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Comments: Proposed Rule and Preliminary Regulatory Analyses

BASF appreciates the opportunity to comment on the Proposed Rule and Preliminary Regulatory Analyses.¹ The following comments are submitted to reemphasize and complement points in our substantive submission from January 28, 2022. Our concerns focus on the following points:

- Regulation of ortho-phthalates as a class.
- Comments on toxicology and exposure to specific ortho-phthalates.
- Comments on publications used to support the cost/benefits analysis.

Ortho-phthalates should not be regulated as a class

As stated in previous BASF comments to Washington Department of Ecology (DOE), and as also noted by DOE, the vinyl flooring market has moved away from ortho-phthalates to alternative plasticizers. 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 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).

¹ BASF manufactures a number of plasticizers including DOTP, DINCH, high molecular weight ortho-phthalates, adipates, and trimellitates. 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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Observed effect on rat fetal testis testosterone production (Furr et al. 2014)

Plasticizers	Alcohol		Outcome
	Carbon chain	C Backbone	
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). A recent publication (van den Driesche et al., 2020) reported a clear differentiation regarding effects from DBP and DINP. US CPSC, based on the absence or expected absence of anti-androgen effects, removed DIDP and DnOP from their list of phthalates restricted in toys and childcare articles and also decided no action was necessary for DPHP and several alternative plasticizers (CPSC 2017).

It is not appropriate to regulate all ortho-phthalates as one class based the known structure activity relationships (Fabjan et al., 2006). In addition, owing to the replacement of ortho-phthalates in vinyl flooring, this action by DOE is arguably a purely “intellectual” exercise without merit but creates a poor precedent with a potential impact on other important markets and applications.

Comments on toxicology and exposure to ortho-phthalates

As noted in our comments from January 2022, the details of assessments for di (2-propylheptyl) phthalate (DPHP), dimethyl phthalate (DMP), and diethyl phthalate (DEP), by Scivera and ToxServices do not appear to be publicly available, so it is difficult to comment on their 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. We find the non-governmental hazard assessment methodologies quite helpful, but the quality of the “screening” process by various profilers may result in incorrect classifications due to the lack of experience of those doing the



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work and to the limited time allotted for the assessments (e.g., Harmon and Otter, 2018). The lack of a robust scientific assessment process by Washington DOE makes any conclusions to support regulation of chemicals as a class less credible and unacceptable as a basis for regulatory action.

Humans are exposed to a several ortho-phthalates as reported in human biomonitoring studies (HBM). As noted in the Preliminary Regulatory Analyses report (PRA), exposures to some products have decreased while others have increased. For example, DEHP exposures have decreased over the past 15 years, and exposures to other ortho-phthalates such as DINP and alternative plasticizers have increased. (CDC, 2021) It is essential also to understand that the replacements have a lower toxicity profile, which results in lower overall risk. US CPSC reported this in their recent Hazard Index (HI) calculations that were part of their cumulative risk assessment for ortho-phthalates. (CPSC, 2017)

Detection of ortho-phthalates in HBM studies, in analyses of indoor dust samples, or in various consumer products do not necessarily indicate any health risks nor are they sufficient alone to support regulatory action similar to what is proposed by DOE. One must consider the context, including the exposures levels relative to established tolerable daily intake (TDI) and NOAELs, as well as whether reported levels in dust, for example, are bioavailable.

We again would like to point to studies cited in our January 2022 comments on ortho-phthalates in house dust that suggest the phthalates found in the dust may not be bioavailable (i.e., DEHP in dust did not correlate at all to urinary metabolite levels, (Becker et al., 2004) and are only a minor source of ortho-phthalate exposure (Fromme et al., 2003). In addition, Edwards et al. 2021 reported on concentrations of ortho-phthalates and replacement plasticizers in fast food items such as hamburgers and chicken burritos. As already noted, these authors provided no context with respect to regulatory limits (e.g., EFSA) for the levels of ortho-phthalates and other plasticizers found. The concentrations of ortho-phthalates and the alternative plasticizers measured in this study were well below established regulatory thresholds (e.g., EFSA TDI). Two recent publications present a critique of the Edwards, et al. paper and other papers written for the purpose of advocacy and only present a very limited interpretation of the data without any context (Harmon and Otter, 2022; Adenuga, 2022).

