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Viewpoint

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

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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.[1] Phthalate plasticizers are a commonly utilized compound, comprising up to 85% of the total plasticizers in the market.[1] 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.[1−4] These findings resulted in global regulation measures and control of typical phthalate plasticizers[5−7] 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.[5,8] 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)[9] due to many reports of its toxicities (e.g., neurocognitive disabilities. reproductive, and developmental defects).[9,10] Subsequently, substitute bisphenols (BPS, BPP, BPZ) have been found to have similar toxicities (endocrine disruptor) or, in some cases, worse.[11,12] 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)	Rochester et al. 2015[11]
	bisphenol-Z (BPZ), bisphenol-P (BPP)	Le Fol et al. 2017[12]
	(endocrine disruptor)	
DDT (reproductive toxicity, endocrine disruptor)	organophosphates and cholorpyrifos (neurotoxicity)	Rahman et al. 2013[13]
		Rehamn et al. 2021[16]
polybrominated diphenyl ethers, PBDEs (Neurotoxicity)	organophosphate ester flame retardants, OPFRs (neurotoxicity)	Blum et al. 2019[17]
lead (Neurotoxicity)	methyl *tert*-butyl ether (aquatic toxicity)	Tickner et al. 2019[18]
methylene chloride (Carcinogenicity)	1-bromopropane (Carcinogenicity)	Tickner et al. 2019[18]
chlorofluorocarbon, CFC (Ozone depletion)	hydrofluorocarbons, HFCs (greenhouse gas)	Tickner et al. 2019[18]
γ-Hexachloro-cyclohexan (Neurotoxicity)	imidacloprid (bee colony collapse)	Fantke et al. 2020[19]
Atrazine (persistency and ecological risk)	terbuthylazine (persistency and ecological risk)	Pérez et al. 2013[20]
		Maertens et al. 2021[21]

other harmful chemicals, such as organophosphates and synthetic pyrethroids.[13,14] Diacetyl's (cell damage) replacement with alpha-diketone (epithelial damage) as butter flavoring is another example of a regrettable substitution.[15] 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,[22] sediments,[5,23−27] biota[27,28] (such as plants and fish), and food items.[29] 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),[30−32] Japan,[33] China,[34] and the United States.[35] High incidence of APs in domestic dust is attributable to migration of plasticizers from toys, childcare articles, and school goods.[32,36,37] A mega-study showed APs metabolites in school kids across Asia (Thailand, Indonesia, and Saudi Arabia).[38] 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[39,40] 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,[41,42] endocrine disrupting[43] and neurotoxicity[8]), diisononyl cyclohexane-1,2 dicarboxylate (cytotoxicity,[44] DNA damage,[44,45] neurotoxicity,[46] metabolic toxicity[46]), tris-2-ethylhexyl phosphate (endocrine disrupting[8,47]), tricresyl phosphate (neurotoxicity,[48,49] DNA damage[49,50]), triphenyl phosphate (reproductive toxicity,[51] developmental toxicity,[52] endocrine disrupting[53−55]), and tris-2-ethylhexyl trimellitate (cell toxicity,[56] estrogenic activity,[56] hepatotoxicity[57]) have potential toxic effects, which needs further exploration. Bis-2-ethylhexyl terephthalate was considered a safe alternative by a few researchers[8,58] in opposition to in silico investigations,[59] while a Japanese[60] 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 pentanyl diisobutyrate,[61] epoxidized soybean oil,[62,63] and glycerin triacetate[64] (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,[66−68] 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.[68]

Preventing regrettable substitutions is a considerable challenge for scientists globally. Green chemistry,[69,70] and intelligent toxicology[71,72] 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,[70] thus eliminating hazardous waste. Emerging intelligent toxicological tools can provide critical information (e.g., AI-based computational tools),[71] 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.[15] This replacement was an intentional transition from a chemical of high concern to safer chemicals of lower concern after thoughtful consideration.[18] However, at later stages concerns have been raised on the aquatic ecotoxicity of ACQ.[15,73] The life cycle assessment (LCA) of new chemicals,[74] and future toxicological and environmental data will help to revisit the chemical status and design to eliminate any future hazards.

