

# Alternative Plasticizers As Emerging Global Environmental and Health Threat: Another Regrettable Substitution?

Abdul Qadeer,\* Kelly L Kirsten, Zeeshan Ajmal, Xia Jiang,\* and Xingru Zhao



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**KEYWORDS:** emerging contaminant, alternative plasticizer, environmental health, polyvinyl chloride, phthalate

Plasticizers are synthetic chemicals that are commonly used in polyvinyl chloride (PVC) based products, food packaging, children's toys, medical devices, and adhesives. There are about 30 000 chemicals can potentially be utilized as plasticizers.<sup>1</sup> Phthalate plasticizers are a commonly utilized compound, comprising up to 85% of the total plasticizers in the market.<sup>1</sup> Phthalate plasticizers have been regarded as hazardous compounds due to numerous reports based on its toxicological effects, including bioaccumulation potential, endocrine disruption, carcinogenicity, and developmental defects.<sup>1–4</sup> These findings resulted in global regulation measures and control of typical phthalate plasticizers<sup>5–7</sup> and the introduction and mass production of alternative plasticizers (APs), including but not limited to adipates, benzoates, phosphate esters, citrates, sebacates, terephthalates, trimellitates, cyclohexane dicarboxylic acids, and biobased alternatives.<sup>5,8</sup> The shift to incorporate APs without completely understanding their toxicities may have similar detrimental impacts, akin to phthalate plasticizers.

Regrettable substitution has an extensive historical narrative and is still a common occurrence (Table 1), resulting in negative

repercussions on public health and environment. For instance, Bisphenol A (BPA) (first made in 1891 by Alexander Dianin), which was commonly applied during the production of polycarbonate plastic, was replaced with various bisphenols (BPS, BPP, BPZ, and BPF, to name a few)<sup>9</sup> due to many reports of its toxicities (e.g., neurocognitive disabilities, reproductive, and developmental defects).<sup>9,10</sup> Subsequently, substitute bisphenols (BPS, BPP, BPZ) have been found to have similar toxicities (endocrine disruptor) or, in some cases, worse.<sup>11,12</sup> The well-known toxic chemical DDT (dichlorodiphenyltrichloroethane)—defects includes developmental issues, endocrine disruption and cancer to name a few—was replaced with

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**Table 1. Prominent Examples of Regrettable Substitutions of the Past and Its Continuous End Game**

concerned chemical	regrettable substitute	reference
bisphenol-A (BPA) (endocrine disruptor)	bisphenol-S (BPS), bisphenol-F (BPF)  bisphenol-Z (BPZ), bisphenol-P (BPP) (endocrine disruptor)	Rochester et al. 2015 <sup>11</sup>  Le Fol et al. 2017 <sup>12</sup>
DDT (reproductive toxicity, endocrine disruptor)	organophosphates and chlorpyrifos (neurotoxicity)	Rahman et al. 2013 <sup>13</sup>  Rehamn et al. 2021 <sup>16</sup>
polybrominated diphenyl ethers, PBDEs (Neurotoxicity)	organophosphate ester flame retardants, OPFRs (neurotoxicity)	Blum et al. 2019 <sup>17</sup>
lead (Neurotoxicity)	methyl <i>tert</i> -butyl ether (aquatic toxicity)	Tickner et al. 2019 <sup>18</sup>
methylene chloride (Carcinogenicity)	1-bromopropane (Carcinogenicity)	Tickner et al. 2019 <sup>18</sup>
chlorofluorocarbon, CFC (Ozone depletion)	hydrofluorocarbons, HFCs (greenhouse gas)	Tickner et al. 2019 <sup>18</sup>
$\gamma$ -Hexachloro-cyclohexan (Neurotoxicity)	imidacloprid (bee colony collapse)	Fantke et al. 2020 <sup>19</sup>
Atrazine (persistence and ecological risk)	terbutylazine (persistence and ecological risk)	Pérez et al. 2013 <sup>20</sup>  Maertens et al. 2021 <sup>21</sup>

other harmful chemicals, such as organophosphates and synthetic pyrethroids.<sup>13,14</sup> Diacetyl's (cell damage) replacement with alpha-diketone (epithelial damage) as butter flavoring is another example of a regrettable substitution.<sup>15</sup> The continuous practice of replacing one harmful chemical with another is a long lasting problem, as represented by many prominent examples of the past in Table 1.

