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RE: Information on potentially exposed or susceptible subpopulations associated with 1,3-butadiene, formaldehyde, and ortho-phthalates undergoing TSCA risk evaluations

Introduction

The main U.S. chemicals law implemented by the U.S. Environmental Protection Agency (EPA), the 1976 Toxic Substances Control Act (TSCA), was reformed in 2016 with the passage of the Frank R. Lautenberg Chemical Safety for the Twenty First Century Act (Lautenberg Act). The law requires that EPA evaluate risks of new chemicals entering the market and existing chemicals in commerce. When EPA determines that an existing chemical presents unreasonable risk to human health or the environment, the agency must promulgate a risk management rule to eliminate that risk. Through procedures established in the law, EPA is currently developing draft risk evaluations for 23 chemicals[1] including 1,3-butadiene, formaldehyde, and seven ortho-phthalates.[2]

In evaluating and managing chemical risks, TSCA explicitly requires consideration of potentially exposed or susceptible subpopulations, defined as:

> a group of individuals within the general population identified by [EPA] who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.[3]

[1] The count of 23 chemicals does not include the ongoing Part II risk evaluation of asbestos.

[2] The seven ortho-phthalates include: (di-n-butyl phthalate) (DnBP); butyl benzyl phthalate (BBzP); di-(2-ethylhexyl phthalate (DEHP); di-isobutyl phthalate (DiBP): dicyclohexyl phthalate (DCPH): diisononyl phthalate (DiNP): and diisodecyl phthalate (DiDP).

[3] TSCA Section 3(12), 15 U.S.C. § 2602(12).

In the first ten risk evaluations completed under TSCA, relevant potentially exposed or susceptible subpopulations (also referred to as vulnerable subpopulations in these comments) were either inadequately considered or were not considered at all. These groups include those explicitly identified in the law and others that fall clearly within the definition of potentially exposed or susceptible subpopulations, such as individuals with pre-existing health conditions and individuals who live, work, learn, play, or worship near a chemical's conditions of use (fenceline communities). Similarly, scoping documents released for 1,3-butadiene, formaldehyde, and the seven ortho-phthalates[4] failed to identify specific potentially exposed or susceptible subpopulations the agency plans to consider in the associated risk evaluations.

Here we discuss key vulnerable subpopulations for 1,3-butadiene, formaldehyde, and the ortho-phthalates as identified in publicly available literature. Specifically, we describe factors such as health status; genetic polymorphisms; lifestyle behaviors; and socio-demographic considerations including fenceline concerns that can put certain individuals and communities at greater risk from exposure to these substances. We recommend EPA to consider the information on potentially exposed or susceptible subpopulations discussed here—in addition to other information on vulnerable subpopulations identified by the agency—when determining whether 1,3-butadiene, formaldehyde, and the ortho-phthalates present unreasonable risk under TSCA. We also urge EPA to use its information authorities under TSCA as necessary to ensure that risks to potentially exposed or susceptible subpopulations are comprehensively evaluated and managed.

1,3-butadiene

Background

1,3-Butadiene is an industrial chemical used primarily in the production of synthetic rubber, including styrene-butadiene rubber (ATSDR, 2012). 1,3-Butadiene is also used to make plastics such as acrylonitrile-butadiene-styrene resin plastics and is present in petroleum-based fuels (ATSDR, 2012). Humans are exposed to 1,3-butadiene mainly through inhalation. Environmental sources of 1,3-butadiene include industrial emissions, automobile exhaust, cooking emissions, and burning of wood, plastics, and rubber. 1,3-Butadiene is also a constituent of cigarette smoke (Nieto et al., 2021; ATSDR, 2012).

Workers involved in petroleum refining, the production of purified 1,3-butadiene, or the production of various 1,3-butadiene-based products (e.g., rubber and certain plastic polymers), may be disproportionately exposed to 1,3-butadiene.[5]

[4] Scoping documents for 1,3-butadiene, formaldehyde, and the seven ortho-phthalates are available at: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/chemicals-undergoing-risk-evaluation-under-tsca

[5] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals. Lyon (FR): International Agency for Research on Cancer; 1992. (IARC Monographs on the Evaluation of

Fenceline Exposures

Communities located near "heavily trafficked areas, refineries, chemical manufacturing plants, and plastic and rubber factories" experience higher environmental exposures to 1,3-butadiene via contaminated air and water relative to the general population (ATSDR, 2012). Data from the Toxics Release Inventory (TRI) reveal high 1,3-butadiene-emitting industrial facilities, refineries, and manufacturing plants across the U.S. (Table 1). Fenceline community members who are employed at these facilities and plants are expected to experience especially high levels of exposures to 1,3-butadiene.

Earthjustice et al. submitted written comments on the draft scopes of the first twenty high-priority substances to undergo TSCA risk evaluation, listing several communities in Texas and Louisiana—many along the Gulf Coast—that are disproportionately exposed to 1,3-butadiene.[6] Data from EPA's EasyRSEI database confirm that these areas have clusters of co-located facilities that emit 1,3-butadiene.[7] These communities are also likely exposed to higher concentrations of secondary formaldehyde than the general population since 1,3-butadiene can react atmospherically with other chemicals to form formaldehyde (Parrish et al., 2012).

