Emerging exposures of developmental toxicants

Mary S. Wolff[a], *Jessie P. Buckley*[c], *Stephanie M. Engel*[b], *Rob S. McConnell*[d], *and Dana B. Barr*[e]

Purpose of review
The purpose of this review is to identify emerging developmental toxicants that are understudied in children's health. Exposures may arise from new products designed to improve utility, to reduce toxicity, or to replace undesirable chemicals. Exposures to less-toxic chemicals may also be significant if they are very commonly used, thereby generating widespread exposure. Sources of exposure include the workplace, personal, home, and office products; food, water, and air.

Recent findings
We describe eight exposure categories that contain numerous potential developmental toxicants. References are discussed if reported in PubMed during the past decade at least 10 times more frequently than in 1990–2000. Examples included phthalates, phenols, sunscreens, pesticides, halogenated flame retardants, perfluoroalkyl coatings, nanoparticles, e-cigarettes, and dietary polyphenols. Replacements are often close structural homologs of their precursors. We suggest biomonitoring as preferred means of exposure assessment to emerging chemicals. Some existing analytic methods would require minimal modification to measure these exposures, but others require toxicokinetic and analytic investigation.

Summary
A deliberate strategy for biomonitoring of emerging replacement chemicals is warranted, especially in view of concerns regarding developmental toxicity. To prevent adverse health effects, it is important to characterize such exposures before they become widely disseminated.

Keywords
child health, environmental exposures, exposure biomarkers, orphan exposures

INTRODUCTION

Emerging exposures are defined as environmental agents with potential for human exposure, in which there is reason for concern about health effects. There may be limited toxicological and biomonitoring data but ample information on possible sources. Developmental toxicants may derive from parental occupational exposures, from use of personal or consumer products that contain toxic chemicals, or from contaminated food, water, or air. Estimating personal exposures to toxicants can sometimes be challenging in the absence of validated biomarkers. However, in some circumstances, they may be reliably estimated by compiling a personal record of products utilized, foods consumed, or aspects of the home environment. Environmental exposure biomarkers are often desirable to quantify individual level exposure and monitor changes in exposure over time. As toxic and, in particular, persistent, chemicals have been discovered in the environment, replacement materials have been developed by industry in response to consumer concerns or regulatory changes. Other new chemicals have arisen from modern technology. Some of these agents are suspected to be toxic, but are overlooked in research because there are no readily available exposure assessment and biomonitoring methods. This article aims to identify emerging exposures and to suggest means of measuring them in people with a focus on organic chemicals.

METHODS

We assembled, in Table 1, a selected list of chemicals and products that are emerging toxicants, based on

[a]Icahn School of Medicine at Mount Sinai, New York, New York, [b]University of North Carolina, Chapel Hill, North Carolina, [c]Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, [d]Keck School of Medicine, University of Southern California, Los Angeles, California and [e]Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

Correspondence to Mary S. Wolff, PhD, Icahn School of Medicine at Mount Sinai, Box 1057, New York, NY 10029, USA. Tel: +1 212 824 7040; e-mail: mary.wolff@mssm.edu

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KEY POINTS

- Biomonitoring of emerging exposures has often lagged peak population exposures, resulting in lapses of health risk assessment.
- Agents without exposure monitoring also lack sufficient information on health effects.
- Valid exposure biomarkers are not available for many well known exposures of interest for child development.

several kinds of use, including compounds that are being phased out or replaced. We selected representative chemicals that are of increasing interest based on having been cited in the past 10 years. We looked for existing analytic methods that could be used to detect these chemicals in the body with minimal modifications. We focus on this means of exposure assessment as there are no comprehensive means of using retrospective recall of product use, diet, home environment, and others that can capture sufficient information.