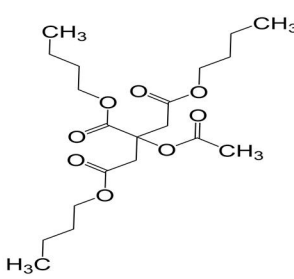
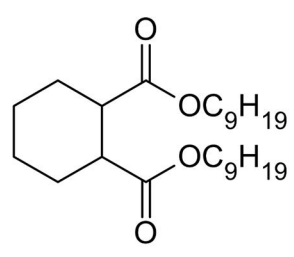
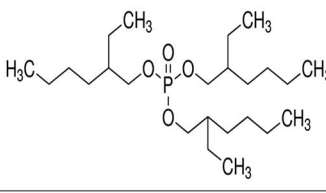
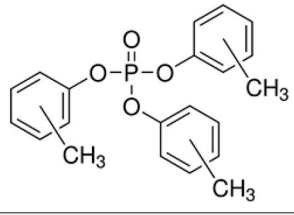
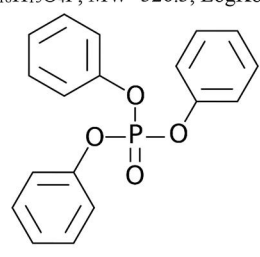
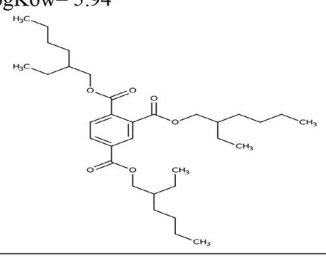
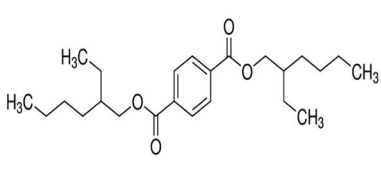
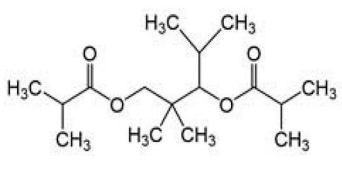
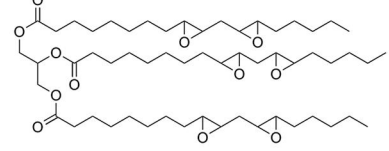
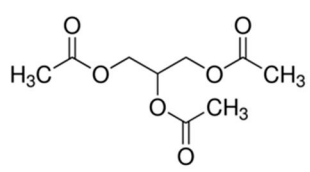
It may be expected that, similar to phthalates, APs are also likely to be pseudopersistent in the environment as APs are not chemically bonded to their products and can easily leach out from their source material. Thus, APs have the potential to pollute and threaten environmental and human health. Emerging reports (mostly from 2020) have indicated that APs contamination has been discovered in aquatic environments,<sup>22</sup> sediments,<sup>5,23–27</sup> biota<sup>27,28</sup> (such as plants and fish), and food items.<sup>29</sup> Additionally, a high number of reports indicated APs contamination in urban domestic soils (e.g., school and home dust) across Europe (Belgium, Ireland, Netherlands, and Sweden),<sup>30–32</sup> Japan,<sup>33</sup> China,<sup>34</sup> and the United States.<sup>35</sup> High incidence of APs in domestic dust is attributable to migration of plasticizers from toys, childcare articles, and school goods.<sup>32,36,37</sup> A mega-study showed APs metabolites in school kids across Asia (Thailand, Indonesia, and Saudi Arabia).<sup>38</sup> Similarly, APs metabolites were detected in adolescents from Flanders, Belgium with their concentration levels comparable to APs in their domestic environment, viz. school and household. APs metabolites have been detected across all age groups and genders<sup>39,40</sup> suggesting a widespread presence of APs in the domestic environment.