Table 1. Summary of 1,3-butadiene emissions into air and water for 2015-2020 from EPA TRI data.

1,3-butadiene			
Medium	**Total number of facilities**	**Number of facilities in the top decile of 1,3-butadiene emitting facilities**	**Range of 1,3-butadiene released from individual facilities among the top decile of emitters (lbs)**
AIR	226	23	81,756 – 940,265
WATER	226	23	0 – 887

Furthermore, information from the U.S. Coast Guard (USCG) National Response Center[8] suggest that releases of 1,3-butadiene are common. The National Response Center maintains reports of environmental discharges provided by the public. We reviewed reports to date for year 2021 and identified over 100 reports involving 1,3-butadiene.[9] According to report details, 90%

Carcinogenic Risks to Humans, No. 54.) 1,3-Butadiene. Available from: https://www.ncbi.nlm.nih.gov/books/NBK424677/

[6] Comments by Earthjustice et al. See EXHIBIT 1. https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0451-0050

[7] EasyRSEI Dashboard. https://edap.epa.gov/public/extensions/EasyRSEI/EasyRSEI.html. Data accessed March 2021

[8] U.S. EPA National Response Center https://www.epa.gov/emergency-response/national-response-center

[9] United States Coast Guard National Response Center, https://nrc.uscg.mil/ Data accessed November 19, 2021.

of these chemical discharges occurred in Texas and Louisiana (Table 2). Our focus on year 2021 is meant to be exemplary; we strongly urge the agency to fully use this data source in evaluating risks to potentially exposed or susceptible populations and to the general population and environment more broadly.

Table 2. Summary of the locations of chemical release incident data for 1,3-butadiene from the U.S. Coast Guard National Response Center (2021 to date).

Number of reports from Texas	Number of reports from Louisiana	Number of reports from other states[a]
88	18	6
Counties with highest number of reports:	**Counties with highest number of reports:**	**Counties with highest number of calls:**
Harris Jefferson Brazoria	Calcasieu East Baton Rouge St. Charles	Jefferson, KY Grundy, IL Summit, OH

[a] Reports also came from Illinois, Kentucky, Ohio, Tennessee, Washington, and Wyoming.

Biomonitoring Information

Nieto et al. (2021) used NHANES (2011-2016) data to characterize population-level exposure to 1,3-butadiene and to assess how cigarette smoking affects concentrations of 1,3-butadiene urinary metabolites. The authors focused on the two most frequently detected urinary metabolites of 1,3-butadiene: N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (34HBMA or DHBMA) and N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine (4HBeMA or MHBMA3).[10]

The investigators presented analyses of biomonitoring and demographic data for smokers and non-tobacco users using creatine-corrected urinary metabolite concentrations of 1,3-butadiene.[11] Smokers were defined as participants who reported daily use of tobacco products (use of pipes, cigars, chewing tobacco, snuff, patch/gum, hookah/water pipes, e-cigarettes, snuff, and dissolvable tobacco) and confirmed by a serum cotinine level greater than 10 mg/mL. A serum cotinine level of less than 10 mg/mL was used to define non-tobacco users. The authors used multiple sample-weighted linear regression models to examine the relationship between smoking status and other demographic variables and urinary 1,3-butadiene metabolite levels. There were noticeable differences in the concentrations of 34BMHA and 4HBeMA between smokers and

[10]Information on NHANES 1,3-butadiene metabolites and percent detections: N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (34HBMA) (greater than 96%); N-acetyl- S-(1-hydroxymethyl-2-propenyl)-L-cysteine (1HMPeMA) (0.66%); N-acetyl-S-(2-hydroxy-3-butenyl)-L-cysteine(2HBeMA) (9.84%); N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine (4HBeMA) (greater than 96%).

[11]Creatinine is a waste product produced by the muscles and excreted by the kidneys at a constant rate. Creatinine-correction is the adjustment of environmental contaminants measured in urine by creatinine to correct for variations in urine diluteness at the time of measurement (Barr et al., 2005).

non-tobacco users. For both metabolites, the median concentrations across all three survey cycles were higher among smokers than non-tobacco users (4HBeMA: smokers=31.5 µg/g creatinine, non-tobacco users= 4.11 µg/g creatinine; 34HBMA: smokers=391 µg/g creatinine, non-tobacco users =296 µg/g creatinine). There also appeared to be a dose-response relationship between tobacco use and exposure. Compared to non-tobacco use, smoking 1–10, 11–20, and >20 cigarettes per day was associated with 475%, 849%, and 1143% higher urinary 4HBeMA ($p<0.0001$) and 33%, 44%, and 102% higher urinary 34HBMA ($p<0.0001$), respectively. Furthermore, even after adjusting for age,[12] weight, race/ethnicity, or NHANES survey cycle, smokers had higher urinary 4HBeMA and 34HBMA than non-tobacco users. Based on these results, tobacco use is a significant source of 1,3-butadiene exposure.