We searched for known, replacement, and other chemicals in PubMed during three time frames: 1990–2000, the 'past 10 years' (a PubMed option), using the terms including 'chemical name', 'urine', and/or 'exposure', limited to humans. Items were included in Table 1 if citations in 'past 10 years' were at least 10 times more frequent than in 1990–2000 and if they were also cited in the past 2 years. To compare with the overall rise in publications, a search for 'exposure' alone found that the number of references doubled in the earlier vs later 10-year periods (90 312 vs 185 167), and 35 385 references appeared for the past 2 years. Publications on 'exposure and urine' increased about 1.5 times for the 10-year intervals (4018 vs 6366), with 1340 in the past 2 years. This suggests that higher numbers for reported agents in Table 1 are not publication bias. Reference count changed over the months of assembling the information, and the table enumeration is that retrieved on 1 October 2016. Not all references were reviewed individually, and so some that do not directly address human exposure may be included in the count. We recognize that PubMed citations are lagged relative to the identification, measurement, and research on contaminants of concern; therefore, there is a need to identify additional exposures using knowledge of prevalent chemicals such as those in commonly used products [1▪].

RESULTS AND DISCUSSION

Table 1 lists selected potential emerging exposures in eight categories. Many of these chemicals occur together in products, thus presenting exposure to a mixture of chemicals from their use [1▪]. Moreover, multiple chemicals also exist in many exposure sources, such as swimming pools [>40 chemicals including 14 ultraviolet (UV) filters] [2]. Many emerging exposures are close structural homologs of the replaced substance that were developed to reduce persistence and absorption in the body. However, replacement chemicals often do not represent an improvement in terms of health effects and may have substantial data gaps from which to estimate toxicity or population prevalence [3]. Almost all of these exposures are nonpersistent organic chemicals. It is remarkable that these exposures with citations before 2000 are also those with reported health effects research.

Phthalates and phenols

Both phthalates and phenols have been associated with health outcomes in children, including neurodevelopment, allergy, and obesity [4–6]. For phthalates, health effects have been observed for exposures prenatally through childhood. Phthalates are used in a wide variety of consumer items including personal care products, food packaging, and building materials, resulting in widespread population exposure. More than 20 phthalate replacements have been reported [3]. Three of the newer ones have been found in human biomonitoring [DINCH (1,2-cyclohexane dicarboxylic acid diisononyl ester); DEHT (bis-(2-ethylhexyl)-terephthalate); and DEHA (bis-(2-ethylhexyl)-adipate)] (Fig. 1) [3,7]. It is unclear whether the replacements are less toxic or less persistent. Of some concern, brominated phthalates are being used as flame retardants [8].

Parabens are phenol preservatives that are extensively used in personal care products, food, and medications. Parabens are commonly detected in urine as the parent compound (largely conjugated). Newly identified specific oxidative metabolites may be more specific indicators of exposure than the parent compounds [9]. Triclosan and triclocarban have been banned recently for soaps, but still exist as biocides in many products [10]. 2,5-Dichlorophenol is the metabolite of 1,4-dichlorobenzene, a putative carcinogen used in mothballs and air and toilet fresheners; levels in the United States population are still considerable 10 years after the ban for use in schools [11]. *bis*-Phenol A (BPA) is a monomer found in dental sealants and food containers. It and several homologs have been measured in indoor environments and urine [12,13]. The BPA family of chemicals possesses strong estrogenic properties [14,15].

Table 1. Emerging exposures – chemicals of concern with little human data, reported from 1 January 1990 to 31 December 1999 and in the past 10 years