The latest studies indicate that APs contamination began to increase across all components of the environment (e.g., water, soil, and sediment) especially in urban dust. Higher levels of APs in the environment can lead to potential ecological and health risks. Generally, data relating to toxicities on emerging alternatives to phthalate plasticizers are extremely limited, however, some typical APs compounds, including acetyl tributyl citrate (ovarian toxicity,<sup>41,42</sup> endocrine disrupting<sup>43</sup> and neuro-

toxicity<sup>8</sup>), diisononyl cyclohexane-1,2 dicarboxylate (cytotoxicity,<sup>44</sup> DNA damage,<sup>44,45</sup> neurotoxicity,<sup>46</sup> metabolic toxicity<sup>46</sup>), tris-2-ethylhexyl phosphate (endocrine disrupting<sup>8,47</sup>), tricresyl phosphate (neurotoxicity,<sup>48,49</sup> DNA damage<sup>49,50</sup>), triphenyl phosphate (reproductive toxicity,<sup>51</sup> developmental toxicity,<sup>52</sup> endocrine disrupting<sup>53–55</sup>), and tris-2-ethylhexyl trimellitate (cell toxicity,<sup>56</sup> estrogenic activity,<sup>56</sup> hepatotoxicity<sup>57</sup>) have potential toxic effects, which needs further exploration. Bis-2-ethylhexyl terephthalate was considered a safe alternative by a few researchers<sup>8,58</sup> in opposition to *in silico* investigations,<sup>59</sup> while a Japanese<sup>60</sup> study suspected it could be a potential endocrine disruptor and reproductive toxicant. There are a considerable number of alternative plasticizers in employment, without any toxicological data available (dibutyl adipate, diethylene glycol dibenzoate, and bis-2-ethylhexyl sebacate, to name a few). Currently, it is challenging to label alternative plasticizer as safe compounds due to the unavailability of quality data; however, a few compounds can be regarded as potentially “least toxic” or a “safe alternative”, including trimethyl pentanoyl diisobutyrate,<sup>61</sup> epoxidized soybean oil,<sup>62,63</sup> and glycerin triacetate<sup>64</sup> (generally regarded as safe). Structure, CAS number, and basic properties of APs are provided in Figure 1.

In marine and freshwater ecosystems, APs compounds may lead to bioaccumulation resulting in potential ecological risks. Generally, octanol–water partition coefficient ( $\log K_{ow}$ ) values higher than 5 can provide a basic indication of the bioaccumulation capacity of hazardous compounds. As previously outlined above, some potentially harmful APs compounds have high  $\log K_{ow}$  values, ranging from 4.59 (Triphenyl phosphate) to 10 (diisononyl cyclohexane-1,2 dicarboxylate), similar to phthalates and legacy pollutants (e.g., polychlorinated biphenyls, PCBs). Biobased plasticizers,<sup>66–68</sup> such as soyabean oil, castor oil (as examples provide in previous paragraph), cardanol, and isosorbide, can provide safe alternatives based on their hypotoxicity, renewability, degradability, and plasticizing performances.<sup>68</sup>

Preventing regrettable substitutions is a considerable challenge for scientists globally. Green chemistry,<sup>69,70</sup> and intelligent toxicology<sup>71,72</sup> can provide a safe way forward as elaborated in a proposed general framework to avoid regrettable substitutions in Figure 2. Green chemistry can enable the design and production of least toxic/safe alternative chemicals based on 12 green principles,<sup>70</sup> thus eliminating hazardous waste. Emerging intelligent toxicological tools can provide critical information (e.g., AI-based computational tools),<sup>71</sup> from chemical toxicity to environmental hazards at early stages of development. It is not only efficient in reducing incidence of regrettable substitution but will also result in greater economic advantage and time efficiency. Although green chemistry approaches and intelligent toxicology can provide comparatively safe alternatives, design and status (safe or toxic) of new chemicals should be continuously revisited and improved as new data emerges. For instance, the replacement of chromated copper arsenate (CCA - carcinogenic) with alkaline copper quaternary (ACQ) as a wood preservative product is considered as successful example of informed substitution.<sup>15</sup> This replacement was an intentional transition from a chemical of high concern to safer chemicals of lower concern after thoughtful consideration.<sup>18</sup> However, at later stages concerns have been raised on the aquatic ecotoxicity of ACQ.<sup>15,73</sup> The life cycle assessment (LCA) of new chemicals,<sup>74</sup> and future toxicological and environmental data will help to revisit the chemical status and design to eliminate any future hazards.