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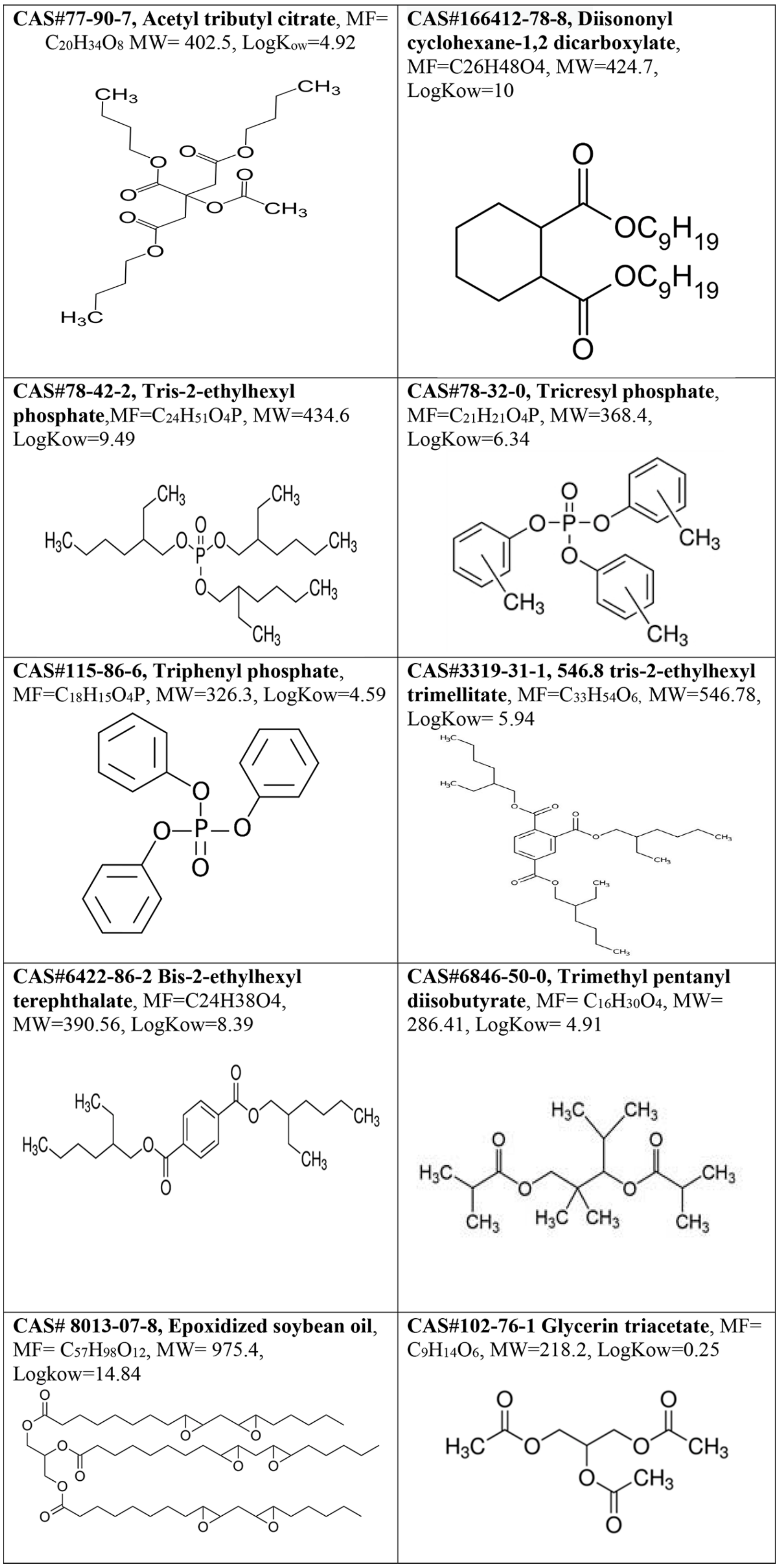

Figure 1. Names, chemical structures, CAS numbers, and basic properties of typical alternative plasticizers. Data was acquired from chemistry database TOXNET and calculation of $\log K_{ow}$ values are based on EPI Suite Model of the USEPA.[65] MF stands for molecular formula, and MW stands for molecular 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,[75] 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

