detection of harms at lower doses.

In chapter 5, I argued that there is a popular perception shaped by the work of Merton (1942) that science and medicine are a separate walled garden, where dedicated men and women are bound by the ethical norms of CUDOS — communism/communalism, universalism, disinterestedness, and organised scepticism. It is unclear whether Merton's norms ever actually existed or served some other ideological purpose (Mulkay, 1976). Mirowski (2011) showed that the passage of the Bayh-Dole Act of 1980 led to the privatisation of the scientific commons and the end of any sort of communism/communalism. Mirowski (2011) and others show that every step in the scientific process in the U.S. is now shaped by corporate influence including: universities (professors, departments, and the university itself); corporate scientific

research (that increasingly relies on trials conducted by contract research organisations in China and the third world); scientific journals (that often accept advertising and struggle with ghost, guest, and gift authorship); government (CDC, FDA, NIH, EPA, and elected officials); and medical school students, doctors, and professional medical associations. Extraordinary conflicts of interest across all aspects of the scientific endeavour have led to the replication crisis and high levels of iatrogenic injury.

In chapter 6, I showed that on three separate occasions, Congress or U.S. federal agencies have acted to block research into possible environmental triggers of autism. I also looked at the regulatory history of phthalates, BPA, and flame retardants. Animal studies raised concerns about the toxicity of phthalates in 1947 and a large body of literature developed over the ensuing years. The European Commission banned six phthalates in 1999. In 2008, the U.S. Congress banned three phthalates (a fourth has since been added) in children's products but left unaddressed the exposure to phthalates via food, beverages, and drugs (the highest phthalate exposures). Furthermore, Congress regulates phthalates individually instead of as a class which considerably slows and limits the regulatory process.

The estrogenic properties of BPA have been known since the 1930s but initially it was viewed as a potentially helpful medical treatment. In the 1950s, BPA was incorporated into the manufacture of plastics. The National Cancer Institute launched a study on the carcinogenicity of BPA of 1977. In 1988, the EPA adopted a relatively high reference dose based on a study produced by a private contractor that had been cited for poor quality control measures and poor pathology practices and that remains the safety standard today. It was discovered that BPA is an endocrine disruptor in 1993. In 2012,

after nearly 100 studies had shown harms from BPA, the FDA “banned” BPA from baby bottles and ‘sippy cups’ — after manufacturers had already removed BPA from those products. The EPA spent more than 20 years trying to develop an Endocrine Disruptor Screening Program but they selected a crude measurement instrument. After the first round of tests finally got off the ground, the EPA announced in 2017 that none of the 52 chemicals tested showed any endocrine disrupting health effects in spite of a large body of scientific evidence showing that they do.

Adding flame retardant chemicals to furniture was the brainchild of the tobacco industry as a way to head off regulations that might require them to produce fire safe cigarettes. Nearly 100% of Americans tested have flame retardant chemicals in their bodies, ‘blood levels of certain widely used flame retardants doubled in adults every two to five years between 1970 and 2004’, and ‘a typical American baby is born with the highest recorded concentrations of flame retardants among infants in the world’ (Callahan & Roe, 2012a, para. 13). Tests show that flame retardant chemicals do not stop fires better than untreated foams. In 2013, California finally changed the flammability standard but these chemicals are so ubiquitous in the environment that it remains to be seen when levels of flame retardant chemicals in the body will begin to decrease.

Many of the pesticides and herbicides used in the U.S. were developed first as chemical weapons in World War I and II (chapter 7). The U.S. government promoted commercial applications of these chemicals and was slow to include public health considerations in evaluating their use. Glyphosate-based herbicides are the most widely used herbicides in the world, there is a growing scientific consensus that they are more toxic to humans than initially believed, and a number of studies (albeit in marginal scientific journals)

have made a link between the increased use of glyphosate-based herbicides and autism. Even as the International Agency for Research on Cancer (2015) has moved to label glyphosate-based herbicides as probable carcinogens and the State of California labeled them as known carcinogens, the FDA and EPA have refused to revisit their previous decisions that permitted their widespread use. The CHARGE study documented that organophosphates, chlorpyrifos, pyrethroids, and carbamates all increase the risk of autism. Dow previously agreed to withdraw chlorpyrifos from residential use but it is still permitted and widely used in agriculture. Congress and the various health and regulatory agencies have failed to take action against the remaining pesticides.

