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Sent: Friday, January 28, 2022 11:15 AM
To: Makarow, Irina (ECY)
Cc: Patrick Harmon
Subject: BASF comments to Washington DOE
Attachments: BASF Comments on Draft Regulatory Determinations Report to the Legislature January 2022 final.pdf

Hi Irina,

Attached are our comments submitted to the state DOE on the Draft Regulatory Determinations Report. I am providing a copy to you also since there are relevant items for the upcoming phthalates action plan. Please let me know if you have any questions.

Kind regards,

Pat

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Submitted online and via email: SaferProductsWA@ecy.wa.gov

Comments: Draft Regulatory Determinations Report to the Legislature

BASF appreciates the opportunity to comment on the Draft Regulatory Determinations Report to the Legislature (DOE Report).[1] Our comments focus on the following points:

- Regulation of ortho-phthalates as a class.
- Comments on toxicology and exposure to specific ortho-phthalates.
- Comments on recent publications.
- Comments on the proposed alternatives assessment process.

Ortho-phthalates should not be regulated as a class

As stated in previous BASF comments to Washington Department of Ecology (DOE), and as noted in the DOE Report, the vinyl flooring market has moved away from ortho-phthalates to alternative plasticizers such as DOTP. To our knowledge ortho-phthalates have largely been replaced in this application; however, some high molecular weight phthalate esters (HMWPE)[2] are particularly important for a number of applications such as wire and cable insulation, roofing membranes, automotive materials, and others. In addition, assessments by regulatory agencies show there is little risk for their use in these "technical" applications.

Reproductive and development effects on the developing male rat fetus that were observed with some ortho-phthalates have been the primary driver of recent regulatory action in North America and Europe. The following table summarizes the results of Furr et al. (2014). US EPA in this paper reported the results of a screening test for effects on fetal testosterone levels in developing rats. The lower molecular weight products (DMP and DEP) and HMWPE products were inactive or less active (DINP), while those with a C3 – C6 carbon backbone were active and led to a

[1] BASF manufactures a number of plasticizers including DOTP, DINCH, high molecular weight ortho-phthalates, adipates, and trimelliates. BASF Corporation is a subsidiary of BASF SE.

[2] HMWPE in this case applies to esters of phthalic anhydride with alcohol primary chain lengths of 7 carbons or greater (Fabjan 2006), such as DINP, DIDP, DPHP, and predominately linear esters such as di-nonyl,undecyl- (911P), and diundecyl phthalate (11P).

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decrease in testosterone levels. Those that were active also are classified in Europe for reproductive and developmental toxicity and are substances of very high concern (SVHC).

Observed effect on rat fetal tetis testosterone production (Furr et al. 2014)

	Alcohol		
Plasticizers	**Carbon chain**	**C Backbone**	**Outcome**
DMP	1	1	Negative
DEP	2	2	Negative
DIBP	4	3	Positive
DBP	4	4	Positive
BBP	4/7	4	Positive
DPenP	5	5	Positive
DHexP	6	6	Positive
DEHP	8	6	Positive
DINP	9	6-9	Weak positive
DPHP	10	7	Negative
DIDP	10	7-9	Negative
Alternatives (non-ortho-phthalate)			
TOTM	8	6	Negative
DINCH	9	7-9	Negative
DOTP/DEHT	8	6	Negative

In addition, the ECHA risk assessment committee (RAC) concluded in 2018 that no classification was necessary for DINP (ECHA 2018). US CPSC, based on the absence or expected absence of anti-androgen effects, removed DIDP and DnOP from their list of phthalates restriction in toys and childcare articles and also decided no action was necessary for DPHP and several alternative plasticizers (CPSC 2017). Therefore, it is not appropriate to regulate all ortho-phthalates as one class.

Comments on specific ortho-phthalates

On Page 141 of the DOE Report, assessments of three ortho-phthalates, DPHP, DMP, and DEP, are summarized. To our knowledge, the details of these assessments by Scivera and ToxServices are not publicly available, so it is difficult to comment on the conclusions. We understand that these consultants and others provide the assessments as part of a subscription or other paid access models; however, given their roles in potential regulatory action by the state, this lack of transparency is unacceptable. The following comments are based on the summary statements in the DOE Report.