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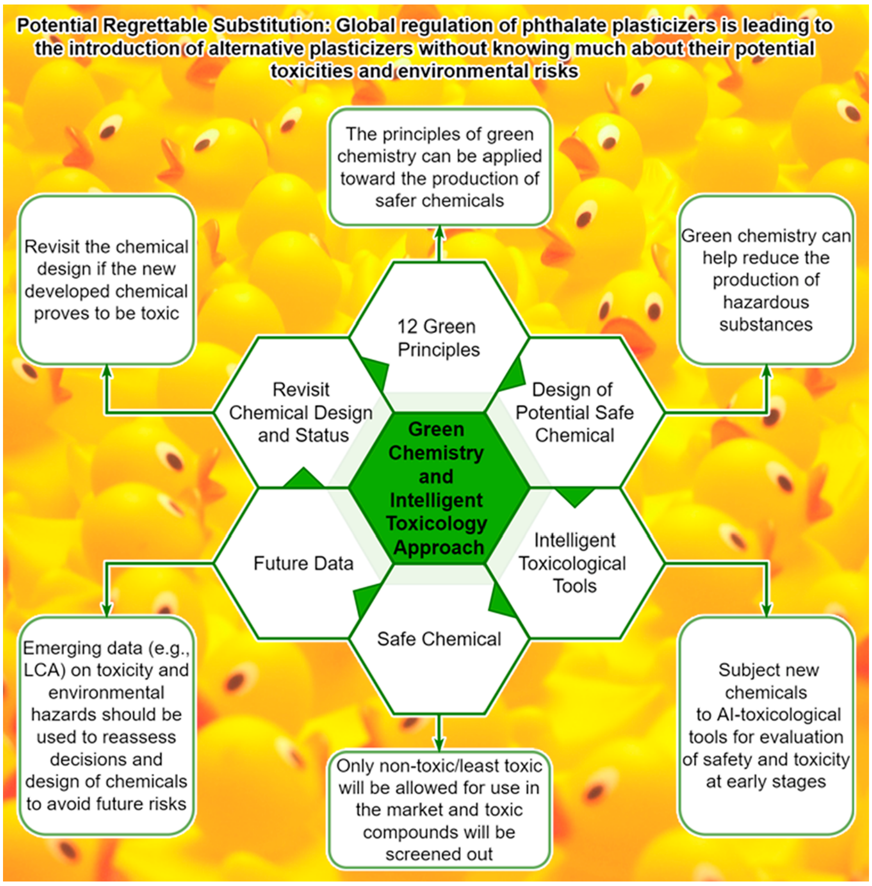

Figure 2. A.Q general framework of green chemistry and intelligent toxicology to prevent regrettable substitutions.

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),[76] the revision may provide the United States Environmental Protection Agency (USEPA) greater authority to regulate commercially used chemicals. However, with more than 60 000[77] chemicals already in use in the market and growing by an estimated 2000+ chemicals per year,[78] 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.

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Notes

The authors declare no competing financial interest.

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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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■ REFERENCES

(1) Godwin, A. D. Plasticizers. In *Appl. Plast. Eng. Handb.*, 2nd ed., 2017, 533−553. DOI: 10.1016/B978-0-323-39040-8/00025-0.

(2) Huang, P. C.; Liou, S. H.; Ho, I. K.; Chiang, H. C.; Huang, H. I.; Wang, S. L. Phthalates Exposure and Endocrinal Effects: An Epidemiological Review. *J. Food Drug Anal.* **2012**, *20* (4), 719−733.

(3) Jurewicz, J.; Hanke, W. Exposure to Phthalates: Reproductive Outcome and Children Health. A Review of Epidemiological Studies. *Int. J. Occup. Med. Environ. Health* **2011**, *24* (2), 115−141.

(4) Mankidy, R.; Wiseman, S.; Ma, H.; Giesy, J. P. Biological Impact of Phthalates. *Toxicol. Lett.* **2013**, *217* (1), 50−58.

(5) Kim, S.; Kim, Y.; Moon, H. B. Contamination and Historical Trends of Legacy and Emerging Plasticizers in Sediment from Highly Industrialized Bays of Korea. *Sci. Total Environ.* **2021**, *765* (xxxx), 142751.

(6) Ventrice, P.; Ventrice, D.; Russo, E.; De Sarro, G. Phthalates: European Regulation, Chemistry, Pharmacokinetic and Related Toxicity. *Environ. Toxicol. Pharmacol.* **2013**, *36* (1), 88−96.

(7) US EPA. Appendix A to 40 CFR, Part 423−126 Priority Pollutants. **2014**, 653−654.