SSRIs represent the clearest case of all of the toxicants listed in this thesis and are potentially the easiest to regulate (chapter 8). Eight studies have shown a statistically significant association between SSRI use in pregnant women and subsequent autism in their offspring. Two other studies found an association but these results were not statistically significant; closer examination of these two studies shows that the authors made scientifically questionable judgement calls that changed the results. To date the FDA has not issued black box warnings, the CDC has not intervened, and the American College of Obstetricians & Gynecologists and the American Psychiatric Association, both of which have financial conflicts of interest, have not taken steps to limit prescriptions for SSRIs for women who are pregnant or want to become pregnant.

In chapter 9, I showed that the debate regarding vaccines and autism is composed of a series of smaller debates about the safety of individual ingredients and the effects and risks of individual vaccines and the whole schedule. With a few notable exceptions, the science in connection with vaccine safety by all parties is characterised by financial

conflicts of interest. There are no studies that demonstrate the safety of the entire vaccine schedule. None of the studies that purport to demonstrate the safety of individual vaccines or individual vaccine ingredients includes a completely unvaccinated control group. The toxicokinetic model developed by the FDA to demonstrate the safety of aluminium as an adjuvant is based on prior studies of one adult male and three rabbits and is thus not statistically valid because the sample sizes are too small. The hepatitis B vaccine has been linked with autism in four studies and appears to be unnecessary for children except those born to mothers who are positive for the hepatitis B virus. The flu vaccine given to pregnant mothers offers few benefits and has been linked with autism in one study. The Wakefield case is more complicated than is usually reported and characterised by financial conflicts of interest on many sides. There is fairly good evidence that Verstraeten, Thompson, and Thorsen all violated sound scientific practices in key vaccine safety studies. Even defenders of the status quo admit that vaccines do not work very well in the first year of life. In spite of the enormous stakes and wide range of conflicting studies, mainstream research in this area slowed considerably following the Institute of Medicine (2004) recommendation to focus on other avenues of inquiry.

The patterns across all of these different products are remarkably similar. There are early concerns about toxicity. Even as *in vitro* and *in vivo* evidence accumulates about potential risks, corporate power is able to shape regulation, shape the science, and delay regulatory action for decades. Only five chemicals have been banned under the Toxic Substances Control Act (TSCA) since it was enacted in 1976 and no chemicals have been banned under the TSCA since 1990 (although some have been voluntarily withdrawn by manufacturers) (GAO, 2006b). The failure of government to effectively

limit potential autism triggers suggests that the purpose of regulation is to protect the profits of the large corporations that write the rules rather than protecting public health (Stigler, 1971; Peltzman, 1976).

The products listed in this thesis are produced by some of the biggest companies in the world and they spend heavily to influence the political system and shape the regulatory environment to favour their interests. Companies lobby and make campaign contributions individually and also through various trade associations. The public tends to think of energy, plastics, flame retardants, pesticides, and pharmaceuticals as separate industries but they are closely intertwined. For example, Bayer makes BPA, pesticides, and pharmaceuticals and spent $112.86 million on lobbying the federal government between 1999 and 2018 to protect and promote its multiple business interests (CRP, 2018, ‘Bayer AG’). There are also interlocking boards — Kenneth C. Frazier serves as Chairman of the board and CEO of Merck and also Director at ExxonMobil (Merck, n.d.); Gregory Boyce formerly was CEO of Peabody Energy Corporation, ‘the world’s largest private-sector coal company’ and served on Monsanto’s board (before the company was acquired by Bayer). From 1999 through 2018, chemical and related manufacturers spent $887.39 million on lobbying (Center for Responsive Politics, 2018, ‘Chemical and related manufacturing’). The pesticide industry is characterised by oligopoly as just four firms (Syngenta-ChemChina, Bayer Cropscience Monsanto, DowDupont, and BASF) control 84% of the market (International Panel of Experts on Sustainable Food Systems, 2017, p. 23) and these firms lobby collectively through groups such as CropLife America and individually to promote their interests. Pharmaceutical companies spent more than $4 billion on lobbying members of Congress from 1999 through 2018 (CRP, 2018, ‘Pharmaceuticals/Health Products’).