The DOE Report stated that structural alerts for carcinogenicity and evidence of developmental effects were identified for DPHP. DPHP is not classified based on a lack of developmental

effects in guideline pre-natal toxicity studies in rats and rabbits and a two-generation reproductive toxicity study in rats (ECHA 2021). While some effects such as decreased body weight in offspring were found, these effects all occurred at doses that also caused significant parental toxicity. CPSC (2019) agreed with this rationale and reported DPHP as "not a teratogen." Some phthalates, such as DEHP, have been shown to cause various reproductive and developmental effects due to androgen deficiency, referred to as "phthalate syndrome." DPHP did not cause these effects in standard reproductive and developmental toxicity studies and a study that specifically assessed fetal testosterone production (Furr et al. 2014). The CPSC report also agreed with the study authors that the increased fetal variations in the rat study were considered secondary to maternal toxicity and that the maternal LOAEL was 1000 mg/kg-day, based on decreased body weight gain and clinical signs; the developmental LOAEL was 1000 mg/kg-day, based on soft tissue and skeletal variations (NOAEL 200 mg/kg bw/day). The NOAEL for teratogenicity was 1000 mg/kg bw/day. The NOAEL for pre-natal developmental toxicity in the rabbit was 127 mg/kg bw/day, which was the highest dose tested due to maternal toxicity observed at higher doses (ECHA 2021). Developmental studies are available for two species (rat and rabbit), and effects were only observed together with maternal toxicity at the highest dose of 1000 mg/kg bw/day. Table 55 on Page 243 of the DOE Report, notes that developmental effects observed at >250 mg/kg bw/day may be classified as “low”. Based on the preceding conclusions it is difficult to understand why “evidence of developmental toxicity” was concluded in the Scivera assessment.

The DOE Report also referred to a structural alert for carcinogenicity in the Scivera assessment. We assume the assessment refers to data for other ortho-phthalates; however, the ECHA REACH dossier provides the following summary: *“There is no data available for DPHP, however analogous substances have been assessed in the EU risk assessment. Additionally, there is a chronic feeding study available for DIDP, which has not been available by the time the EU risk assessment for DIDP was conducted.*

For DINP, the risk assessment concluded that "there was a significant excess of liver neoplasia in rats and mice after chronic oral administration. This is consistent with a peroxisome proliferation mode of action for hepatic tumor induction specific in rodents. It has been established that peroxisome proliferators exhibit their pleiotropic effects to activation of PPARα (peroxisome proliferator activated receptor α) and that PPARα is expressed only at low level in humans, explaining the absence of significant response to the action of peroxisome proliferators. Thus, there is no concern for a potential carcinogenic effect in humans."

For mononuclear cell leukemia, a clearly increased incidence was observed in two studies of DINP conducted with Fisher rats. However, this was considered as a common neoplasm in this strain of rat with no known counterpart in humans. Kidney tumors found in the rat study were not regarded as relevant to humans as they underlie the species and sex-specific alpha 2μ globulin mechanism.” (ECHA 2021)

The conclusion with respect to peroxisome proliferation was*: "Furthermore, in humans, activation of peroxisome proliferator-activated receptor α (PPARα) does not lead to increased relative liver weights, oxidative enzyme induction or other responses typically associated with sustained PPARα activation observed in wild-type mice (Corton et al. 2018). The weight of evidence supports the conclusion that adverse effects related to a PPARα MOA is either "not relevant" or "unlikely to be relevant" in humans (Felter et al. 2018)."*

In addition, *"changes in the thyroid and pituitary gland are secondary to the changes observed in the liver: peroxisome proliferation and parallel induced xenobiotic metabolism, which results in an increased elimination of T3/T4 from rat serum by increased glucuronidation. This mode of action has been extensively studied with Perchlorate and Phenobarbital for example (Meek et al., 2003 Critical Reviews in Toxicology, 33(6):591–653; Lewandowski et al., 2004 Regulatory Toxicology and Pharmacology 39, 348–362; McClain et al., 1989 Toxicology and Applied Pharmacology 99,216 -228; Fisher et al., 2013 Joural of Environmental Science and Health, Part C, 30:81 -105) and is therefore well understood. It is not relevant to humans as rodents are more sensitive to thyroid effects (summarised in Meek et al., 2003 Critical Reviews in Toxicology). Accordingly, Bhat et al. (2014), Regulatory Toxicology and Pharmacology 70, 65 - 74, who published the comprehensive oral risk assessment undertaken by the US EPA chaired Health Advisory board of NSF International, reduced the interspecies extrapolation factor for derivation of the oral reference dose (RfD) to 1 applying the US EPA guidance. The lack of human relevance of these thyroid effects is also reflected in the opinion of the German MAK Commission (2015). Furthermore, in humans, activation of peroxisome proliferator-activated receptor α (PPARα) does not lead to increased relative liver weights, oxidative enzyme induction or other responses typically associated with sustained PPARα activation observed in wild-type mice (Corton et al. 2018). The weight of evidence supports the conclusion that adverse effects related to a PPARα MOA is either "not relevant" or "unlikely to be relevant" in humans (Felter et al. 2018).*