The results of the regression models showed significant differences in urinary metabolite concentrations by age (Table 3). Regardless of smoking status, adults aged 40 years and older had significantly higher 4HBeMA and 34HBMA concentrations than adults aged 20-39 years (the reference group). Among non-tobacco users, children (aged 3-11 years old) had significantly higher 4HBeMA concentrations than the reference group. Among non-tobacco users, children and adolescents (aged 3-19 years old) had significantly higher 34HBMA concentrations than the reference group.

Table 3. Adapted from Tables 4, 5, 8, and 9 of Nieto et al. (2021). Sample-weighted multiple linear regression models for urinary 34HBMA/DHBMA or 4HBeMA/MHBMA3 concentrations (mg/mL) among 2011–2016 NHANES stratified by smoking/tobacco use.

4HBeMA/MHBMA3				
	Non-Tobacco Users[a] (N=5171)		**Smokers[b] (N=726)**	
Demographic Variable	**Coefficient [95% CI][c]**	**p-value**	**Coefficient [95% CI]**	**p-value**
Male	ref	--	ref	--
Female	-0.0218 [-0.0903, 0.0467]	0.5257	0.3291 [0.1588, 0.4994]	**0.0003**
3-5 years	0.2985 [0.1372, 0.4597]	**0.0005**	n/a	--
6-11 years	0.3697 [0.2703, 0.4690]	**<.0001**	n/a	--
12-19 years	-0.0441 [-0.1337, 0.0455]	0.3268	-0.0316 [-0.2878, 0.2246]	0.8051
20-39 years	ref	--	ref	--
40-59 years	0.0995 [0.0059, 0.1931]	**0.0377**	0.2316 [0.1100, 0.3531]	**0.0004**
≥60 years	0.2129 [0.1279, 0.2979]	**<.0001**	0.3537 [0.1451, 0.5622]	**0.0013**
Non-Hispanic White	ref	--	ref	--
Non-Hispanic Black	-0.0527 [-0.1197, 0.0144]	0.1210	-0.3690 [-0.5338, 0.2043]	**<.0001**
Hispanic	0.0078 [-0.0739, 0.0895]	0.8483	-0.1129 [-0.3109, 0.0851]	0.2573
Other Race/Multi-Racial	-0.0812 [-0.1904, 0.0280]	0.1413	-0.0091 [-0.3497, 0.3316]	0.9576
34HBMA/DHBMA				
	Non-Tobacco Users[a] (N=5171)		**Smokers[b] (N=726)**	
Demographic Variable	**Coefficient [95% CI][c]**	**p-value**	**Coefficient [95% CI]**	**p-value**
Male	ref		ref	--

[12] Tobacco use information is not sampled as part of NHANES for children under 12 years of age.

Female	0.0088 [-0.0373, 0.0548]	0.7033	0.0754 [-0.0226, 0.1735]	0.1285
3-5 years	0.5862 [0.4689, 0.7034]	**<.0001**	n/a	--
6-11 years	0.3707 [0.3040, 0.4373]	**<.0001**	n/a	--
12-19 years	0.0671 [0.0229, 0.1113]	**0.0037**	-0.0416 [-0.1923, 0.1091]	0.5812
20-39 years	ref	**--**	ref	--
40-59 years	0.1013 [0.0426, 0.1600]	**0.0011**	0.1150 [0.0205, 0.2094]	**0.0181**
≥60 years	0.3083 [0.2498, 0.3669]	**<.0001**	0.2419 [0.0764, 0.4074]	**0.0051**
Non-Hispanic White	ref	**--**	**ref**	**--**
Non-Hispanic Black	-0.1417 [-0.2077, -0.0756]	**<.0001**	-0.1712 [-0.2770, 0.0654]	**0.0021**
Hispanic	-0.0051 [-0.0686, 0.0584]	0.873	0.0645 [-0.0432, 0.1722]	0.2346
Other Race/Multi-Racial	-0.1092 [-0.1812, -0.0372]	**0.0037**	0.0366 [0.1820, 0.2552]	0.7377

Ref=reference group

[a] Sample-weighted participants reporting not using cigarettes (and no other tobacco products) 5 days prior to physical examination and with serum cotinine measurement ≤10 mg/mL.

[b] Sample-weighted participants reporting using cigarettes (and no other tobacco products) 5 days prior to physical examination and with serum cotinine measurement>10 mg/mL

[c] The dependent variable, biomarker concentration, was natural log-transformed for the regression model.