Environmental groups have begun to spend more heavily on lobbying — $289 million over that same 20-year period (CRP, 2018, ‘Environment’) — with the bulk of that money focused on climate change legislation. However, the spending race is still wildly asymmetrical — in the U.S., corporations spend 34 times more money on lobbying than all public interest groups combined (Drutman, 2015). All of these actors also spend heavily on campaign contributions and new ‘dark money’ vehicles make total campaign spending impossible to track (Mayer, 2016).

10.2 Implications of my findings

There are a number of implications that emerge from my findings.

1. In the U.S. today, medical science is social, medical science is political, medical science is capitalistic, but medical science is not very scientific at least not in the Mertonian sense of the word. The funding effect is a social phenomenon. The evidence shows that when a company provides free samples, free food, or makes a financial contribution of any kind, subtly, unconsciously, yet consistently the study results tend to favour the sponsor’s desired outcomes. Time and again the research presented in this thesis shows scientists making sure their results conformed with the expectations of their clients or peer group. In chapter 5, I quoted a CRO executive boasting that he could give clients whatever results they want. Science-for-hire firms and academic research centres that accept corporate sponsorship give their corporate clients the results that they need to fend off regulation and to win in court. Favourable scientific studies are a commodity that can be purchased on the open market; this is legal and the scientific community has done little to stop it. In chapter 9, I showed e-mails of Thomas

Verstraeten repeatedly checking in with his supervisors asking them to guide him to their preferred outcomes. William Thompson wrote to CDC Director Julie Gerberding seven days before the IOM meeting in February 2004 so that she would have ample time to remove him from the program before he shared his damaging findings. According to William Thompson — Frank DeStefano, Tanya Bhasin, Marshalyn Yeargin-Allsopp, and Coleen Boyle met *as a group* to destroy documents. Far from the image of the lone scientist toiling in the lab or the heroic scientist announcing breakthrough results, autism research is characterised by a sort of bureaucratic echolocation as government and corporate scientists frequently check in to make sure that their results stay within the bounds of what is expected of them. A Nobel Prize likely awaits whoever figures out the causes of autism and yet Verstraeten et al. (2003), DeStefano et al. (2004), and Zerbo et al. (2017) used questionable scientific methods to make their statistically significant results go away — and they were rewarded for these actions by their peers. It is both necessary and helpful for scientists to collaborate with each other, challenge each other, and fix errors in their work. But what seems to be happening with autism research is markedly different from that. With autism research there is evidence of scientists going to great lengths to step outside the norms of accepted scientific practice (adding in corrupted data to dilute findings, destroying data, applying Bonferroni adjustments without justification) so that they can stay within accepted social norms and avoid being displeasing to funders and/or superiors.

2. Because of their unique epistemic position, science and medicine are incredibly powerful but also uniquely vulnerable to the corrupting influence of profit. That has created a series of internal crises (including ghost authorship, the reproducibility crisis, and high levels of iatrogenic injury) that pose an existential threat to science itself.

Obstetrics, psychiatry, and paediatrics *as professions* are all characterised by widespread conflicts of interest and their failure thus far to engage in autism prevention research is troubling and appears to show these professionals putting class interests ahead of their duty of care.