The No Observed Adverse Effect Level (NOAEL) was found to be 500 ppm (39 mg/kg bw/d) for peroxisomal proliferation in liver of male and female Wistar rats, but the NOAEL for hazards relevant to human is 2500 ppm (196 mg/kg bw/d) for hematological effects." (ECHA 2021)

The Scivera assessment also identified evidence of reproductive toxicity for DMP. The REACH dossier includes a summary of a two-generation study for DEP, since a two-generation study is not available for DMP.

"There is no one- or two-generation study available for DMP, but a read-across can be made to DEP, a close structural analogue. DEP was tested in a 2-generation study by Fuji et al. (2005). The 2-generation reproduction toxicity study according to OECD TG 416 was performed to evaluate the effects of diethyl phthalate on parental reproduction performance, including features of the endocrine system and development and growth of the offspring at dietary dose levels of 0, 600, 3000 and 15000 ppm (nominal concentration in diet). Actual ingested doses in

F0 males were: 28-64, 141-315, 721-1594 [mg/kg bw/day], in F0 females: 32-90, 160-453, 815-2191 [mg/kg bw/day]; in F1 males: 29-73, 142-369, 722-1901 [mg/kg bw/day], in F1 females: 33-91, 158-428, 809-2140 [mg/kg bw/day]. In F0 and F1 parents, no treatment-related adverse effects were observed considering clinical findings, body weights, food consumption, reproductive parameters and gross- or histopathological findings in any treated group. Increased liver weights and enhanced activities of metabolic enzymes were observed in F0 males at 15000 ppm. F0 males also exhibited an increase in the content of CYP3A2, a cytochrome P450 isoenzyme, at 15000 ppm, and a decrease in the levels of serum testosterone at 3000 and 15000 ppm, suggesting sex steroid metabolism might be changed. However, these effects were not considered as adverse effects because the degree of change was to slight to affect the reproductive capability to produce progeny. Adverse effects are reduced body weight gains (F1: M -18%, F -19%; M -12%, F2 -12%; all values are in percentage compared to the control) before weanling in F1 and F2 pups. Furthermore, vaginal opening was slightly delayed in F1 females at 15000 ppm. Additionally, at the highest dose liver weights were increased in both male and female pups. However, no changes were observed in the reproductive performance. Therefore, the NOAEL from this study is considered to be 15000 ppm (nominal concentration, F0 and F1 parental toxicity) for parental animals and 3000 ppm for development and growth of pubs (nominal concentration, F1 and F2 offspring toxicity).

DMP was tested in a BASF AG [1999] uterotrophic assay similar to OECD TG 440. The test substance was applied orally (gavage) daily on 4 consecutive days to 10 immature female Wistar rats at two doses, 180.3 and 2008 mg/kg bw/day (analytical concentration). A standard dose volume of 5 ml/kg bw was used. The negative control (vehicle: olive oil) and the positive control DES-DP (diethylstilbestrol-dipropionate; 5 mg/kg bw/day) were both valid. DES-DP caused as expected an increase in uterus weight. No substance related effects were detected for DMP. No mortalities occurred and no abnormalities were reported. Only one animal showed piloerection for 1 day (1 day after treatment), the following days were without abnormality. The test substance had no effect on uterine weight (absolute and relative). Thus, no estrogenic activity was observed.

Estrogen receptor binding was also assessed in vitro in several publications. DMP was not estrogenic in T47-D human breast cancer cells or in two yeast reporter gene assay, nor did the test substance bind to estrogen receptors obtained from rat uterus cytosol.

