REVIEW

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# The role of endocrine-disrupting phthalates and bisphenols in cardiometabolic disease: the evidence is mounting

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**Purpose of review**
There is substantive and accumulating evidence that endemic exposure to plastic-associated chemicals (PACs) contribute to the pathophysiology of metabolic conditions, like obesity, diabetes, and heart disease. The consequences of this endemic exposure in inducing a pro-inflammatory state in adipose tissues as a critical link between exposure and disease is reviewed.

**Recent findings**
In general, PACs are classified as nonpersistent *in vivo* because of their rapid metabolism to easily excreted forms. The parental chemicals, however, are typically lipophilic, with the potential to bioaccumulate. Recent data from selected association studies suggest exposure to PACs drive predisease states like obesity and inflammation of the adipose tissues. A range of experimental studies are discussed with a focus on biological mechanisms that are susceptible to the influence of PACs and which may promote metabolic disease, the detection of PACs within susceptible tissues and biological effects that are detectable at doses that correspond to real-life exposures to these chemicals.

**Summary**
If we hypothesize the toxic pressure from chronic exposure to PACs will progress disease processes, then individuals with comprehensively characterized indicators of premetabolic disease could undergo trials of quantifiable interventions to reduce exposure to PACs to test if the trajectory of disease-associated analytes, is altered.

**Keywords**
adipose tissue, bisphenols, endocrine-disrupting chemicals, phthalates, reservoir

## INTRODUCTION

### Endocrine-disrupting chemicals

Endocrine-disrupting chemicals (EDCs) that include polychorinated phenyls, phthalates, and bisphenols, interfere with naturally occurring hormones, the activity of nuclear and steroid hormone receptors, and disrupt normal metabolism. There is an increasing number of scientific studies that have implicated the presence of these chemicals in our environment with the pathogenesis of infertility, autoimmune and metabolic conditions. However, direct attribution of these chemicals to adverse health outcomes in humans remains challenging and contentious [1,2▪,3▪▪], as more conventionally diseases have been attributed to genetic susceptibilities combined with the lifestyle choices of sufferers, especially diet, exercise, and smoking. An obvious contributor to the exposure of EDCs is their endemic use in plastics, with the annual production of nonbiodegradable plastic of over 3 000 000 tons, with much of it ending in landfill or the ocean [4] where it fragments progressively to smaller particles; and by 2050 an estimated 33 billion tonnes will contribute to the current burden [5]. The recognition of the scale of plastic pollution is one factor that

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## KEY POINTS

- There is mounting evidence that plastic-associated chemicals (PACs) interfere with metabolic pathways.
- The critical threshold and relative contribution of PAC exposure in causing disease is not known.
- The potential effect and extent of bioaccumulated PACs is not known.
- The metabolic pathways affected by chronic PAC exposure are under investigation.
- Randomized controlled trials altering PAC exposure are currently missing.

underlies the growing public interest directed at human associated effects on the environment, and this is providing political support to revisit and extend policies to decrease exposure to dietary and extradietary exposure to plasticizers like phthalates and bisphenols. However, to date direct benefits to health have not been demonstrated.

### Aim

Here we describe new published evidence highlighting contemporary exposure levels to plastic-derived EDCs, investigations into putative mechanisms responsible for altered cellular function and epigenetic changes and discuss recently identified effects on immune function within susceptible tissues.

### Plastics as a significant exposure source of endocrine-disrupting chemicals

Plastics are utilized in almost every aspect of contemporary life, including food and drink packaging, clothing, furnishings, and personal care products. This has resulted in a widespread and continuous exposure of the human population to plastic-associated chemicals (PACs).

Bisphenol A (BPA) is a small molecule or monomer used in the manufacture of polycarbonate plastic consumer products, including food and water containers, lining of cans, baby bottles and toys, medical tubing, resins, and dental fillings. Polycarbonate plastics are most frequently single use items, are not biodegradable, and litter human and animal ecosystems. BPA leaches into food and water especially after heating and has oestrogen-like properties [6,7]. Despite the proposition that plastic contamination is detrimental to human health being contentious, some countries have banned plastic production, which utilizes BPA, and recommended its substitution with derivative molecules, such as bisphenol S and F. And increasing levels of these molecules are being detected in the urine collected by contemporary studies [8▪▪]. Importantly, there is growing evidence that these are not well tolerated alternatives [9▪,10▪▪,11▪▪,12,13▪▪].