(8) Bui, T. T.; Giovanoulis, G.; Palm, A.; Magnér, J.; Cousins, I. T.; Wit, C. A. De Human Exposure, Hazard and Risk of Alternative Plasticizers to Phthalate Esters. *Sci. Total Environ.* **2016**, *541*, 451−467.

(9) Trasande, L. Exploring Regrettable Substitution: Replacements for Bisphenol A. *Lancet Planet. Heal.* **2017**, *1* (3), No. e88-e89.

(10) Rochester, J. R. Bisphenol A and Human Health: A Review of the Literature. *Reprod. Toxicol.* **2013**, *42*, 132−155.

(11) Rochester, J. R.; Bolden, A. L. Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol a Substitutes. *Environ. Health Perspect.* **2015**, *123* (7), 643−650.

(12) Le Fol, V.; Aït-Aïssa, S.; Sonavane, M.; Porcher, J. M.; Balaguer, P.; Cravedi, J. P.; Zalko, D.; Brion, F. In Vitro and in Vivo Estrogenic Activity of BPA, BPF and BPS in Zebrafish-Specific Assays. *Ecotoxicol. Environ. Saf.* **2017**, *142*, 150−156.

(13) Rahman, M. M. Insecticide Substitutes for DDT to Control Mosquitoes May Be Causes of Several Diseases. *Environ. Sci. Pollut. Res.* **2013**, *20* (4), 2064−2069.

(14) Liu, W.; Zhang, J.; Hashim, J. H.; Jalaludin, J.; Hashim, Z.; Goldstein, B. D. Mosquito Coil Emissions and Health Implications. *Environ. Health Perspect.* **2003**, *111* (12), 1454−1460.

(15) Zimmerman, J. B.; Anastas, P. T. Toward Substitution with No Regrets. *Science (80-.).* **2015**, *347* (6227), 1198−1199.

(16) Ubaid ur Rahman, H.; Asghar, W.; Nazir, W.; Sandhu, M. A.; Ahmed, A.; Khalid, N. A Comprehensive Review on Chlorpyrifos Toxicity with Special Reference to Endocrine Disruption: Evidence of Mechanisms, Exposures and Mitigation Strategies. *Sci. Total Environ.* **2021**, *755*, 142649.

(17) Blum, A.; Behl, M.; Birnbaum, L. S.; Diamond, M. L.; Phillips, A.; Singla, V.; Sipes, N. S.; Stapleton, H. M.; Venier, M. Organophosphate Ester Flame Retardants: Are They a Regrettable Substitution for Polybrominated Diphenyl Ethers? *Environ. Sci. Technol. Lett.* **2019**, *6* (11), 638−649.

(18) Tickner, J.; Jacobs, M. M.; Mack, N. B. Alternatives Assessment and Informed Substitution: A Global Landscape Assessment of Drivers, Methods, Policies and Needs. *Sustain. Chem. Pharm.* **2019**, *13*, 100161.

(19) Fantke, P.; Huang, L.; Overcash, M.; Griffing, E.; Jolliet, O. Life Cycle Based Alternatives Assessment (LCAA) for Chemical Substitution. *Green Chem.* **2020**, *22* (18), 6008−6024.

(20) Pérez, J.; Domingues, I.; Monteiro, M.; Soares, A. M. V. M.; Loureiro, S. Synergistic Effects Caused by Atrazine and Terbuthylazine on Chlorpyrifos Toxicity to Early-Life Stages of the Zebrafish Danio Rerio. *Environ. Sci. Pollut. Res. 2012 207* **2013**, *20* (7), 4671−4680.

(21) Maertens, A.; Golden, E.; Hartung, T. Avoiding Regrettable Substitutions: Green Toxicology for Sustainable Chemistry. *ACS Sustain. Chem. Eng.* **2021**, *9* (23), 7749−7758.

(22) Nagorka, R.; Koschorreck, J. Trends for Plasticizers in German Freshwater Environments - Evidence for the Substitution of DEHP with Emerging Phthalate and Non-Phthalate Alternatives. *Environ. Pollut.* **2020**, *262*, 114237.

(23) Kim, S.; Lee, Y. S.; Moon, H. B. Occurrence, Distribution, and Sources of Phthalates and Non-Phthalate Plasticizers in Sediment from Semi-Enclosed Bays of Korea. *Mar. Pollut. Bull.* **2020**, *151* (September 2019), 110824.