No antiandrogenic or androgenic effects were observed in vivo (Gray 2000). Further details on this study are provided in the section on teratogenicity. Oishi (1980) fed diets containing 2% DMP (app. 2000 mg/kg) to 10 male rats for one week. Tests and kidney weights as well as testes, liver, and kidney zinc content were unaffected by treatment. There were no histopathological changes in the three examined organs. Liver weights were increased likely due to increased metabolism at this rather high dose. Decreased testosterone levels are considered secondary to increased metabolism, especially in combination with the negative results from the in vivo study

by Gray (2000). Foster (1980) also did not observe changes in zinc content of testes, liver and kidneys and no histopathological changes after treating rats with 1400mg/kg for four days.

In summary, DMP does neither cause androgenic, antiandrogenic nor estrogenic effects in vivo and in vitro. (ECHA 2021)

In addition, DEP, a surrogate for DMP, was evaluated through the CoRAP process based on suggested concerns for CMR effects and endocrine disruption. The reviewers concluded that no classification and further regulatory actions were required based on the available data that included a two-generations study and developmental studies (ECHA 2015). Based on these conclusions it is hard to understand why DEP and DMP were assigned a moderate classification. Conclusions by regulatory bodies reached after several months of review should be considered and given more weight than "screening" assessments by non-governmental bodies.

Comments on recent publications

DOE webinars on the forthcoming phthalate action plan and this draft regulatory determination referred to two recent publications that have received media attention. There are serious concerns about these two papers; therefore, we believe they should be viewed with some skepticism and caution. The first is Trasande, Liu, Bao (2021), which concluded that phthalates were associated with "all-cause and cardiovascular mortality". The critical commentary by Gregory Bond (2021) provides some context and rational perspective on this paper. In addition, a colleague calculated that according to the Trasande report, phthalates potentially contribute to almost half of all deaths caused by heart disease, cerebrovascular diseases, and cancer in the 55 – 64-year-old group in the U.S. – it is unlikely that any reasonable person would view this as credible.

A second paper from Edwards et al. 2021 reported on concentrations of ortho-phthalates and replacement plasticizers in fast food items such as hamburgers and chicken burritos. As noted in the attached Comment that has been submitted to the journal, the authors incorrectly stated that limited data were available for the three replacement plasticizers detected in the study (DOTP, DINCH, and DEHA) and provided no context with respect to regulatory limits (e.g., EFSA) for the levels of ortho-phthalates and other plasticizers found (Appendix I). As also identified in the DOE report these three replacements are well studied with demonstrated low toxicity. The concentrations of ortho-phthalates and the alternative plasticizers found in Edwards et al. were well below established regulatory thresholds (e.g., EFSA TDI), particularly for ortho-phthalates. These types of publications often are written for the purpose of advocacy and only present a very limited interpretation of the data without any context.

Exposure from dust

The draft regulatory report notes on p. 152 that phthalates are detected in house dust and may be a source of exposure. Some recent studies suggest that exposure to phthalates by inhalation is relatively low compared to ingestion, for example, and that phthalates contain in dust particles may not be bioavailable.

Fromme et al. (2003) reported on phthalate concentration in indoor air and dust in apartments and kindergartens in Berlin.

> Abstract. In this study, the occurrence of persistent environmental contaminants room air samples from 59 apartments and 74 kindergartens in Berlin were tested in 2000 and 2001 for the presence of phthalates and musk fragrances (polycyclic musks in particular). These substances were also measured in household dust from 30 apartments. The aim of the study was to measure exposure levels in typical central borough apartments, kindergartens and estimate their effects on health. Of phthalates, dibutyl phthalate had the highest concentrations in room air, with median values of 1083 ng/m3 in apartments and 1188 ng/m3 in kindergartens. With around 80% of all values, the main phthalate in house dust was diethylhexyl phthalate, with median values of 703 mg/kg (range: 231–1763 mg/kg). No statistically significant correlation could be found between air and dust concentration. Musk compounds were detected in the indoor air of kindergartens with median values of 101 ng/m3 [1,3,4,6,7,8- hexahydro-4,6,6,7,8,8- hexamethylcyclopenta-(g) 2-benzopyrane (HHCB)] and 44 ng/m3 [7-acetyl-1,1,3,4,4,6-hexamethyl-tetraline (AHTN)] and maximum concentrations of up to 299 and 107 ng/m3 respectively. In household dust HHCB and AHTN were detected in 63 and 83% of the samples with median values of 0.7 and 0.9 mg/kg (Maximum: 11.4 and 3.1 mg/kg) each. On comparing the above phthalate concentrations with presently acceptable tolerable daily intake values (TDI), we are talking about only a small average intake [di(2-ethylhexyl) phthalate and diethyl phthalate less than 1 and 8% of the TDI] by indoor air for children. The dominant intake path was the ingestion of foodstuffs. For certain subsets of the population, notably premature infants (through migration from soft polyvinyl chloride products), children and other patients undergoing medical treatment like dialysis, exchange transfusion, an important additional intake of phthalates must be taken into account.