Phthalates are a group of low (LMW) and high molecular weight (HMW) man-made chemicals with applications in the medical (devices) and automotive industries and found in many consumer products. HMW phthalates (i.e. Di(2-Ethylhexyl) Phthalate; DEHP) are typical plasticizers in PVC materials, whereas LMW phthalates, such as DiMethyl Phthalate (DMP), DiEthyl Phthalate (DEP) and Di-n-Butyl Phthalate (DBP) are ingredients in cosmetics and personal care products acting as fixatives, adhesives and solvents [14]. There is significant environmental leaching of phthalates because of noncovalent bonds with 'parent materials' and metabolite markers of eight phthalates have been found in 89–98% of a United States population [15].

Phthalates and bisphenols, including analogue bisphenols S or F, are ingested, inhaled as particulates in household dust [16] or absorbed cutaneously, and it can be assumed that human exposure to these common chemicals is direct, continuous, begins at gestation and persists across the lifespan. A national survey in the USA [17] reported that 93% of the population had detectable levels of BPA. These chemicals effect humans systemically with BPA and/or phthalates measured in samples of urine, serum, nasal secretions, semen, adipose and brain tissue [6,18–20,21▪▪,22–24,25▪,26–28].

### Current regulatory levels of acceptable exposure levels

Regulations that specify the maximum acceptable level of exposure are expressed as milligrams of the substance per kilogram of body weight per day and has been determined following the review of a range of mostly experimental exposure studies conducted in small animal models, with the tolerable daily intake (TDI) calculations being based on dividing the published no observed adverse effect level (NOAEL) for a chemical by an uncertainty factor; typically in the range of 100 to 1000 (Table 1). Monitoring programs that measure the levels of PACs in a range of common dietary foodstuffs are periodically performed and act to assure consumers of the food chain safety. Assessments of the contribution of PACs from environmental exposure to an individual's TDI for PACs are not performed and the development of such environmental monitoring are currently experimental, with the number of studies being published rapidly increasing since the late 1990s. Thus, the levels of an individuals' exposure to PACs is likely underestimated.

**Table 1.** Historical regulatory limits for common plastic-associated chemicals

| Chemical | Authority | Type | Level (μg/kg body weight/day) |
|---|---|---|---|
| Bisphenol A | US FDA (2002) | NOAEL | 5000 |
| | US FDA (2002) | TDI | 10 |
| | US EPA | RfD | 5 |
| | EFSA (2007) | TDI | 50 |
| | EFSA (2015) | TDI | 4 |
| Di(2-Ethylhexyl) Phthalate | EFSA (2005) | TDI | 0.05 |
| Benzyl Butyl Phthalate | EFSA (2005) | TDI | 0.5 |
| Di-Butyl Phthalate | EFSA (2016) | TDI | 0.01 |

EFSA, European Food Safety Authority; FDA, Food and Drug Administration; NOAEL, no observed adverse effect level; RfD, reference dose; TDI, total daily intake.

Importantly, there is accumulating evidence that exposure to PACs at levels found in the general population (0.2–20 ng/ml) is associated with adverse health effects [10▪▪].

## Evidence of plastic-associated chemicals disrupting endocrine function

The rationale for the suspicion that PACs may disrupt endocrine function initially came from the structural similarities of BPA with oestrogen and the demonstration that BPA could bind to the oestrogen receptor in a rat model, albeit at four orders less efficiency than oestrogen [29]. Subsequently, evidence emerged that BPA and structurally related bisphenols influence oestrogen-dependent biological processes, such as gene regulation [30], oestrogen-dependent breast cell proliferation [31], alteration of other thyroid signalling [32] and disruption of glucose homeostasis [33]. A recently sampled cohort ($n = 353$) from the heavily industrialized city of Shenzhen, representing both sexes and ranging in age from 20 to 60 years old were tested for the presence of nine different bisphenol derivatives and measures of oxidative stress, endocrine function were performed. The results showed that high levels of serum BPA (mean 42 ng/ml) and bisphenol FL (mean 0.423 ng/ml) positively correlated with elevated levels of oxidative stress indices of malonaldehyde and 8-hydroxy-2-deoxyguanosine, whilst higher levels of serum bisphenol AF, bisphenol B and 4,4-dihydroxybenzophenone positively correlated with higher levels of oestradiol, follicle-stimulating hormone and luteinizing hormone, respectively [21▪▪]. Phthalates whilst structurally not directly interacting with hormone signalling have been shown to be associated with altered DNA methylation patterns [34,35], leading to the proposition that interactions between phthalates and histones influence gene transcription, leading to changes in reproductive and metabolic function [36].