(24) Lee, Y. S.; Lim, J. E.; Lee, S.; Moon, H. B. Phthalates and Non-Phthalate Plasticizers in Sediment from Korean Coastal Waters: Occurrence, Spatial Distribution, and Ecological Risks. *Mar. Pollut. Bull.* **2020**, *154*, 111119.

(25) Liu, Y. E.; Luo, X. J.; Huang, C. C.; Zeng, Y. H.; Lu, Q.; Wang, S.; Mai, B. X. Legacy and Alternative Plasticizers in Surface Sediment of Black-Odorous Urban Rivers across China: Occurrence, Spatial Distribution, and Ecological Risk Assessment. *Chemosphere* **2021**, *283*, 131206.

(26) Kim, Y.; Kim, S.; Liao, C.; Moon, H. B. Severe Contamination and Time Trend of Legacy and Alternative Plasticizers in a Highly Industrialized Lake Associated with Regulations and Coastal Development. *Mar. Pollut. Bull.* **2021**, *171*, 112787.

(27) Jebara, A.; Albergamo, A.; Rando, R.; Potortì, A. G.; Lo Turco, V.; Mansour, H. B.; Di Bella, G. Phthalates and Non-Phthalate Plasticizers in Tunisian Marine Samples: Occurrence, Spatial Distribution and Seasonal Variation. *Mar. Pollut. Bull.* **2021**, *163*, 111967.

(28) Liu, Y.; Tang, B.; Liu, Y.; Luo, X.; Mai, B.; Covaci, A.; Poma, G. Occurrence, Biomagnification and Maternal Transfer of Legacy and Emerging Organophosphorus Flame Retardants and Plasticizers in Water Snake from an e-Waste Site. *Environ. Int.* **2019**, *133*, 105240.

(29) Edwards, L.; McCray, N. L.; VanNoy, B. N.; Yau, A.; Geller, R. J.; Adamkiewicz, G.; Zota, A. R. Phthalate and Novel Plasticizer Concentrations in Food Items from U.S. Fast Food Chains: A Preliminary Analysis. *J. Expo. Sci. Environ. Epidemiol.* **2021**, *2021*, 1−8.

(30) Christia, C.; Poma, G.; Harrad, S.; Wit, C. A.; De Sjostrom, Y.; Leonards, P.; Lamoree, M.; Covaci, A. Occurrence of Legacy and Alternative Plasticizers in Indoor Dust from Various EU Countries and Implications for Human Exposure via Dust Ingestion and Dermal Absorption Christina. *Environ. Res.* **2019**, *171*, 204−212.

(31) Larsson, K.; Lindh, C. H.; Ag, B. J.; Giovanoulis, G.; Bibi, M.; Bottai, M.; Bergström, A.; Berglund, M. Phthalates, Non-Phthalate Plasticizers and Bisphenols in Swedish Preschool Dust in Relation to Children's Exposure. *Environ. Int.* **2017**, *102*, 114−124.

(32) Giovanoulis, G.; Nguyen, M. A.; Arwidsson, M.; Langer, S.; Vestergren, R.; Lagerqvist, A. Reduction of Hazardous Chemicals in Swedish Preschool Dust through Article Substitution Actions. *Environ. Int.* **2019**, *130*, 104921.

(33) Takeuchi, S.; Kojima, H.; Saito, I.; Jin, K.; Kobayashi, S.; Tanaka-Kagawa, T.; Jinno, H. Detection of 34 Plasticizers and 25 Flame Retardants in Indoor Air from Houses in Sapporo, Japan. *Sci. Total Environ.* **2014**, *491−492*, 28−33.

(34) Tang, B.; Christia, C.; Malarvannan, G.; Liu, Y. E.; Luo, X. J.; Covaci, A.; Mai, B. X.; Poma, G. Legacy and Emerging Organophosphorus Flame Retardants and Plasticizers in Indoor Microenvironments from Guangzhou, South China. *Environ. Int.* **2020**, *143* (July), 105972.

(35) Subedi, B.; Sullivan, K. D.; Dhungana, B. Phthalate and Non-Phthalate Plasticizers in Indoor Dust from Childcare Facilities, Salons, and Homes across the USA *. *Environ. Pollut.* **2017**, *230*, 701−708.

(36) Xie, M.; Wu, Y.; Little, J. C.; Marr, L. C. Phthalates and Alternative Plasticizers and Potential for Contact Exposure from Children's Backpacks and Toys. *J. Expo. Sci. Environ. Epidemiol.* **2016**, *26* (1), 119−124.