Becker et al. (2004) reported on urinary metabolites of DEHP in children and DEHP in house dust.

> Abstract. Urine sampies from the 2001/2002 pilot study for the German Environmental Survey on children (GerES IV) were analyzed for concentrations of the primary DEHP metabolite MEHP (mono(2-ethylhexyl) phthalate) and two secondary DEHP metabolites 50H-MEHP (2-ethyl-5-hydroxy-hexylphthalatea) and 5-oxo-MEHP (2-ethyl-5-oxo-

hexylphthalate). Urine samples had been taken from 254 children aged 3 to 14. In addition, DEHP was analyzed in house dust samples. These samples had been collected and sieved to the 63-µm size fraction from vacuum cleaners in the homes of the children. The geometric mean (GM) was 7.9 ug/1 for MEHP in urine, and the GMs for the secondary metabolites 5OH-MEHP and 5Oxo-MEHP were 52.11 ug/l and 39.9 ug/1. 5OH-MEHP and 5Oxo-MEHP concentrations were highly correlated (r = 0.98). The correlations of 5OHMEHP and 5Oxo-MEHP with MEHP were also high (r=0.72 and r=0.70). The concentrations of 5OH-MEHP and 5Oxo-MEHP were 8.0-fold and 6.2-fold higher than the concentrations of MEHP. The ratios 5OH-MEHP/5Oxo-MEHP and 5Oxo-MEHP/MEHP decreased with increasing age. Boys showed higher concentrations than girls for all three metabolites of DEHP in urine. Children aged 13 -14 bad the lowest mean concentrations of the secondary metabolites in urine. The house dust analyses revealed DEHP contamination of all samples. The GM was 508 mg/kg dust. **No correlation could be observed between the levels of any of the urinary DEHP metabolites and those of DEHP in house dust.**

More recently, Weiss et al. (2018) compared the intake of phthalates, MEHP, and DINCH by ingestion and inhalation.

Abstract. Phthalate esters, suspected endocrine disrupting chemicals, are used in a wide range of applications. Because phthalate esters are not covalently bound, they can easily leach into the indoor environment and associate to dust particles. Thus, exposure may occur through inhalation, ingestion, or contact with the skin. However, it is unclear to what degree indoor dust contributes to the daily intake of phthalate esters. This study investigates household dust as an exposure pathway for seven phthalate esters, the monoester MEHP, and the plasticizer DINCH. Household dust collected from children's sleeping rooms and from living rooms were analysed using gas and liquid chromatography tandem mass spectrometry. To compare two exposure pathways, different dust particle sizes were generated: a respirable fraction (<5 µm) and an ingested particle fraction in the anticipated size range of skin adherence (<75 µm). Modelling of dust inhalation and ingestion showed that the daily intake of dust-bound phthalate esters was likely to be 2 times (inhalation) to 12 times (ingestion) higher for 21-month-old children than for adults. These children's daily uptake of phthalate esters was 40 - 140 times higher through ingestion than inhalation [high particle exposure scenario, whereas the intake of MEHP was calculated to be as much as 160 times higher by ingestion]. Furthermore, dust may be an exposure pathway for phthalate esters as well as for MEHP. Therefore, phthalate monoesters could be environmental contaminants of their own and need to be considered in health risk assessments.

These data suggest that the **inhalation route may constitute just a minor pathway of exposure** to dust particles and attached pollutants. The role of indoor dust for the daily

intake of phthalate esters or their monoesters remains unclear, and new insights are needed to fully understand the impact of dust on the development of diseases in children.