## Evidence of plastic-associated chemicals' association with metabolic disease

The incidence of obesity and metabolic syndrome has risen over the last decades coinciding with increased levels of synthetic organic and inorganic chemicals used in the human environment. A review of the available evidence published in 2002 [37] posited that exposure to these chemicals may have damaged homeostatic mechanisms important for weight control. Later the term 'obesogen' was termed to describe chemicals that promote obesity via a variety of mechanisms including altering gut microbiota, hormonal control of appetite and increasing the number of adipocytes [38]. These and other observations lead researchers to sub-classify EDCs as metabolism-disrupting chemicals (MDCs).

Metabolic syndrome is characterized by central or abdominal obesity in association with dysglycaemia, hypertriglyceridemia, low LDL cholesterol and arterial hypertension. Obesity and insulin resistance precede the development of metabolic syndrome and arise from increased adipocyte hypertrophy and dysplasia. Ben-Jonathan *et al.* describe a model representing the contribution of BPA to obesity-related metabolic syndrome purporting that BPA suppresses adiponectin and stimulates inflammatory cytokines [6]. Phthalates may also induce metabolic syndrome via direct effects on the PPAR family of nuclear receptors [39▪]. There is evidence that treatment with DEHP (50 μg to 500 mg/kg/day) on rodents affects fat distribution in female mice [40,41] and in male mice on a high fat diet [42]. Additionally, mice treated with DEHP (5–200 mg/kg/day) show signs of general liver toxicity and altered lipid profiles, higher cholesterol and triglycerides and decrease high-density lipoproteins (HDL) [42].

Association studies show negative associations of phthalates with lipid components including cholesterol and low-density lipoprotein cholesterol (LDL-C) [43▪]. In a recently published analysis on a Dutch cohort of healthy volunteers ($n = 662$, 42% male participants) a range of EDCs including three bisphenols, thirteen metabolites of eight phthalates, as well as five parabens, were detected in 24 h urine collected in 2012 sample collections. This study performed a multivariate analysis for cardiometabolic traits and the EDC concentrations. Although most chemicals were detected in all samples and the only associations were detected for Mono-iso-butyl

phthalate (MiBP) and Mono-Benzyl Phthalate (MzBP) and adiposity traits, no association was detected for EDCs and lipid measures. Whenever corrections were performed for multiple testing, the observations fell below statistical significance, which the authors conclude was because of lack of power of the cohort size for this multivariate study design and the fact that the cohort positively selected healthy individuals [44▪▪]. A previous larger study ($n = 2719$) included a significant proportion of participants with clinical evidence of metabolic syndrome (MetS) and demonstrated a significant odds ratio of 2.20 for the prevalence of MetS and higher concentrations of DEHP [45]. Similarly, a large cross-sectional study examined randomly selected children and adolescent's ($n = 2838$) controlled urinary BPA levels looking at BMI as the main outcome measure and controlling for race/ethnicity, age, caregiver education, poverty to income ratio, sex, serum cotinine level, caloric intake, television watching, and urinary creatinine level. The study found a significant association of BPA exposure and obesity with individuals from the lowest BPA exposure quartile having significantly lower levels of obesity than individuals than the other three higher BPA exposure quartiles (OR >2 for each comparison) [46].

## Inflammatory biomarkers as hallmarks of chemical disruption

Mammals' protection from infection is provided by an initial rapid and broad response from the innate immune system, and then a delayed and epitope-targeted response of the adaptive immune system. Local inflammation begins following the detection of pathogens in damaged tissue. This inflammation is mediated by soluble factors released from the tissue that increase vascular perfusion, recruit immune cells and increases the supply of nutrients and oxygen during the immune response and subsequent tissue repair. Inflammation is maintained whilst soluble factors continue to be released in the damaged tissue and resolves following effective immunity and tissue repair. Chronic inflammation occurs when tissue is not effectively repairable because of ongoing damage from inappropriate immune responses directed against the tissue (autoimmunity) or driven by ongoing cell death, for example, following adipocyte hypertrophy [47], which may be associated with accumulating biotoxins, such as PACs. The soluble mediators of inflammation include pro-inflammatory cytokines, for example, members from the interleukin (IL) 1 and tumour necrosis factor (TNF) superfamilies [6]. Although cytokines from the IL1-superfamily are critical for immunity and tissue repair, their deregulated expression is often linked to autoimmune and inflammatory diseases [48]. IL-33, a member of the IL-1 superfamily, is critical in fine tuning metabolic inflammation of the adipose tissue, via its impact on visceral adipose tissue T regulatory cells (VAT-Treg) [49] which express its specific receptor, ST2. Adipocytes secrete IL-33 constitutively, levels are increased dramatically when stimulated by pro-inflammatory cytokines [50]. VAT-Treg cells are functionally specialized tissue-resident cells that prevent obesity-associated inflammation and preserve insulin sensitivity and glucose tolerance, and which uniformly express the transcription factor PPAR-γ [51]. The influence PACs have on fat biology include evidence discussed above of the phthalate DEHP acting as an inducer of obesity *in vivo* in mice. PACs, such as DEHP metabolites (low μmol/l doses [52]) and BPA (nmol/l doses [53]), have been demonstrated to drive adipogenesis of the 3T3L1 pre-adipocyte line *in vitro*. The proposed mechanism responsible for BPA's effect on enhanced adipogenesis is thought to be via the induction of higher PPAR-γ expression in 3T3L1 cells [53], whilst structural modelling, binding interaction assays and bioassays have confirmed that DEHP metabolites, MEHP and MEOHP, rather than DEHP, directly interact with PPAR-γ at low μmol/l doses [52,54] and effecting its induction of gene transcription. This highlights that adipose tissue may be particularly sensitive to the presence of PACs.