3. It is commonplace to believe that the U.S. has a regulatory system in place to protect public health and safety by limiting exposures to toxic chemicals. In reality the regulatory system is porous. Almost everything gets through the FDA on the first try and postmarket surveillance is generally inadequate. The EPA is toothless by design. The NIH has blurred the line between public good and private gain. The CDC actively works on behalf of industry. This is a reflection of the extraordinary degree of cultural and financial capture of government by corporations. This is also an indictment of a century of progressive reforms of the state that stemmed from the belief that the state could be harnessed to protect the public interest. Regulation is a reflection of political power not scientific reasoning nor public health considerations per se. Even when there is evidence of harms, it can take *a century* to get effective regulatory action.

4. The patterns uncovered in this thesis serve as a stark reminder of the dangers of economic liberalism. In science and medicine, laissez faire has led to privatisation of the commons, skyrocketing costs, dwindling output of truly novel treatments, oligopoly, and catastrophic levels of iatrogenic injury. But the patterns uncovered in this thesis also serve as an unexpected defence of political liberalism. Toxic trespass appears to be at the centre of the autism epidemic. Individuals must regain the right to control what goes into their bodies as a check against corporate power. Labelling laws such as California's Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) are a

good start. Changes to toxic tort laws would give individuals greater access to redress for toxic trespass. And vaccine choice must be protected by state and federal law to guard against possible corruption in medicine.

5. The U.S. is facing a political economy problem that is preventing a public health response to the autism epidemic. The political economy problem is the distorting influence of capitalism on science and medicine and the cultural and financial capture of government by corporations. Until the U.S. addresses the political economy problem it will likely be unable to address the public health problem.

10.3 Limitations, paradoxes, and contradictions of the research

Most of the studies I cite show correlation but causation is more difficult to demonstrate. Indeed, some of those at the forefront of autism research argue that we may never have definitive causation in connection with autism because there will always be too many confounding variables. But again, one can stop an epidemic even in the absence of establishing causation through natural experiments created by policy changes.

The entire theory of the case from environmental epidemiologists and autism advocacy groups could be incorrect. Like the history of peptic ulcers, there could be some as yet unknown bacteria or virus or other factor like radiation, diet, or lifestyle that is causing autism. However, even if that is the case, current public health funding strategies focused largely on genetics are not well suited to find it.

As yet, there are no biomarkers for autism just as there are no biomarkers for any mental health condition. This makes any research in this area highly fraught and opens the door to the perception that rising autism rates may be a result of medicalisation. With autism, like schizophrenia, bipolar disorder, and depression, I contend that we have pretty good observation-based diagnostic measures but observation necessarily involves interpretation and so organised scepticism is always warranted. Furthermore, autism is not solely a brain issue — it also appears to involve the digestive system, the immune system, and the central nervous system — which adds extraordinary complexity to any discussion of causal factors.

Others have noted that I am using scientific studies (Sismondo, Krimsky, Ioannidis, Gøtzsche, Angell, Lexchin, Cosgrove, etc.) to make the case that science is broken or at least strongly influenced by capitalism. But that suggests that some "good" science is still getting published so perhaps science really is self-correcting? It seems to me that in any institution or field of knowledge there are a range of different actors and some are more ethical than others. The authors that I think have done the best work often struggle on the sidelines of the field — marginalised by their peers precisely because of the fact that they have staked out positions that run counter to the dominant discourse. Many criticise their profession only after retiring (Angell) or because they feel that they have nothing to lose (Gøtzsche). Others operate in the social sciences (Sismondo, Mirowski, Krimsky) criticising corruption in science and medicine from the outside but have relatively little traction within the profession. Furthermore, no matter how insightful their research, their impact on policy is always in doubt.

Readers will also note that in the case of all of the potential environmental triggers except vaccines, the government funded studies are often the “good” studies, whereas with vaccine safety research I argue that the FDA, CDC, and NIH are conflicted parties and should be treated as such. How is that possible — can government really be *differentially* captured by agency and by issue? A closer look reveals interesting wrinkles. Critical research discounting the role of diagnostic expansion and substitution as well as highlighting the risks of hazardous air pollutants and pesticides comes from the UC Davis MIND Institute that was set up by parents of children on the autism spectrum and established with funds from the California legislature. Furthermore, it is one thing for public health officials to criticise phthalates made by oil companies and another matter to criticise vaccines which would implicate nearly every doctor and public health department in the country. Pharmaceutical companies spend more money on lobbying and campaign contributions than any other industry, so it would make sense that the degree of capture would be greatest in connection with the regulation of pharmaceuticals.