Comments on the process to identify safer alternatives

We generally agree with and applaud the process developed to identify safer alternatives. Alternatives should be selected only if there is sufficient data to show they have a lower toxicity than the incumbent materials and if they are available and feasible (Harmon and Otter, 2018). Methodologies such as GreenScreen®, ChemFORWARD, and programs such as EPA Safer Choice and CleanGredients are important for making information on the alternatives available to formulators, brand, retailers, and other downstream stakeholders.

Hazard assessment methodologies

As described in Harmon and Otter (2018), screening methodologies such as GreenScreen® are an important part of the alternatives assessment process but the results must be viewed in the context of available governmental and other non-governmental assessments.

GreenScreen, for example, has some limitations. The use of authoritative lists for hazard classifications can make the assessment "easy", but, unfortunately, some lists may be precautionary and not reflect the true hazard potential for humans (e.g., IARC and Proposition 65). Endocrine activity is one endpoint that in our experience is quite subjective. The manufacturer of a material is forced to "prove a negative" because there are no clear criteria for determining a low hazard for endocrine activity. Equivocal data might be resolved by some profilers by "rounding up" to the next hazard level with the desire to be precautionary; this may, however, result in conclusions that are in conflict with regulatory decisions by global governmental agencies.

The various hazard assessment methodologies available today, are important tools for formulators, brands, retailers, and other stakeholders to identify safer alternatives. To this point, DOTP and DINCH were identified in the DOE Report as safer, feasible, and available alternatives for vinyl flooring. On the other hand, the assessments using these methodologies are often subjective and precautionary; therefore, they are not appropriate *alone* for making regulatory determinations.

Within class assessments

On p. 233 of the DOE Report, it is stated that "to be considered a safer alternative within the priority chemical class, a chemical must meet the minimum or additional criteria for safer and within class criteria" and that these materials are subject to "more protective requirements." Alternatives to chemicals of concern, whether inside or outside of that class, should have sufficient data to confirm their lower toxicity with special attention to endpoints of concern for the incumbent chemicals; however, if high quality guideline compliant studies are available for

the within class alternatives, and if the results show low toxicity, this should be sufficient. The within-class criteria for safer criteria on p. 240, requires that in-class alternatives have data for the endpoints associated the priority chemical class. In addition, if a specific mechanism of action (e.g., anti-androgenicity or estrogenicity) is associated with a priority class, these data for the within class alternative are required, even though there might not be enough information to "assign a GreenScreen® score" for endocrine activity. We agree that this is a good approach; however, a similar requirement should be expected for alternatives outside of the class. More specifically, alternatives to ortho-phthalates should have data for reproductive and developmental toxicity and anti-androgenic effects.

Additional criteria for safer (p. 239).

We agree that the EPA Safer Choice program and the SCIL are excellent programs to promote and support formulating with lower hazard materials. The decision that chemicals listed in the SCIL processing aids and additives section "can be considered equivalent to meeting our (DOE) additional criteria for safer" is inconsistent with the process laid out in the preceding sections of the DOE Report. As the report notes, some chemicals on this part of the SCIL have "characteristics that are *indicative of low hazard and anecdotal evidence* suggesting long-standing use." Anecdotal evidence, for example, hardly seems to be sound criteria for identifying safer alternatives. In addition, some chemicals under the processing aids and additives list such as sulfuric acid (H_2SO_4) can hardly be considered non-hazardous. Their inclusion in the SCIL list makes sense because they are used at very low concentrations in products typically covered by the Safer Choice program and are low risk (e.g., pH of the final product is within the allowed range of 2 – 11.5). These ingredients may or may not present a low risk in other applications, which points to the limitations of a hazard driven approach for identifying safer chemicals in the absence of considering the respective applications and subsequent risk.

Respiratory sensitization (p. 246).

It is likely that most materials show a data gap for respiratory sensitization given the challenges for properly carrying out these studies. ECHA has published endpoint specific Guidance on Chemical Safety (ECHA, 2017) that suggest that in the absence of any endpoint specific animal data, analysis for respiratory sensitization may be performed based on weight of evidence from 1) in-vivo dermal sensitization assays, which are expected to capture sensitizers with immunological mode of action, 2) QSAR modelling, and 3) human data, which may reflect both immunological and non-immunological responses. ECHA states in the document that "based on current knowledge, all low molecular weight respiratory sensitizers are also skin sensitizers, however this is not true in reverse."

Please contact me if there are any questions at patrick.harmon@basf.com or 346-252-4123.