The lung is another tissue at risk of environmental exposure to PACs. There is evidence gained from a mouse model of allergic airway inflammation that very low exposures of BPA (0.06–25 pmol/l BPA/animal 25 g/week) co-instilled into the lung with the model OVA antigen could significantly increase Th2 cytokine production, including that of IL-33, even at the lowest BPA dose tested and increase immune cell infiltration within the lung [55]. The ILC2 (type 2 innate lymphoid cell) lung cell appears susceptible to phthalate exposure as shown when primary murine lung ILC2 cells were cultured in the presence IL-33 with or without DEHP (nmol/l doses) they released significantly higher amounts of the Th2 cytokine interleukin 5 [56▪]. Altering the level and type of cytokine release in the lung is likely to exacerbate immune reactions and contribute to allergic airway disease.

## Adipose tissue might act as a sink for lipophilic toxins, which upon release may cause disease

Despite evidence that bisphenols and phthalates are rapidly metabolized and excreted with half- lives measured in hours, the lipophilic properties of the

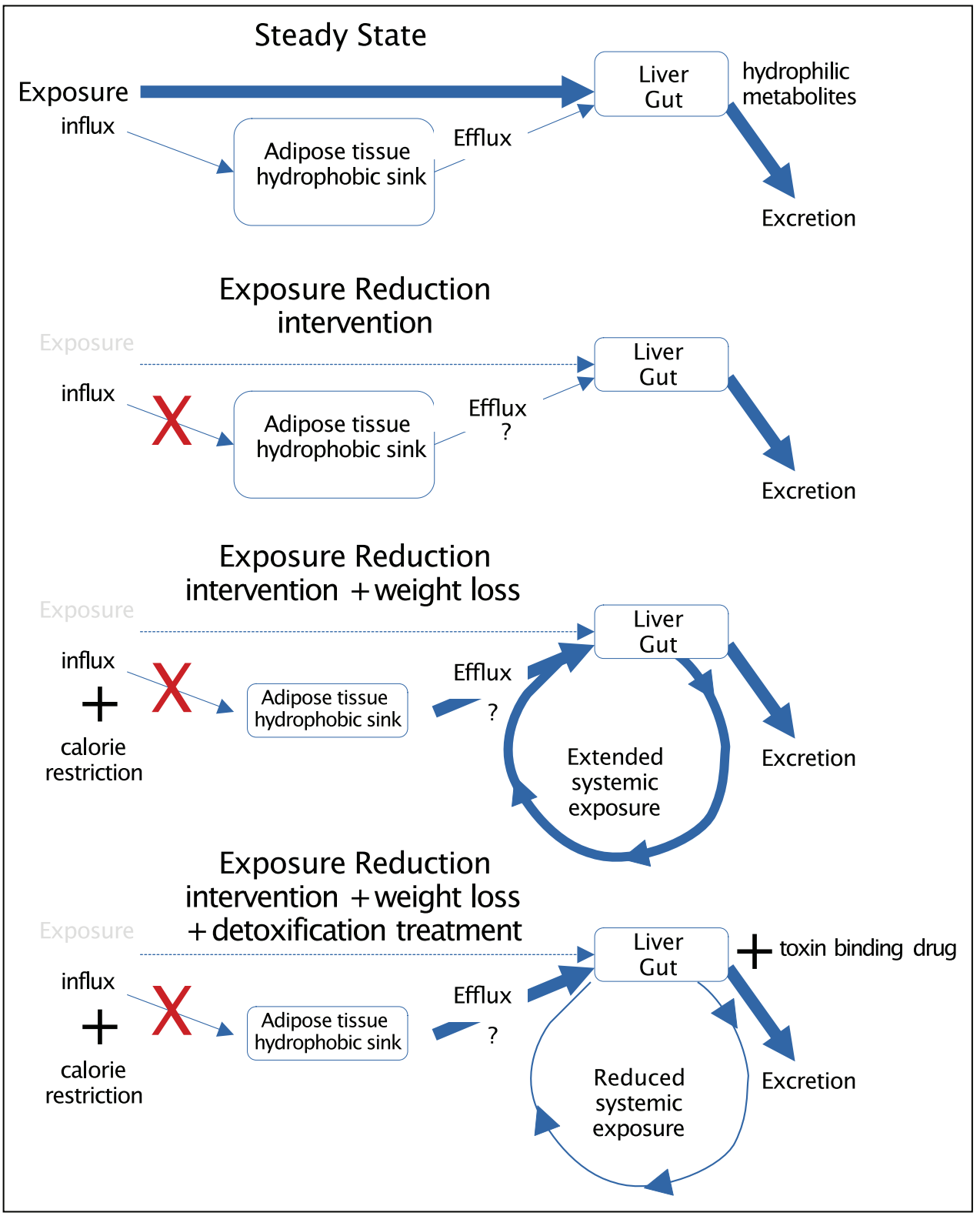


**FIGURE 1.** Model of plastic associated chemical flux under conditions of changing exposure and/or weight loss.

parental contaminating chemicals suggest that adipose tissue might act as sink for a proportion of PAC exposure. The relationship of bioaccumulated chemicals in the fat under normocaloric and the potential for their rapid release into circulation under hypocaloric diet, is not understood. Precedents for toxicity following the release of polychlorinated compounds from the fat tissue is well

demonstrated with clinical outcomes that include 'chloracne' [57].

Whilst less accessible than samples of urine or blood, it is possible to obtain tissue measures of chemical contamination, with BPA being detected in the ng/g range within the adipose tissue, liver and brain, following autopsy of 11 individuals [22]. Dynamic sampling of a relevant tissue type is technically possible as shown for the detection of leptin and adiponectin in adipose tissue via microdialysis of visceral and normal breast tissue [58] and might provide important insights into the dynamics and consequences of lipophilic PACs exposure.