Jain (2015) used NHANES data (2011-2012) to evaluate the variability in urinary metabolite concentrations of 1,3-butadiene in children aged 6-11 years old. The authors focused on two urinary metabolites commonly used to assess 1,3-butadiene exposure: N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMA) and N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine (MHBMA). The authors used regression models to assess the relationship between urinary levels of 1,3-butadiene and age, gender, race/ethnicity, and smoking status, or environmental tobacco smoke (secondhand tobacco smoke). Models were adjusted for urinary creatinine and other covariates to control for potential confounding.[13]

The authors reported that exposure to environmental tobacco smoke was positively associated with metabolites of 1,3-butadiene in a dose-dependent manner in children aged 6-11. Concentrations of the metabolites DHBMA and MHBMA3 decreased with increasing child age, such that younger children had higher levels of both metabolites. Additionally, children had statistically significant higher unadjusted urinary metabolite concentrations than non-smoking adults aged 20 years and older. Furthermore, concentrations of DHBMA in children aged 6-11 years increased in a dose-dependent manner as the number of reported smokers inside the home increased. Taken all together, this evidence points to individuals exposed to second-hand smoke as a susceptible subpopulation for 1,3-butadierne exposure.

Biological Susceptibility: Genetic Polymorphisms

Certain polymorphisms in metabolic enzymes affect the toxicokinetics of 1,3-butadiene and, as a result, may make some individuals more susceptible to its effects. Abdel-Rahman et al. (2001) studied 49 male workers from two styrene/butadiene polymer plants in Southeast Texas. Blood

[13] In particular, regression models were adjusted for gender, age, body mass index, poverty income ratio, total number of rooms in the house, total number of smokers smoking inside the house, and race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanics, non-Hispanic Asians, unclassified race/ethnicities).

samples from participants were genotyped for Tyr113His in the microsomal epoxide hydrolase enzyme (*mEH*) gene[14,15] and polymorphisms in the glutathione S-transferase genes (*GSTM1* and *GSTT1*).[16] Additionally, blood samples were assessed for frequencies of *hprt* mutant lymphocytes. [17] Exposure to 1,3-butadiene was assessed by collecting personal breathing zone samples for full work shifts on multiple days before blood sampling. Participants were then grouped into two exposure groups for analyses: <150 (low) and >150 (high) time-weighted average ppb of 1,3-butadiene in blood.

Workers in the high exposure group had significantly higher *hprt* mutant lymphocytes than workers in the low exposure group. Among workers in the high exposure group, individuals with the polymorphic *mEH* allele had significantly higher mean frequency of mutant lymphocytes than workers without the polymorphic *mEH* allele. In the low exposure group, frequencies of *hprt* mutant lymphocytes did not differ based on individual genotypes. In combined polymorphism analyses, individuals with at least one *mEH* His allele (Tyr/His or His/His) and either the *GSTM1* or *GSTT1* null genotypes had higher mean frequency of mutant lymphocytes. This response was limited to workers in the high exposure group.

The study suggests that the *mEH* genotype in particular may play an important role in 1,3-butadiene sensitivity (Abdel-Rahman et al., 2001). Similar studies by the same group have also reported increased *hprt* mutation frequencies in U.S. 1,3-butadiene workers with various polymorphisms in the microsomal epoxide hydrolase enzyme (Abdel-Rahman et al. 2003, 2005 as cited in ATSDR, 2012).

The ATSDR Tox profile for 1,3-butadiene (2012; Section 3.10) includes several other references for polymorphisms that may affect a person's sensitivity to toxic 1,3-butadiene metabolites. Overall, the results suggest that polymorphisms in metabolic enzymes render individuals more susceptible to the effects of 1,3-butadiene (ATSDR, 2012).

Conclusions

Our review identified several key vulnerable subpopulations that EPA should consider, along with any other such groups identified by the agency, in the risk evaluation of 1,3-butadiene. To summarize:

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[14]*mEH*- Tyr113His- Histidine replaces tyrosine at residue 113. The presence of the histidine decreases the enzymatic activity of the microsomal epoxide hydrolase enzyme (mEH).

[15]*mEH* is a biotransformation enzyme known for converting epoxides into diols (Václavíková et al., 2015)

[16]Glutathione S-transferase- (Abdel-Rahman et al., 2001) Results from in vitro studies suggest that there is increased sensitivity to reactive 1,3-butadiene species in cultured lymphocytes from individuals with deletion polymorphisms for GSTM1 and GSTT1 genes.

[17] The hypoxanthine-guanine phosphoribosyl transferase (HRPT) assay in one step identifies and selects mutant cells, against a background of normal cells, by taking advantage of the biochemical pathways by which a cell synthesizes DNA (Compton et al., 1991).

- Nieto et al. (2021) found that concentrations of 1,3-butadiene metabolites were significantly higher among smokers compared to non-tobacco users, making these individuals a potentially exposed subpopulation. Furthermore, children (non-tobacco users) had higher levels of 1,3-butadiene metabolites than adult non-tobacco users.
- Findings from Jain (2015) reveal that children exposed to secondhand tobacco smoke have higher levels of 1,3-butadiene metabolites compared to children unexposed to secondhand smoke. As such, children exposed to secondhand smoke represent a vulnerable subpopulation for 1,3-butadiene exposure.
- Certain polymorphisms in metabolic enzymes can increase individuals' susceptibility to the effects of 1,3-butadiene exposure.
- Data from EPA TRI and the USCG National Response Center reveal that certain groups, especially fenceline communities, are disproportionately exposed to environmental releases of 1,3-butadiene and represent subpopulations at greater risk to 1,3-butadiene.