(37) Babich, M. A.; Bevington, C.; Dreyfus, M. A. Plasticizer Migration from Children's Toys, Child Care Articles, Art Materials, and School Supplies. *Regul. Toxicol. Pharmacol.* **2020**, *111*, 104574.

(38) Lee, I.; Pälmke, C.; Ringbeck, B.; Ihn, Y.; Gotthardt, A.; Lee, G.; Alakeel, R.; Alrashed, M.; Tosepu, R.; Jayadipraja, E. A.; Tantrakarnapa, K.; Kliengchuay, W.; Kho, Y.; Koch, H. M.; Choi, K. Urinary Concentrations of Major Phthalate and Alternative Plasticizer Metabolites in Children of Thailand, Indonesia, and Saudi Arabia, and Associated Risks. *Environ. Sci. Technol.* **2021**. 5516526.

(39) Wenzel, A. G.; Reiner, J. L.; Kohno, S.; Wolf, B. J.; Brock, J. W.; Cruze, L.; Newman, R. B.; Kucklick, J. R. Biomonitoring of Emerging DINCH Metabolites in Pregnant Women in Charleston, SC: 2011−2014. *Chemosphere* **2021**, *262*, 128369.

(40) Bastiaensen, M.; Malarvannan, G.; Gys, C.; Ait Bamai, Y.; Araki, A.; Covaci, A. Between- and within-Individual Variability of Urinary Phthalate and Alternative Plasticizer Metabolites in Spot, Morning Void and 24-h Pooled Urine Samples. *Environ. Res.* **2020**, *191*, 110248.

(41) Rasmussen, L. M.; Sen, N.; Liu, X.; Craig, Z. R. Effects of Oral Exposure to the Phthalate Substitute Acetyl Tributyl Citrate on Female Reproduction in Mice. *J. Appl. Toxicol.* **2017**, *37* (6), 668−675.

(42) Rasmussen, L. M.; Sen, N.; Vera, J. C.; Liu, X.; Craig, Z. R. Effects of in Vitro Exposure to Dibutyl Phthalate, Mono-Butyl Phthalate, and Acetyl Tributyl Citrate on Ovarian Antral Follicle Growth and Viability. *Biol. Reprod.* **2017**, *96* (5), 1105−1117.

(43) Sheikh, I. A.; Beg, M. A. Structural Characterization of Potential Endocrine Disrupting Activity of Alternate Plasticizers Di-(2-Ethylhexyl) Adipate (DEHA), Acetyl Tributyl Citrate (ATBC) and 2,2,4-Trimethyl 1,3-Pentanediol Diisobutyrate (TPIB) with Human Sex Hormone-Binding Globu. *Reprod. Toxicol.* **2019**, *83*, 46−53.

(44) Vasconcelos, A. L.; Silva, M. J.; Louro, H. In Vitro Exposure to the Next-Generation Plasticizer Diisononyl Cyclohexane-1,2-Dicarboxylate (DINCH): Cytotoxicity and Genotoxicity Assessment in Human Cells. *J. Toxicol. Environ. Heal. - Part A Curr. Issues* **2019**, *82* (9), 526−536.

(45) Eljezi, T.; Pinta, P.; Richard, D.; Pinguet, J.; Chezal, J. M.; Chagnon, M. C.; Sautou, V.; Grimandi, G.; Moreau, E. In Vitro Cytotoxic Effects of DEHP-Alternative Plasticizers and Their Primary Metabolites on a L929 Cell Line. *Chemosphere* **2017**, *173*, 452−459.

(46) Saad, N.; Bereketoglu, C.; Pradhan, A. Di(Isononyl) Cyclohexane-1,2-Dicarboxylate (DINCH) Alters Transcriptional Profiles, Lipid Metabolism and Behavior in Zebrafish Larvae. *Heliyon* **2021**, *7* (9), No. e07951.

(47) Pelletier, G.; Rigden, M.; Wang, G. S.; Caldwell, D.; Siddique, S.; Leingartner, K.; Kosarac, I.; Cakmak, S.; Kubwabo, C. Comparison of Tris(2-Ethylhexyl) Phosphate and Di(2-Ethylhexyl) Phosphoric Acid Toxicities in a Rat 28-Day Oral Exposure Study. *J. Appl. Toxicol.* **2020**, *40* (5), 600−618.