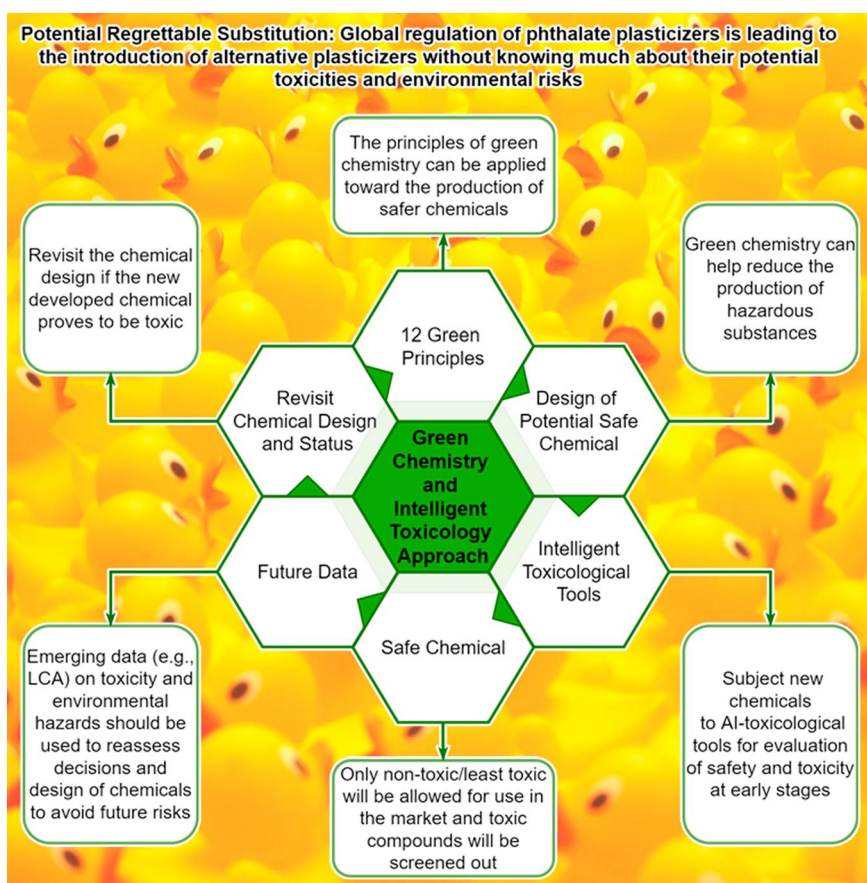
<p><b>CAS#77-90-7, Acetyl tributyl citrate</b>, MF=<math>C_{20}H_{34}O_8</math> MW= 402.5, LogK<sub>ow</sub>=4.92</p> 	<p><b>CAS#166412-78-8, Diisononyl cyclohexane-1,2 dicarboxylate</b>, MF=<math>C_{26}H_{48}O_4</math>, MW=424.7, LogK<sub>ow</sub>=10</p> 
<p><b>CAS#78-42-2, Tris-2-ethylhexyl phosphate</b>, MF=<math>C_{24}H_{51}O_4P</math>, MW=434.6 LogK<sub>ow</sub>=9.49</p> 	<p><b>CAS#78-32-0, Tricresyl phosphate</b>, MF=<math>C_{21}H_{21}O_4P</math>, MW=368.4, LogK<sub>ow</sub>=6.34</p> 
<p><b>CAS#115-86-6, Triphenyl phosphate</b>, MF=<math>C_{18}H_{15}O_4P</math>, MW=326.3, LogK<sub>ow</sub>=4.59</p> 	<p><b>CAS#3319-31-1, 546.8 tris-2-ethylhexyl trimellitate</b>, MF=<math>C_{33}H_{54}O_6</math>, MW=546.78, LogK<sub>ow</sub>= 5.94</p> 
<p><b>CAS#6422-86-2 Bis-2-ethylhexyl terephthalate</b>, MF=<math>C_{24}H_{38}O_4</math>, MW=390.56, LogK<sub>ow</sub>=8.39</p> 	<p><b>CAS#6846-50-0, Trimethyl pentanyl diisobutyrate</b>, MF= <math>C_{16}H_{30}O_4</math>, MW= 286.41, LogK<sub>ow</sub>= 4.91</p> 
<p><b>CAS# 8013-07-8, Epoxidized soybean oil</b>, MF= <math>C_{57}H_{98}O_{12}</math>, MW= 975.4, Logk<sub>ow</sub>=14.84</p> 	<p><b>CAS#102-76-1 Glycerin triacetate</b>, MF= <math>C_9H_{14}O_6</math>, MW=218.2, LogK<sub>ow</sub>=0.25</p> 

**Figure 1.** Names, chemical structures, CAS numbers, and basic properties of typical alternative plasticizers. Data was acquired from chemistry database TOXNET and calculation of logK<sub>ow</sub> values are based on EPI Suite Model of the USEPA.<sup>65</sup> MF stands for molecular formula, and MW stands for molecular weight.