Exposure class	Search terms	No. of citations, 1990–2000[a]	No. of citations, last 10 years[a]
Phthalates and phenols			
Phthalates	Urine	14	449
Phthalate replacements (long chain: decyl, nonyl, and isononyl)	Urine	0	28
DINCH (1,2-cyclohexane dicarboxylic acid diisononyl ester)	Exposure	1	16
DEHT [bis-(2-ethylhexyl)-terephthalate]	Exposure	0	5
DEHA [bis-(2-ethylhexyl)-adipate]	Exposure	0	10
Bisphenol A	Urine	9	399
Bisphenol F, bisphenol S	Urine	0	16
Nonyl phenol	Exposure	1	6
Parabens	urine	1	84
Triclosan, trichlocarban	Urine and exposure	9	143
2,5-Dichlorophenol (2,4-dichlorobenzene metabolite)	Exposure	3	36
Sunscreens			
Benzophenone-3 or oxybenzone	Exposure	5	59
Other terpenes (limonene, citronella, linalool, and mexoryl)	Exposure	22	68
Avobenzene (butyl methoxydibenzoylmethane, methoxydibenzoylmethane)[b]	Exposure	2	13
Polyphenols, including phytoestrogens	Urine	84	386
Pesticides			
Neonicotinoids	Urine and exposure	0	10
Halogenated flame retardants			
PBDEs (polybrominated diphenylether)	Exposure, plasma, or serum	4	445
		1	179
TBBP-A	Exposure	0	12
Hexabromocyclododecane	Exposure	0	96
Brominated organophosphates	Exposure	1	13
Brominated phthalates clusters (2-ethylhexyl tetrabromobenzoate, bis(2-ethylhexyl) tetrabromophthalate)	Exposure	0	13
Chlorinated flame retardants	Exposure	3	59
Coatings, PFOA (perfluorooctanoic acid) replacements			
Long-chain perfluoroalkyl acids	Exposure	1	14
PFOA	Exposure	4	428
NANO PARTICLES OR NANOPARTICLES OR NANOPARTICLE	Exposure	0	2220
Nano titanium, Zn, Ag, Au	Exposure	0	523
Nano organics		0	60
E-cigarettes	Exposure	1	208
E-cigarettes, flavorings	Exposure	0	11
Nicotine, cotinine, e-cigarettes	Urine	0	17
Volatiles (acetoin/3-hydroxybutanone, diacetyl, pentanedione/acetyl propionyl)	e-Cigarettes	3	70

Searched and not listed because recent references were too few (past 10 or 2 years): PAH; fuel additives; cotinine; Pb; Mn; Ti; PBB; PCB; DDT; DEET; nitrophenol; chlorpyrifos; pentachlorophenol; 2,4,5-TCP; 2,4-D; atrazine; DAPs; 4-*t*-octyl-phenyl-phenol; and ortho-phenyl-phenol; benzophenone-2 or benzophenone-4; octyl methoxycinnamate (octinoxate); homosalates (trimethylcyclohexenyl salicylate); octisalate (octyl salicylate); hydrofluoropolyether; perfluoroalkyl acids; perfluoroether carboxylic acids (PFECAs); and perfluoroether sulfonic acids (PFESAs) including GenX – $CF_3CF_2CF_2OCF(CF_3)COOH{\cdot}NH_3$, Adona 3*H*-perfluoro-3-[(3-methoxy-propoxy)propanoic acid, ADONA, 3(4-methylbenzylidene)camphor (4-MBC), and glyphosate.

[a]Search was done in October 2016, limited to humans; items for these two intervals are listed if citations in 'past 10 years' (a PubMed option) were 10 times more frequent than in 1990–2000. Search parameters were as shown, for example, 'PFOA exposure', limited to humans, limited to [date].

[b]Avobenzene was included because of its potential wide exposure to humans, although the number of citations is slightly different than 10 times in past 10 years.