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Appendix I

Submitted to J Exp Sci Environ Epidem

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Comment to the publication "Phthalate and novel plasticizer concentrations in food items from U.S. fast food chains: a preliminary analysis" by Edwards L, et al. (2021).

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We read the recent paper from Edwards et al. [1] with great interest and have significant concerns and questions, particularly with respect to the statement that only "limited data" are available for the three replacement plasticizers detected in the study, the suggestion that data from industry studies must be viewed cautiously, and the lack of context for the quite low levels of ortho-phthalate and replacement plasticizers found in the analyses.

While the increased use of alternative plasticizers was mentioned in the paper, the corresponding decrease in ortho-phthalates was not. It is also important to note that market forces have led to a dramatic decrease in the use of ortho-phthalates in the last two decades. These alternative plasticizers have been widely adopted due to toxicology studies showing none of the toxicity of DEHP.

The following statement was made on Page 6: *"However, unlike the ortho-phthalates, there is limited toxicity and health evidence for the replacement plasticizers, and research suggests that these replacements are increasing in use before their health effects are well-characterized."* For the three products discussed in this paper, di-2-ethylhexyl adipate (DEHA), diisononyl cyclohexane-1,2-dicarboxylate (DINCH), and di-2-ethylhexyl terephthalate (DEHT), this statement is incorrect. Recent assessments by the European Food Safety Authority (EFSA), [2, 3] the U.S. Consumer Product Safety Commission (CPSC), [4, 5, 6, 7] NSF International, [8, 9] the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), [10, 11] and the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) [12] describe the breadth of studies and overall low toxicity of these substances.

Data for DEHT and DINCH and conclusions from the above-referenced governmental and non-governmental assessments show no concern for carcinogenicity, mutagenicity, reproductive, or developmental toxicity. In addition, a recent review for potential endocrine disruption effects by ANSES under the REACH RMOA (Regulatory Management Option Analysis) process concluded no risk management measures were required for either substance. It is also clear that the key studies were completed *prior to or concurrent* with their increased use as replacement plasticizers. All of these agencies and organizations had access to published studies or full study reports for guideline compliant studies that are available for both substances for critical endpoints such as carcinogencity, mutagenicity, reproductive, and pre-/peri-/postnatal developmental toxicity; no relevant effects were observed. Specific studies also have confirmed no anti-androgenic or estrogenic effects. Overall, a significant amount of toxicity information is

currently available on these chemicals including toxicokinetic studies. We believe few commercial chemical substances have the same broad toxicological databases with demonstrated low toxicity.

Owing to what was perceived as a lack of toxicity data, the authors refered to the US EPA ToxCast high throughput screening results. Our look at the same results from the CompTox dashboard data showed that DINCH was active in 21 of 857 total assays, [13] DEHT was active in 10 of 882, [14] and DEHA was active in 11 of 855. [15] For comparison purposes, DBP was active in 110 of 1136 assays and DEHP was active in 102 of 1150. In an earlier CompTox dashboard view of EDSP21 results for estrogen receptor, androgen receptor, thyroid, and steriodogenesis bioactivity, DINCH was active in 0 of 48 assays, DEHT was active in 1 of 68 assays, and DEHA was active in 1 of 44 assays. The high throughput methods are helpful as screening tools, but it certainly is unclear what these results may mean, particularly when, for example, DEHT and DINCH show no relevant adverse effects in vivo and, particularly, no anti-androgenic or estrogenic effects (cf. the preceding references).

In addition, human biomonitoring methods have been developed for all three. It is important to note that exposure levels derived from back-calculation of urinary metabolites represent the summarized exposure from all routes and sources. Data for all three plasticizers are published and show very low exposures to the general human population and support the safe use conclusion for these plasticizers (e.g., ref. 16, 17, and 18).

Another comment in the paper notes that the DEHT data come largely from “industry-funded publications” and claims that they be should be interpreted with

caution. Indeed, the majority of studies are necessarily carried out by industry since the studies are undertaken to investigate the hazard profile of these plasticizers and are used to register the substances and meet requirements of the chemicals legislation that apply in different regions. In reality, if not for this work by industry, few if any studies might be available on these substances. Further, specific applications such as food contact and medical devices require additional studies and detailed evaluation and risk assessment of the existing data before approval is granted by government authorities. In contrast to some academic studies, “industry” studies are undertaken by trained and qualified staff, mainly at independent third-party laboratories, and according to peer-reviewed regulatory guidelines from Organization of Economic Cooperation and Development (OECD), EU, or EPA, and with Good Laboratory Practice (GLP) compliance. Many governmental agencies inspect and use these same third-party labs for their own testing needs. It is important to mention that academic studies may often be undertaken to test hypotheses, which is an important part of the scientific process. On the other hand, these studies may use only a small number of animals, do not reference historical controls as historical control data do not exist in the lab, and may include only one dose level; i.e., they may have limited use in regulatory assessment of potential hazard and risk.