Formaldehyde

Background

Formaldehyde is a high production volume chemical to which people may be exposed outdoors and indoors (Lam et al., 2021). Concentrations of formaldehyde are can be higher indoors, in places such as such as school, work, and home (Franklin, 2007). Formaldehyde is used in many commercial and consumer products including wood and particleboard-based furniture, textiles, carpeting, medicines, cosmetics, dishwashing liquids, carpet cleaners, glues, lacquers, and preservatives (in some cases, in foods) (Kim et al., 2011; Lam et al., 2021). In addition to formaldehyde releases from products, formaldehyde is also released into the air from commercial and industrial operations using or manufacturing formaldehyde and from automobile exhaust and cigarette smoke (ATSDR, 1999). People are exposed primarily via inhalation of gas or vapor; however, oral and dermal absorption of formaldehyde are also relevant routes of exposure (Kim et al., 2011; ATSDR, 1999; NTP, 2016).

In addition to cigarette smoke, emerging research suggests smoking e-cigarettes (or vaping) can lead to exposure to formaldehyde. E-cigarettes contain mixtures of various liquids such as propylene glycol or glycerol (or both), nicotine, and flavorant chemicals. The addition of flavorants to e-cigarettes make them more appealing to teenagers and adolescents (Ambrose et al., 2015) and creates additional concern about use and exposure among these age groups.

Vapers, people who vape, are exposed to formaldehyde from vaping e-cigarettes because formaldehyde is a known degradation product of propylene glycol. Additionally, formaldehyde hemiacetals - formaldehyde releasing-agents - are formed from the reaction of formaldehyde with propylene glycol and glycerol. Hemiacetals are particularly concerning because they are capable of depositing formaldehyde more deeply in the lungs than gaseous formaldehyde (Jensen et al., 2015; Salamanca et al., 2018).

In Salamanca et al., (2018), the authors used a cigarette smoking machine calibrated to a puffing regimen that matches e-cigarette user data to generate and collect aerosol for analysis. The authors reported that the collected aerosol contained more formaldehyde hemiacetals than gaseous formaldehyde, and both were detected at concentrations above OSHA guidelines (Salamanca et al., 2018). These data add to the evidence that e-cigarettes can also contribute to formaldehyde exposure among users.

EPA has recently promulgated rules to restrict the manufacture and import of pressed wood products with excessive formaldehyde; thus, new such products should have lower levels of formaldehyde (EPA, 2016). However, pressed wood products already in use, and other consumer products not covered by the regulation, continue to expose people to formaldehyde indoors. Lam et al. 2021 indicates that this is of particular concern for communities of lower income living in homes built with less costly building materials. (Lam et al., 2021). Additionally, measures to reduce indoor concentrations of formaldehyde may be inaccessible for some groups. For example, using fans and air conditioners in homes increases ventilation which can reduce formaldehyde levels (Nirlo et al., 2014). However, these options may present a financial burden for certain groups.

Certain occupations can result in higher exposure to formaldehyde compared to the general population, putting these workers at greater risk (Table 4).

Table 4. Occupations associated with formaldehyde exposures.

Agriculture workers	Insulators
Botanists	Laboratory researchers/workers
Carpet manufacturers/installers	Lacquer producers and users
Disinfectant producers/users	Medical professionals
Dressmakers	Oil field workers
Drug makers	Paint and varnish manufacturers
Dye manufacturers	Paper manufacturers
Embalming fluid producers	Plastics manufacturers
Fabric store personnel	Plywood and particle board manufacturers
Fertilizer manufacturers and blenders	Poultry processors
Formaldehyde producers	Rubber workers
Formaldehyde resin producers	Sanitation workers
Foundry workers	Science instructors/teachers
Furniture makers and finishers	Taxidermists
Glue and adhesive makers	Textile workers: finishers, printers, cutters
Hazardous waste handlers	Veterinarians
Ink makers	Wood preservers
Dairy farm workers[a]	Cosmetologists and Beauticians[b]

Unless otherwise noted, information on occupations is collected from N.C. Department of Labor Guide to Formaldehyde (2013)

[a] Doane and Sarenbo, 2014

[b] Asare-Donkor et al, 2020

Fenceline Exposures

Formaldehyde poses major environmental justice challenges. Communities proximal to formaldehyde-emitting facilities, such as certain manufacturing facilities, power plants, and incinerators, and to highways experience disproportionate exposure to formaldehyde (ATSDR, 1999). Research has established that people of color and people of low socioeconomic status are more likely to live near polluting facilities, and experience relatively higher levels of traffic and air pollution (Collins et al., 2016; Pratt et al., 2015).