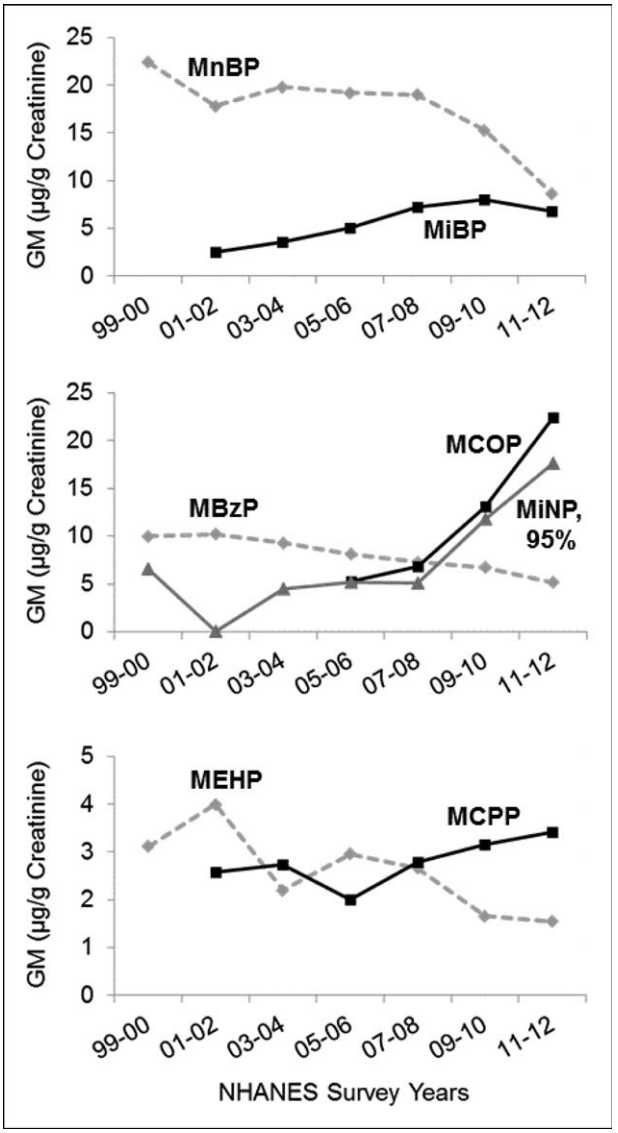

FIGURE 1. Phthalate urinary metabolites and long-chain replacements measured in the United States (geometric means, all NHANES 1999–2012 [11]).

Existing analytic methods can be used to measure the phthalate monoester metabolites and many phenols in urine [16]. Urine is the preferred matrix, as phthalate and phenol metabolites are most highly concentrated there and there is less possibility of specimen contamination by extraneous sources. For nonyl phenol, a valid method is not yet available, as it is metabolized to multiple oxidative phenols [17].

Sunscreens (ultraviolet filters)

Sunscreens typically contain a mixture of 2–8 UV filtering agents, including multiple phenols [e.g., benzophenone-3 (BP3), avobenzene, and paraben] as well as zinc oxide and titanium dioxide, the nanoparticle UV filters. Although BP3, a phenol UV filter, has been measured in many epidemiology studies, the others have not. They do not appear in PubMed searches. Limited findings on development and somatic growth in children have been reported [18]. BP3, its analogs, and other chemicals from personal products are found in swimming pools and in the Pacific Ocean, where Hawaii has asked bathers not to use them, with the aim of protecting coral [19]. For many of the sunscreen ingredients, pharmacokinetic and metabolism information is needed to guide design of biomonitoring methods.

Other polyphenols including phytoestrogens

Phytoestrogens are natural polyphenols homologous molecularly to hormones and environmental phenols. They share biological activity with synthetic phenols, such as hormone antagonism and obesogenicity. They include isoflavones (soy), quercetin (fruits), and lignan metabolites (flax) and have long been considered as healthy micronutrients. Recently, more than 80 phytoestrogens in urine were measured in a large European study and, in one report, 4/37 urinary biomarkers had concentrations exceeding 10 µm in urine [20]. Their dietary sources were mainly six foods [21▪].

Pesticides and herbicides

Pesticide residues such as DDE and the herbicide contaminant tetrachlorodibenzodioxin have declined steeply in recent decades in developed countries. For example, breast milk DDE and PCBs in Sweden declined 10–20-fold over the past 30 years (Fig. 2; [22▪]). Pesticides that replaced the persistent halogenated compounds, such as organophosphates, have also declined [11], but newer, less-persistent pesticides are in use, with limited information on human exposure. Neonicotinoids have been measured in urine in a few human studies [23,24]. 2,4-Dichlorophenoxyacetic acid and glyphosate have also long been in continuous use as herbicides, with recent concerns about toxicity and carcinogenesis [25]. Urinary 2,4-dichlorophenoxyacetic acid levels increased from 1999 to 2010 in NHANES [11]. Glyphosate is the most commonly used pesticide in the United States; however, few methods exist to measure it in urine and those that do exist are extremely cumbersome. Newer methods should be developed to make the measurement of glyphosate more accessible and conducive to adding in other analytes for measurement. Another area of interest is the burgeoning use of thiazole fungicides in which almost no studies have been done to understand toxicokinetics or exposure.