Colleagues have asked if all or even most of the research is conflicted why should we trust some results and not others? A related issue is that if COI are disqualifying because of the funding effect, then there is almost no research left on which to base policy so how can one make decisions? A strong case can be made that paradigm shifts in general and the autism debate in particular are not about evidence per se. The available evidence can be used to construct a wide range of different (and conflicting) plausible narratives. How one sees the issue is also a question of interpretation and one’s interpretation is influenced by a host of factors including one’s class, metaphysics, ontology, and epistemology. If one believes that U.S. society is meritocratic, that

capitalism is self-regulating, and that science is generally self-correcting, one will be inclined to support the dominant narrative. If one believes that elite discourse tells us about power not truth, that capitalism tends to cause unnecessary harms, and that parents have a unique and superior epistemological position from which to make claims about what happened to their children, one will be inclined to construct a more critical narrative. Social science research shows that beliefs come first and logic and evidence are assembled after the fact to justify belief (Haidt, 2012). The important point here is that all of this recommends a political economy approach to understanding autism and other public health issues because it requires that one have a conversation about all of these levels of belief, influence, evidence, and knowledge. I think when we debate the evidence in its context this leads to better analysis than traditional positivist approaches.

10.4 Possibilities for further research

Historical epidemiology is often able to reconstruct the early days of an epidemic or disease. Olmsted and Blaxill (2010) figured out the family histories of Kanner's early autism patients (and they make the case that many of these families had high levels of exposure to mercury). Sheffer (2018) has done extraordinary historical research on Asperger's patients. To date, no one has attempted to reconstruct the medical history of Sukhareva's first patients but such research could provide important insights into autism. The obstacles there are enormous — for example it is unclear what archival records from Moscow from the 1920s still exist, it is unclear if any of Sukhareva's records exist, or if there are any surviving relatives of any of Sukhareva's patients. But if Sukhareva's patients really do mark the start of the modern autism epidemic it would be helpful to figure out the toxicological, viral, and bacterial context in Moscow prior to the first

cases and then attempt to identify the factors that changed that might have triggered this new disorder.

A large number of lawsuits have been filed against Monsanto for alleged harms from its herbicide, Roundup. Three hundred and twenty of those lawsuits have been combined into a class action suit that is being heard in U.S. District Court (2019). The judge in that case, Vince Chhabria, has ruled that internal Monsanto documents, turned over in discovery can be unsealed and made available to the public (U.S. District Court, 2019). This creates a large body of new documents that researchers can use to better understand Monsanto's own research into the toxicity of Roundup and potential harms.

There is an urgent need for more cross-national comparisons between countries with different autism rates and different regulatory structures. For example one could compare the regulatory framework for 200 high volume toxic chemicals, serum levels of those toxicants in the bodies of citizens, and prevalence rates of neurodevelopmental disabilities including autism between different countries. While limiting confounding variables (diet, weather, genetics) is difficult, this is a challenge that faces many cross-national comparisons and is not insurmountable.

There are likely natural experiments as a result of policy changes or unforseen events around the world that could be studied to better understand the potential role of environmental triggers in the autism epidemic. For example a coal fired power plant or a chemical plant that shuts down for maintenance or that is damaged by a natural disaster might lead to lower emissions that result in changes in autism prevalence in the area. The E.U.'s more aggressive regulation of phthalates, pesticides, and other

chemicals as compared with the U.S. could also lead to interesting comparative studies of exposures and health outcomes.

Autism is likely to be an issue of growing political and economic importance for the foreseeable future. In addition to the research projects mentioned above, the political economy of autism can and should become an entire subfield within the social sciences. In a post-positivist world, the social sciences are a vital and necessary part of the debate that involves the intersection of science, society, power, health, medicine, environment, politics, and economics.

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