A review of incident data from the USCG National Response Center identified about a dozen chemical release reports involving formaldehyde during 2021 to date.[18] Data from TRI indicate significant releases of formaldehyde into both air and water (Table 5).

Table 5. Summary of formaldehyde emissions into air and water for 2015-2020 from EPA TRI data.

Formaldehyde			
Medium	**Total number of facilities**	**Number of facilities in the top decile of formaldehyde emitting facilities**	**Range of formaldehyde released from individual facilities among the top decile of emitters (lbs)**
AIR	824	82	98,898 – 773,382
WATER	824	82	2,124 – 145,072

Certain communities are disproportionately exposed to formaldehyde via secondary sources. Secondary production of formaldehyde occurs during the atmospheric oxidation of ethene, propene, and higher terminal alkenes (e.g., 1,3-butadiene, isoprene) (Bastien et al., 2019; Buzcu Guven et al., 2011; Parrish et al., 2012), putting communities that live, work, learn, play, or worship around facilities releasing these chemicals at greater risk from formaldehyde exposure. Oxidation of alkanes and aromatic compounds also leads to the generation of secondary formaldehyde, although this is a slower process (Parrish et al., 2012). A report published by the One Breath Partnership, a nonprofit, nonpartisan coalition that advocates for clean air in Houston, Harris County and the surrounding region, found that ambient formaldehyde in the greater Houston, TX area is predominantly produced secondarily.[19] The production of secondary formaldehyde from 1,3-butadiene exemplifies the need for EPA to consider how relevant mixtures of chemicals could impact the risk of individual chemicals, particularly as they relate to chemicals undergoing risk evaluation (Sprinkle and Payne-Sturges, 2021).

[18] United States Coast Guard National Response Center, https://nrc.uscg.mil/ Data accessed November 19, 2021.

[19] One Breath Partnership report, https://environmentalintegrity.org/wp-content/uploads/2021/07/Houston-Formaldehyde-Report-Final-2021.pdf

Biomonitoring Information

Jain (2020) used NHANES (2015-2016) data for children aged 6–11 years, adolescents aged 12–19 years, and adults aged 20 years and up to characterize formaldehyde exposure. Interesting findings were identified when comparing smokers versus non-smokers. The author presented the results for both unadjusted and adjusted geometric means of formaldehyde in whole blood.[20] Unadjusted geometric means did not vary by smoking status for adults or adolescents. Adjusted geometric means of formaldehyde did not vary based on smoking status for adolescents. However, adults who smoked had higher levels of formaldehyde than nonsmokers using adjusted geometric means for formaldehyde.

Biological Susceptibility: Asthma

Persons with asthma are believed to be particularly susceptible to the effects of formaldehyde exposure (ATSDR, 1999; ATSDR, 2010). Because formaldehyde irritates the airways, it may aggravate or exacerbate preexisting asthma, asthma symptoms, or other respiratory infections and diseases (Kim et al., 2011; Kim et al., 2015). A recent systematic review by Lam et al. (2021) concluded that there was "sufficient evidence" of an association between formaldehyde exposure and asthma in children and adults (Lam et al., 2021). Based on an evaluation of the available literature, the authors concluded that there was positive association between exposure to formaldehyde and asthma diagnosis and asthma symptoms in adults. For children, the authors conducted a meta-analysis for childhood asthma diagnosis and exacerbation (n=10 and 5 studies, respectively). The authors reported positive associations between formaldehyde exposure and asthma diagnosis and asthma exacerbation in children (Lam et al., 2021). However, the authors noted that this evidence does not address whether formaldehyde leads to the development of asthma or triggers an asthma flare-up in a previously undiagnosed child.

Conclusions

Our review identified several key vulnerable subpopulations that EPA should consider, along with any other such groups identified by the agency, in the risk evaluation formaldehyde. To summarize:

- Research suggests that smokers have higher levels of formaldehyde than non-smokers. Recent studies also indicate that e-cigarettes contain formaldehyde including in a form, formaldehyde hemiacetals, that can penetrate the lungs more deeply. Related e-cigarette research has found that levels of gaseous formaldehyde and formaldehyde hemiacetals in e-cigarette aerosols can exceed OSHA guidelines. EPA should consider smokers of traditional and electronic cigarettes potentially exposed subpopulations.
- Persons with asthma are more susceptible to the effects of formaldehyde, including children. Asthmatics should be considered susceptible subpopulations.

[20] Adjusted results included the following covariates: gender (male or female), age, poverty income ratio, numbers of smokers inside the home, number of days smokers smoked (excluding children), age specific body mass index percentiles (children and adolescents only), body mass index (adults only), and race/ethnicity (non-Hispanic white, non-Hispanic Black, Mexican-American, Hispanics other than Mexican-Americans, non-Hispanic Asians, and unclassified race/ethnicity)

- EPA TRI data and the USCG National Response Center data reveal that fenceline communities are disproportionately exposed to formaldehyde. These exposures include primary releases and discharges of formaldehyde into the environment, and significantly, secondary formation formaldehyde resulting from atmospheric oxidation reactions of certain chemicals such as 1,3-butadiene.