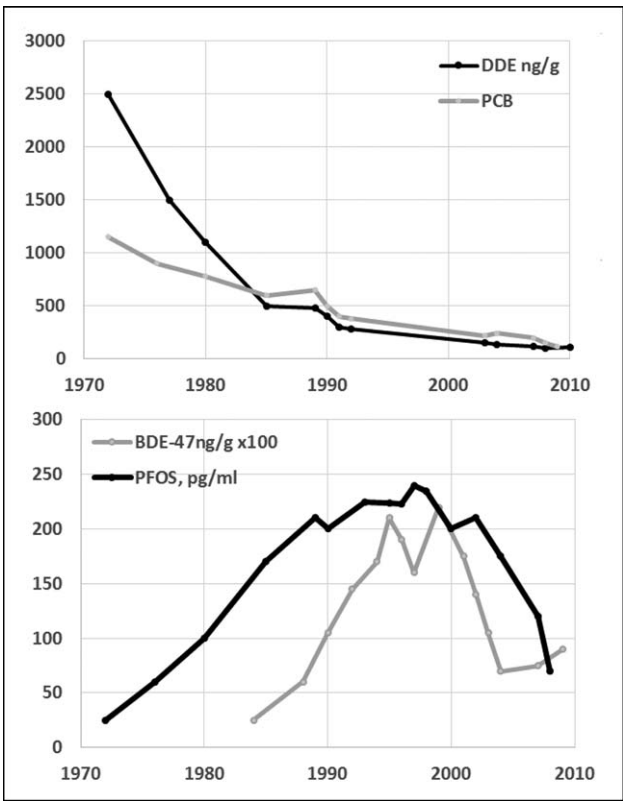

FIGURE 2. Levels of DDE, PCB, 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47) and PFOS in breast milk in Sweden, data extracted from Fang *et al.* [22▪].

Halogenated flame retardants

Polybrominated diphenylether (PBDE) flame retardants replaced molecularly homologous polybrominated biphenyls (PBB) after a tragic accident contaminated cattle and the entire state of Michigan during 1974–1976 [26]. PBDE levels began to increase worldwide (Fig. 2), and newer replacements have come into being. Although PBB and PBDE are persistent with half-lives in humans of 4–40 years, newer fire retardants are less persistent, and they have polar metabolites that can be detected in urine. These chemicals are also being controlled in the United States, particularly in products used by children, such as sleeping mats [27]. Multiple halogenated organophosphates have been found in human biomonitoring studies, suggesting that they co-occur in home items or are often used in items in the home [28].

Perfluorinated coatings

Perfluorinated alkyl carboxylic acids (PFCs) are used in oil and water-resistant coatings for fabric and cookware, fire-retardant foam, and floor polish. Following the typical manufacturing practice, PFCs including perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), are being replaced with homologous longer chain chemicals. In Sweden and the United States, biomonitoring levels of PFOS have declined since 2000 after increasing in the 1990s (Fig. 2). More than 20 replacement compounds have been reported, many with structures similar to PFCs [29]. It is not clear that these are less toxic or less persistent [30].

Nanoparticles

Nanomaterials are submicron sized fibers, tubes, and large molecules made of metal, polymer, or carbon materials. They are controversial in terms of human exposure and toxicity, as it is contended that they are poorly absorbed from sunscreens and clothing [31▪]. However, they are also being applied as drug delivery systems including to the brain, suggesting that absorption or penetration is possible. Nanoparticles may be inhaled. Immune effects, inflammation, and possible developmental toxicity have been reported [31▪,32,33]. Validated methods for measuring nanoparticles in humans are limited to respiratory intake. However, limited literature suggests that they are absorbed, as they have been measured in body fluids, including Au-U [34]. Their disparate use makes use of recall methods almost impossible.