Interestingly, a study published by Gray LE Jr et al. (2000, see Reference 43) also is referred to as an “*industry-funded publication and the results should be interpreted with caution*;” however, the study authors are employed by US EPA and Colorado State University and did not declare any conflict of interest. Similarly, a study published by Wirnitzer U et al (2011, see Reference 42) was not a plasticizer industry-

funded study; it was commissioned by B Braun as part of their due diligence in researching a replacement for DEHP in its medical devices.

Headlines for some media articles about this study reported that "*high*" or "*shocking*" levels were found. The absence of any provided context with respect to potential human exposures and established regulatory limits could have led to this misinterpretation. For example, the median concentration of DEHT in hamburgers was reported to be 2.2 mg/kg. We found the average weight of a Whopper from Burger King was 0.271 kg; therefore, for a 70 kg adult, the exposure was 0.0085 mg/kg bw/day and well below the Tolerable Daily Intake (TDI) of 1 mg/kg bw/day established by EFSA [3] as well as the conservative RfD of 0.2 mg/kg bw/day calculated by NSF International for the NSF/ANSI Standard 61 for drinking water systems.[8] When using the 95th percentile concentration of 3.2 mg/kg, the exposure was 0.0124 mg/kg bw/day, which also was well below the TDI. The margin of safety (MOS) for the 95th percentile was 81 relative to the EFSA TDI, which already includes a safety factor of 100. For the chicken burrito weighing 0.19 kg (calculated by summing the amount of fat, protein, and carbohydrate using the Chipotle nutrition calculator), the median concentration of 6 mg/kg corresponds to 0.016 mg/kg bw/day; for the 95th percentile value of 12 mg/kg, the exposure was 0.033 mg/kg bw/day.

Similar calculations may be done for DINCH and DEHA and show exposures below EFSA and other regulatory limits. The median concentrations of DINCH were all below the method detection limit (MDL), but the highest 95th percentile value was 0.59 mg/kg in burgers. This corresponded to an exposure of 0.0023 mg/kg bw/day, which was below the EFSA TDI of 1 mg/kg bw/day and the NSF RfD of 0.7 mg/kg bw/day. The

highest 95th percentile concentration of DEHA was 0.17 mg/kg in chicken burritos, which corresponded to an exposure of 0.00046 mg/kg bw/day (compared to the EFSA TDI of 0.3 mg/kg bw/day). For many of the ortho-phthalates the median and 95th percentile concentrations were less than the respective MDL values. One of the higher 95th percentile concentrations was for DEHP in chicken burritos; 0.078 mg/kg corresponds to an exposure of 0.00021 mg/kg bw/day, which is below the EFSA TDI of 0.050 mg/kg bw/day (MOS = 238).

One could assume in each of these cases a higher intake of fast food, but if a person ate fast food 2 – 3 times per day, obesity and other health issues might be expected and would be independent of trace exposures to the plasticizers discussed in the paper but directly related to the high caloric intake. We also are aware of concerns about aggregate exposure from multiple sources for the respective products; however, as noted above, the human biomonitoring data are representative of exposures from all uses and are well below levels of concern, particularly for DEHT, DINCH, and DEHA.

In summary, DEHT, DINCH, and DEHA are well-studied replacement plasticizers with low toxicity as confirmed by high quality guideline studies. Actual human exposures also are well below thresholds established by regulatory authorities. Given the low measured values for the plasticizers in the paper and where those measurements place against the existing regulatory limits, we are curious what “regulatory exposure reduction strategies” the authors believe would be appropriate?

CONFLICT OF INTEREST

SB is employeed by Eastman Chemical Company, a manufacturer of DEHT, DEHA, and others. PH and RO are employees of BASF Corporation and BASF SE, respectively; BASF is a manufacturer of DEHT, DINCH, DEHA, and other plasticizers.

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