Phthalates[21]

Dibutyl phthalate (DBP) or (Di-n-butyl phthalate) (DnBP)
Butyl benzyl phthalate (BBzP)
Di-(2-ethylhexyl phthalate (DEHP)
Diisobutyl phthalate (DiBP)
Dicyclohexyl phthalate (DCPH)
Diisononyl phthalate (DiNP)
Diisodecyl phthalate (DiDP)

Background

Ortho-phthalates ("phthalates") are a class of high production volume, multi-functional chemicals. Dibutyl phthalate (DBP) (also known as di-n-butyl phthalate (DnBP)) and diisobutyl phthalate (DiBP) are low molecular weight phthalates (NRC, 2008). Di-2-ethylhexyl phthalate (DEHP), butyl benzyl phthalate (BBzP), dicyclohexyl phthalate (DCPH), diisononyl phthalate (DiNP), and diiosdecyl phthalate (DiDP) are high molecular weight phthalates (NRC, 2008). Phthalates are widely used as plasticizers in materials such as food packaging, flooring, gloves, toys, and medical equipment (CDC, 2009; NRC, 2008; NTP, 2003; Tickner et al., 2001). They may also be used in medications as excipients, scent retainers in personal care products, and adhesives (Kelley et al., 2012; Koniecki et al., 2011; NRC, 2008).

As non-reactive chemical additives, phthalates can easily migrate out of products and product packaging to enter the human body via ingestion, inhalation, and dermal absorption (Adibi et al., 2003; Blount et al., 2000; Rudel et al., 2003). Human exposure to phthalates is widespread and people are continuously exposed to multiple phthalates. Urinary metabolites of phthalates are detected in greater than 98% of the U.S. population (Zota et al., 2014).

While certain sources of phthalate exposure are outside of TSCA's direct regulatory authority (e.g., food and food packaging, medical devices, and cosmetics which are regulated by the Food and Drug Administration (FDA)), EPA *must* account for these background sources of exposure when evaluating potential risks from conditions of use under TSCA.

Diet is an important source of exposure for certain phthalates (Serrano et al., 2014). Phthalates can migrate into foods from phthalate-containing materials used in the production, packaging,

[21] Phthalic anhydride is also currently undergoing risk evaluation. It is an intermediate used to synthesize phthalate esters but is not an ortho-phthalate.

and cooking/handling of foods (Cao, 2010; Carlos et al., 2018, 2021; Cirillo et al., 2011; Petersen et al., 2016; Tsumura et al., 2001). Garcia-Fabila et al. conducted a literature review to summarize concentrations of ortho-phthalates in different foods using peer-reviewed study data published from 2001 to 2019 (Garcia-Fabila et al., 2020). DEP, DnBP, and DEHP were detected across a variety of food categories including groceries, oils and fats, condiments, poultry, meat, fish and seafood, cereals and tubers, fruits and vegetables, and dairy products,[22] indicating widespread contamination of foods. Additionally, consumption of fast food is linked to phthalate exposure (Buckley et al., 2019; Martinez Steele et al., 2020; Zota et al., 2016) and phthalates have been detected in fast food items from U.S. chains (Edwards et al., 2021).

There are environmental justice concerns regarding fast food as a source of phthalates. Available data indicate that Black people in the U.S. consume more fast food than other racial/ethnicity groups (Fryar et al., 2018). Furthermore, an NHANES study reported a stronger association between fast food intake and urinary metabolites of DEHP among Non-Hispanic Blacks compared to Non-Hispanic Whites and Hispanics in the U.S. (Zota et al., 2016). These studies suggest that people of color, particularly, Black people could be disproportionately exposed to phthalates from fast foods.

Beauty and personal care products such as nail polish, hair products, deodorants, lotion, and skin cleansers are also a significant source of phthalate exposures. In a survey of 252 products sold in Canada, diethyl phthalate (DEP), was the predominant phthalate detected in products, with the highest levels found in fragrances (Koniecki et al., 2011). Hairdressers can be disproportionately exposed to phthalates through their occupational use of beauty products (Boyle et al., 2021). Research has found that people of color are exposed to higher levels of phthalates through beauty and personal care products (Zota and Shamasunder, 2017). For example, in a study examining hair product usage across a racially/ethnically diverse population of women, African-American and African-Caribbean women were more likely to use all of the hair products included in the study (James-Todd et al., 2012). Helm et al (2018) measured endocrine-disrupting and asthma-inducing chemicals in hair products used by U.S. Black women and children and found that many of these products contained multiple endocrine-disrupting chemicals. Diethyl phthalate (DEP), used as a fragrance marker, was among several chemicals detected at the highest concentrations and was detected most frequently in the products included in the study (Helm et al., 2018).