Electronic-cigarettes

Electronic-cigarettes (e-cigarettes) were introduced into the United States tobacco market in 2007; ever-use rapidly increased after 2010, especially among youth, to include 16% of high school students by 2015 [35]. The active ingredient in e-cigarette liquid is nicotine. E-cigarette use results in nicotine urinary metabolites similar in level and pattern to those from users of tobacco and smokeless tobacco products. However, the oxidative nicotine metabolites are lower in users of e-cigarettes [36]. Diacetyl, 2,3-pentadione, and acetoin are structurally similar compounds that have been shown to cause bronchiolitis obliterans in exposed workers or laboratory animals [37]. They are also ubiquitous in fruity and sweet e-liquid flavorings used in marketing to children, as well as in traditional tobacco flavorings such as menthol [38▪,39,40]. Although these compounds are well tolerated for ingestion, they cause lung toxicity when inhaled at concentrations likely to be generated by commercially available e-cigarette liquids. Other flavor ingredients, which are 'generally recognized as safe' (GRAS) to ingest by the Flavor and Extract Manufacturers Association (FEMA), and that are commonly added to food, have been identified by FEMA as potentially toxic to the lung, if inhaled

[41,42]. There has been limited research to determine whether these aldehydes and other reactive flavorings are present in e-cigarette liquids. However, the implication by manufacturers that flavor ingredients used in e-cigarettes and related devices (e.g., hookahs) are well tolerated for inhalation because they have FEMA GRAS status for use in food has been stated to be 'false and misleading' by FEMA [43]. Unintentional nicotine poisoning of children as a result of e-cigarette liquid exposure has emerged recently as a public health problem [44,45▪].

Multiple and mixed exposures

Various chemicals we have described can occur in many different products, so that multiple exposures exist with everyday use. In NHANES exposure biomarker surveys, a large proportion of the more than 250 measured chemicals is more than 50% detectable, meaning that many coexist in the bodies of most people. Multiple sources of exposure exist; for example, parabens might be absorbed from food, sunscreen, lotion, and lipstick. In addition, as noted above, many products contain more than one ingredient, which constitutes a mixture, so that users would be exposed to several chemicals at once (e.g., organic and nanoparticle UV filters with paraben in sunscreen). When 38 975 products were surveyed for developmental toxicant contents, 30% had one or more chemical of interest and 1059 contained three phenols [1▪].

Fundamental/overarching needs

Before adequate biomonitoring methods can be developed for emerging chemicals, we need to conduct toxicological studies in animals or *in silico* to understand the toxicokinetics of these chemicals. It is imperative to know what metabolites are formed from nonpersistent chemicals before we begin trying to monitor them in biological matrices. Experience, for example, with high molecular weight phthalates, showed that even similar chemicals in the same class may not metabolize similarly resulting in measurement of inappropriate or less useful biomarkers. In addition, one of the biggest challenges in methods' development for emerging chemicals is the lack of authentic standards for measurement. It would be quite useful if industries introducing new chemicals into manufacture could conduct toxicokinetic studies to inform exposure scientists about potential biomarkers and to synthesize or isolate standards for the measurement of these biomarkers. Without metabolic information and standards, valid biomarker methods cannot be developed.

CONCLUSION

Many developmental toxicants can be determined using biomarkers. A number of these have been widely detected in the United States with levels of exposure biomarkers rising in recent years [11]. Overall, however, attention has focused on a limited number of chemicals that have validated biomarkers or that have been most convenient to analyze. Historically, comprehensive health information has followed the discovery of widespread exposure, for example, to lead, PCBs, and PFOA. We cited a number of exposures that have been introduced to replace or to improve other agents. Many products have more than one additive, and little is known about how mixtures or multiple chemicals interact. Biomonitoring or personal exposure assessment can characterize individual body burden more efficiently than information using recalled exposure sources.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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One of the first articles to show that chronic health effects of children using e-cigarettes.