(48) Chang, Y.; Cui, H.; Jiang, X.; Li, M. Comparative Assessment of Neurotoxicity Impacts Induced by Alkyl Tri-n-Butyl Phosphate and Aromatic Tricresyl Phosphate in PC12 Cells. *Environ. Toxicol.* **2020**, *35* (12), 1326−1333.

(49) Yang, Y.; Xiao, Y.; Chang, Y.; Cui, Y.; Klobučar, G.; Li, M. Intestinal Damage, Neurotoxicity and Biochemical Responses Caused by Tris (2-Chloroethyl) Phosphate and Tricresyl Phosphate on Earthworm. *Ecotoxicol. Environ. Saf.* **2018**, *158*, 78−86.

(50) Shi, Q.; Wang, Z.; Chen, L.; Fu, J.; Han, J.; Hu, B.; Zhou, B. Optical Toxicity of Triphenyl Phosphate in Zebrafish Larvae. *Aquat. Toxicol.* **2019**, *210*, 139−147.

(51) Li, Y.; Chen, R.; He, J.; Ma, H.; Zhao, F.; Tao, S.; Liu, J.; Hu, J. Triphenyl Phosphate at Environmental Levels Retarded Ovary Development and Reduced Egg Production in Japanese Medaka (Oryzias Latipes). *Environ. Sci. Technol.* **2019**, *53* (24), 14709−14715.

(52) Yuan, S.; Li, H.; Dang, Y.; Liu, C. Effects of Triphenyl Phosphate on Growth, Reproduction and Transcription of Genes of Daphnia Magna. *Aquat. Toxicol.* **2018**, *195*, 58−66.

(53) Preston, E. V.; McClean, M. D.; Claus Henn, B.; Stapleton, H. M.; Braverman, L. E.; Pearce, E. N.; Makey, C. M.; Webster, T. F. Associations between Urinary Diphenyl Phosphate and Thyroid Function. *Environ. Int.* **2017**, *101*, 158−164.

(54) Meeker, J. D.; Cooper, E. M.; Stapleton, H. M.; Hauser, R. Exploratory Analysis of Urinary Metabolites of Phosphorus-Containing Flame Retardants in Relation to Markers of Male Reproductive Health. *Endocr. Disruptors* **2013**, *1* (1), No. e26306.

(55) Isales, G. M.; Hipszer, R. A.; Raftery, T. D.; Chen, A.; Stapleton, H. M.; Volz, D. C. Triphenyl Phosphate-Induced Developmental Toxicity in Zebrafish: Potential Role of the Retinoic Acid Receptor. *Aquat. Toxicol.* **2015**, *161*, 221−230.