Fenceline Exposures

Unlike 1,3-butadiene and formaldehyde, the seven ortho-phthalates are not currently included in EPA's Toxic Release Inventory, limiting the information available to assess their environmental releases from industrial and federal facilities. EPA should move immediately to add phthalates to

[22] Food categories in Garcia-Fabila et al 2020 correspond to the basic "Mexican diet".

the TRI,[23] while using available TSCA information authorities to develop sufficient information to characterize fenceline exposures in the current risk evaluations underway.

Biological Susceptibility: Early Life-stages

Early life exposure to phthalates is particularly concerning given the ever-growing body of evidence showing that events during pre- and post-natal periods of development may have long-term effects on adult health and overall development (Gluckman et al., 2008). As a result of these sensitive and critical windows of development, pregnant women and young children are populations with greater susceptibility to the adverse effects of phthalates.

Animal studies have shown that in utero exposure to phthalates can affect the male reproductive system by decreasing circulating testosterone levels. Phthalates such as DEHP, DINP, DBP, DIBP, and BBzP are potent with respect to producing phthalate syndrome, a cluster of abnormalities that includes decreased anogenital distance and sperm count, infertility, cryptorchidism, and other reproductive-tract malformations (NRC, 2017; NRC, 2008). In studies investigating DEHP's role as a male reproductive toxicant, results often indicate that younger rodents are more susceptible to adverse health effects than older rodents (ATSDR, 2019). Additionally, in a recent systematic review of the human epidemiology literature investigating the effects of phthalates on male reproductive outcomes, the authors described studies indicating that these effects occur at exposure levels found in the general population (Radke et al., 2018). Given the extensive body of evidence in animals demonstrating phthalates' anti-androgenic effects, in 2008, the National Research Council recommended that a cumulative risk assessment approach be taken to evaluate the health risks of phthalate exposures (NRC, 2008). In support of this and decades of evidence about the effects of phthalates, Project TENDR (Targeting Environmental Neurodevelopmental Risks), a group of scientists and health professionals with expertise in toxic chemicals and neurotoxicity, wrote a letter to the EPA Office of Pollution Prevention and Toxics (OPPT) recommending that the agency take a cumulative risk approach to the seven ortho-phthalates currently undergoing risk evaluation under TSCA.[24]

In a recent systematic review of the human epidemiology literature investigating neurodevelopmental effects associated with phthalate exposure, the authors described studies revealing greater effects on the mental development index for girls relative to boys[25] (Radke et al., 2020). Additionally, in a recent study by Project TENDR, the authors concluded that there is substantial evidence linking phthalate exposures to increased risks for children's learning, attention, and behavioral problems (Engel et al., 2021). There is also evidence that suggests that

[23] In their comments on the Tiered Data Reporting Rule, Earthjustice also urged the agency to include all chemicals currently undergoing risk evaluation to TRI https://www.regulations.gov/comment/EPA-HQ-OPPT-2021-0436-0056.

[24] Project TENDR Letter https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0503-0043

[25] EDF notes that study authors used the terms "girls" and "boys" and did not provide details regarding consideration of sex and gender identification.

neurodevelopmental and behavioral outcomes, in addition to other concerning health effects such as metabolic effects, obesity, and changes in hormone levels, are occurring at levels that are lower than some of the reference doses for individual ortho-phthalates (Maffini et al., 2021).

Frequent hospitalizations and medical care can lead to high acute exposure to phthalates due to their prevalent use in medical equipment (Calafat et al., 2004; Tickner et al., 2001). Phthalates used in medical tubing or blood storage bags can leach into biological fluids during blood transfusions or migrate into surrounding tissues (ATSDR, 2019); thus, people with hemophilia, dialysis patients, and preterm infants may be disproportionately exposed to phthalates (ATSDR, 2019; (Calafat et al., 2004; Schettler, 2006). Preterm infants are particularly vulnerable to phthalate exposures because phthalates are commonly used in PVC-based flexible plastic devices used in neonatal intensive care units (NICUs) (Bickle-Graz et al., 2020; Fischer et al., 2013; Santos et al., 2015). Stroustrup et al. 2020, reported a significant association between urinary DEHP metabolites and respiratory support equipment used in the NICU (Stroustrup et al., 2020). Furthermore, these exposures occur during a sensitive developmental time period and have been hypothesized to contribute to altered development in infants (Braun, 2017; Engel et al., 2021).

Conclusions

Our review identified several key vulnerable subpopulations that EPA should consider, along with any other such groups identified by the agency, in the risk evaluation of the ortho-phthalates. To summarize:

- Data from both animal and human studies indicate that pregnant women and young children are populations with greater susceptibility to the adverse effects of phthalates.
- Phthalates are not currently included in TRI. In addition to immediately acting to add phthalates to the TRI, the agency should also use its information authorities under TSCA to develop sufficient information to characterize fenceline exposures.
- Research suggests that there are environmental justice concerns regarding fast foods and beauty and personal care products as sources of phthalates. Although these products fall outside of TSCA's direct regulatory authority, EPA must account for these background sources of exposures and should consider how different groups may face greater exposures than others.

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