It has been estimated that the global plasticizer market is expected to grow from 13 967.9 million dollars in 2018 to 16 700.6 million dollars in 2024,<sup>75</sup> thereby indicating the

potential magnitude of this emerging environmental problem. As previously discussed, some APs have the potential to cause toxicological effects similar to phthalate plasticizers, which could





**Figure 2.** A.Q general framework of green chemistry and intelligent toxicology to prevent regrettable substitutions.

lead to another regrettable substitution scenario. Urban communities, particularly children, are the most vulnerable due to the high incidence of APs in their environment. In 2016, the Lautenberg Chemical Safety Act updated the 40 year old Toxic Substances Control Act (TSCA),<sup>76</sup> the revision may provide the United States Environmental Protection Agency (USEPA) greater authority to regulate commercially used chemicals. However, with more than 60 000<sup>77</sup> chemicals already in use in the market and growing by an estimated 2000+ chemicals per year,<sup>78</sup> a massive undertaking would be required to get a full assessment of each chemical in use. Ideally, the process would require that each chemical be assessed as an individual, irrespective of its similarity to the parent chemical, to overcome the historical repetition of regrettable substitution. Indeed, a time-consuming and resource heavy, yet necessary undertaking. This should be seen as a priority for agencies and governments when allocating their budgetary resources and should include staff training and consistent funding. The role of green chemistry is inevitable for the design and production of safe alternatives to avoid future regrettable substitution. The application of intelligent toxicological tools can help to identify the potential harmful alternatives at early stages so that ecological and health risks as well as economic consequences can be avoided. Currently, there is a general lack of APs toxicological and environmental impact studies. Research on toxicological profiles and environmental impacts are urgently needed to avoid regrettable substitution of phthalate plasticizers with APs. Additionally, further environmental monitoring of APs in different environmental mediums (air, water bodies, and biota) are required.

## AUTHOR INFORMATION

### Corresponding Authors

**Abdul Qadeer** – State Key Laboratory of Environmental Criteria and Risk Assessment, National Engineering Laboratory for Lake Pollution Control and Ecological Restoration, Chinese Research Academy of Environmental Sciences, Beijing 100012, China; [orcid.org/0000-0001-7018-4958](https://orcid.org/0000-0001-7018-4958); Email: [Dr.AQ.Geographer@gmail.com](mailto:Dr.AQ.Geographer@gmail.com)

**Xia Jiang** – State Key Laboratory of Environmental Criteria and Risk Assessment, National Engineering Laboratory for Lake Pollution Control and Ecological Restoration, Chinese Research Academy of Environmental Sciences, Beijing 100012, China; Email: [jiangxia@craes.org.cn](mailto:jiangxia@craes.org.cn)

### Authors

**Kelly L Kirsten** – Department of Geological Sciences, University of Cape Town, Cape Town 8001, South Africa

**Zeeshan Ajmal** – College of Engineering, China Agricultural University, 100083 Beijing, China

**Xingru Zhao** – State Key Laboratory of Environmental Criteria and Risk Assessment, National Engineering Laboratory for Lake Pollution Control and Ecological Restoration, Chinese Research Academy of Environmental Sciences, Beijing 100012, China

Complete contact information is available at: <https://pubs.acs.org/10.1021/acs.est.1c08365>

### Notes

The authors declare no competing financial interest.

## Biographies



Dr. Abdul Qadeer (Dr. AQ) is a Young Environmental Scientist working at the Chinese Research Academy of Environmental Sciences, Beijing, China. He earned a PhD degree from East China Normal University, Shanghai in Environmental Geography. His research focuses on legacy and emerging pollutants in the environment and risks. Currently, he is working on emerging pollutants in environmental multiphase and their bioaccumulation processes by using models and field studies. He has published several research articles, book chapters, and perspectives in prestigious journals. He received an excellent research award in 2019. He is open to international/local collaborations and opportunities.



Dr. Kelly Kirsten is a researcher at the Department of Geological Sciences at the University of Cape Town, South Africa. She has earned a PhD degree in Environmental and Geographical Science. Her work focuses on understanding the long-term development and responses of water bodies to climate variability in South Africa. The goal for her climapAfrica research project is to provide a sound understanding of climate system variability during the Quaternary for the interior of South Africa, and determine how these changes impact human development, both past, present and future.

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