(56) Iwase, H. Biological Effects of the Plasticizer Tris (2-Ethylhexyl) Trimellitate. *Clin. Pharmacol. Biopharm.* **2014**, *S2* (e001). DOI: 10.4172/2167-065X.S2-004.
(57) Chen, X. H.; Ma, L.; Hu, Y. X.; Wang, D. X.; Fang, L.; Li, X. L.; Zhao, J. C.; Yu, H. R.; Ying, H. Z.; Yu, C. H. Transcriptome Profiling and Pathway Analysis of Hepatotoxicity Induced by Tris (2-Ethylhexyl) Trimellitate (TOTM) in Mice. *Environ. Toxicol. Pharmacol.* **2016**, *41*, 62−71.
(58) Faber, W. D.; Deyo, J. A.; Stump, D. G.; Navarro, L.; Ruble, K.; Knapp, J. Developmental Toxicity and Uterotrophic Studies with Di-2-Ethylhexyl Terephthalate. *Birth Defects Res. Part B - Dev. Reprod. Toxicol.* **2007**, *80* (5), 396−405.
(59) Sheikh, I. A.; Yasir, M.; Abu-Elmagd, M.; Dar, T. A.; Abuzenadah, A. M.; Damanhouri, G. A.; Al-Qahtani, M.; Beg, M. A. Human Sex Hormone-Binding Globulin as a Potential Target of Alternate Plasticizers: An in Silico Study. *BMC Struct. Biol.* **2016**, *16*, 11−20.
(60) Koizumi, M. H.; Mika, T.; Mariko, M.; Tomoko, K.; Atsushi, O.; Akihiko, H. Toxicity Effects of Phthalate Substitute Plasticizers Used in Toys. *Kokuritsu Iyakuhin Shokuhin Eisei Kenkyusho. Hokoku* **2012**, No. 130, 31−32.
(61) Maag, J.; Lassen, C.; Brandt, U. K.; Kjølholt, J.; Molander, L.; Mikkelsen, H.; Cowi, A. S. Identification and Assessment of Alternatives to Selected Phthalates, Environmental Project No. 1341. *Danish Environ. Prot. Agency* **2010**.
(62) Bueno-Ferrer, C.; Garrigós, M. C.; Jiménez, A. Characterization and Thermal Stability of Poly(Vinyl Chloride) Plasticized with Epoxidized Soybean Oil for Food Packaging. *Polym. Degrad. Stab.* **2010**, *95* (11), 2207−2212.
(63) ECHA. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/VPvB Assessment.; **2014**. .
(64) Fiume, M. Z. Final Report on the Safety Assessment of Triacetin. *Int. J. Toxicol.* **2003**, *22* (suppl2), 1−10.
(65) *Toxnet Data.* PubChem, National Library of Medicine https://pubchem.ncbi.nlm.nih.gov/ (accessed 2021/12/3).
(66) Alhanish, A.; Abu Ghalia, M. Developments of Biobased Plasticizers for Compostable Polymers in the Green Packaging Applications: A Review. *Biotechnol. Prog.* **2021**, *37*, No. e3210.
(67) Hu, Y.; Liu, C.; Wang, P.; Li, G.; Wang, A.; Cong, Y.; Liang, X.; Li, W.; Zhang, X.; Li, N. Sustainable Production of Safe Plasticizers with Bio-Based Fumarates and 1,3-Dienes. *Ind. Eng. Chem. Res.* **2020**, *59* (16), 7367−7374.
(68) Jia, P.; Xia, H.; Tang, K.; Zhou, Y. Plasticizers Derived from Biomass Resources: A Short Review. *Polym. 2018, Vol. 10, Page 1303* **2018**, *10* (12), 1303.
(69) Harmon, J. P.; Otter, R. Green Chemistry and the Search for New Plasticizers. *ACS Sustain. Chem. Eng.* **2018**, *6* (2), 2078−2085.
(70) Jessop, P. G.; Trakhtenberg, S.; Warner, J. The Twelve Principles of Green Chemistry. *ACS Symp. Ser.* **2008**, *1000*, 401−436.
(71) Pérez Santín, E.; Rodríguez Solana, R.; González García, M.; García Suárez, M. D. M.; Blanco Díaz, G. D.; Cima Cabal, M. D.; Moreno Rojas, J. M.; López Sánchez, J. I. Toxicity Prediction Based on Artificial Intelligence: A Multidisciplinary Overview. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2021**, *11* (5), No. e1516.
(72) Krebs, J.; McKeague, M. Green Toxicology: Connecting Green Chemistry and Modern Toxicology. *Chem. Res. Toxicol.* **2020**, *33* (12), 2919−2931.
(73) Velleux, M.; Redman, A.; Paquin, P.; Santore, R.; England, J. F.; Julien, P. Y. Exposure Assessment Framework for Antimicrobial Copper Use in Urbanized Areas. *Environ. Sci. Technol.* **2012**, *46* (12), 6723−6732.
(74) Lankey, R. L.; Anastas, P. T. Life-Cycle Approaches for Assessing Green Chemistry Technologies. *Ind. Eng. Chem. Res.* **2002**, *41* (18), 4498−4502.
(75) P&S Intelligence. *Plasticizers Market | Industry Forecast*, **2024**,; 2019.
(76) USEPA. *The Frank R. Lautenberg Chemical Safety for the 21st Century Act* | US EPA https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/frank-r-lautenberg-chemical-safety-21st-century-act (accessed 2021/12/21).
(77) Trasande, L. Updating the Toxic Substances Control Act to Protect Human Health. *JAMA* **2016**, *315* (15), 1565−1566.
(78) Joseph, A.. Stop playing whack-a-mole with hazardous chemicals. *The Washington Post.*https://www.washingtonpost.com/opinions/stop-playing-whack-a-mole-with-hazardous-chemicals/2016/12/15/9a357090-bb36-11e6-91ee-1adddfe36cbe_story.html?utm_term=.008b72651ba3 (accessed 2021/12/21).

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