## CONCLUSION

If we accept the premise that the endemic exposure to PACs is likely contributing to the burden of metabolic disease, then how could a successful intervention reducing the personal exposure to PACs be applied? As adipose tissue is a sink for lipophilic toxins, that include PACs, the potential consequence of interventions that reduce the steady state endemic exposure to such pollutants is postulated in Fig. 1. Firstly, in the steady state, input of PACs from endemic exposure from all sources (food, drink, and environment) is balanced by metabolism and elimination of the PACs, resulting in a low background level of PACs both in the circulation and tissues. Secondly, if an intervention is introduced that reduces the influx of PAC exposure from all sources and includes a normocaloric diet, there is precedent that levels of PACs and their metabolites will approach zero in excreta; however, it is not clear how this would affect the levels of PACs in adipose tissue. Thirdly, a similar intervention in the context of a hypocaloric diet might achieve a rapid loss of PACs and other lipotoxins from the adipose tissue with unpredictable but short-term systemic effects, until levels drop due metabolism and excretion. Finally, to reduce the potential systemic exposure to PACs released from the tissue, a hypocaloric intervention that includes a theoretical detoxifying drug to absorb rapidly released PACs, might also achieve effective and safe reduction of PACs.

The potential harmful effects of plastics and PACs on the environment and human health is increasingly recognized by health professionals, national regulators, the plastics industry and the general population. Whilst conservative targets for contaminant levels in food products are currently regulated in many jurisdictions, the mounting evidence that biological effects are mediated by even very low levels of EDCs, that include PACs, will likely result in a revision of such limits. Stronger evidence might be obtained by studying reduced PAC exposure in ''at risk'' individuals looking for improvements in, or normalisation of, metabolic and cardiovascular health.

Improved clarity can be achieved through improvements to study methodologies, particularly in exposure assessment, identification of confounders, and via highly powered cohort studies. Given the complex pattern of human exposure to EDC, biostatistical methods that account for multiple and overlapping interactions and exposures are required.

These questions need answering to address the community's high and credible concern of the risk that PACs have to human health and to provide sufficient evidence to influence changes in health policy that reduce human exposure to current chemicals and future derivatives.

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### Conflicts of interest

*There are no conflicts of interest.*

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