Epidemiological studies have been published in recent years that suggest a link between ortho-phthalate exposure and various illnesses. While one must look at these studies seriously, we are reminded of the famous quote from Lloyd Tapper, formerly Commissioner for Science at US FDA, that “DEHP is an etiology in search of a disease.” The quote is from the early 1970’s and represents a long history of speculation about possible health effects from DEHP and other ortho-phthalates. Unfortunately, most of the epidemiological work to date has involved small cohorts and may be in conflict with the results of more robust animal studies. Such associations of exposure to chemicals with selected effects would need a mode of action and a clear dose-response. To our knowledge, there have been very limited or no use of these studies as a basis for



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regulatory action on ortho-phthalates in North America or Europe. We suggest reviewing the summary of the epidemiological data for DEHP in the most recent SCENIHR report on DEHP and other plasticizers in medical device applications (SCENIHR, 2016). Their conclusions for the various health effects are summarized in the table below:

Epidemiological finding	SCENIHR Conclusion
Effects on testosterone production	Weak association with considerable variation and inconsistency of results for DEHP.
Breast tumors	Weak association in one study with DEHP and contrasting results for other phthalate metabolites.
Hypospadias and cryptorchidism	No association.
Decreased anogenital distance	Inconsistent evidence.
Mother/infant exposure levels	Some studies show association between phthalate exposure and low birth weight. Other studies do not.
Childhood growth and pubertal development	No evidence of anti-androgenic effects in healthy boys. Boys - no association with pubertal timing, testosterone levels or pubertal gynaecomastia. Girls - no association and age of menarche or onset of breast development. Two studies showed no association with precocious puberty; one other showed a positive association.
Endometriosis	Inconclusive evidence.
Effect of DEHP metabolites on neurobehavior	Inconsistent evidence.
Association with obesity, insulin resistance, and Type-2 diabetes	Inconsistent evidence. Recent meta-analysis of 18 studies concluded there was no association.

As noted above, we believe these types of studies must be considered carefully; however, publications with conclusions such as weak association, no association, or inconsistent evidence, hardly are sufficient as a justification for regulatory action on specific ortho-phthalates or this whole class of chemicals. More recently, the EU Risk Assessment Committee (RAC) disregarded the epidemiological associations in the DINP Classification and Labelling decision with the following rationale: “RAC noted that no clear cut conclusions can be drawn from the epidemiological studies presented in the CLH report. Among a large number of possible associations between exposure levels and reproductive endpoints some positive associations were found which **were possibly due to random error.**” (ECHA 2018)

Comments on cost/benefit analyses

We were disappointed in the quality of the analyses described in Section 4.2.1.2, Hazards of ortho-phthalates, of the PRA report. It appears to be an “extrapolation of extrapolations” from a few speculative studies of questionable credibility and also has some errors in the citations.³

Previously, we raised serious concerns about Trasande, et al. (2022) and stated that it should be viewed with some skepticism and caution. The authors concluded that phthalates were associated

³ Trasande (vs. Trassande) is misspelled on p. 48. Engel (vs. Engle) is misspelled on p. 46. Some incomplete citations are used such as Ref 40 (NAS, 2008) and Ref 41 (Wang et al., 2019); i.e., which Wang publication and NAS report are cited here. We assume these are the publications cited in the Final Regulatory Report from June 2022, but this should be more clear and transparent.



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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. – this is nonsense, and it is unlikely that any reasonable person would view this as credible.

As noted in the previous section, exposure via dust is likely a minimal contributor to ortho-phthalate exposure, and the ortho-phthalates detected may not be bioavailable to a relevant proportion. In addition, the epidemiological studies must be looked at seriously but also must be viewed with some caution and skepticism.

The PRA report describes regulation of vinyl flooring with ortho-phthalates as a “potential” benefit because of uncertainty around the link with asthma. While some papers suggest a link, others such as Odebeatu, et al. (2019) do not for most ortho-phthalates, and earlier studies concluded that common ortho-phthalates do not show a consistent and proven ability to enhance allergic sensitization under conditions that are relevant for human health (Kimber and Dearman, 2010).

Benefits for restricting ortho-phthalates in fragrances in the PRA report was based on the detection of mono-ethyl phthalate (MEP), a metabolite of diethyl phthalate (DEP), in human biomonitoring studies and the “potential reductions in endocrine-related diseases and reproductive and developmental health improvements.” (PRA, p. 48) The publication of NHANES and other HMN data over 20 years ago created much media attention, particularly for DEP; however, David (2000) calculated intake levels from the human urinary metabolite levels and compared them to previous estimates from various risk assessments. For example, the mean for DEP was 12.34 mg/kg-bw/day versus a previous estimate of 57 mg/kg-bw/day and the EPA RfD of 800 mg/kg-bw/day. Similar mean intake levels calculated by NIEHS and CDC and in Europe (Kohn et al., 2000; Koch, et al., 2003) ranged from 2.32 mg/kg-bw/day in the European study to 12.3 mg/kg-bw/day for the U.S. (identical to the results from David, 2000). We do not believe this is evidence of high exposure and concern, particularly since the manufacture and use of DEP has decreased over the past 20 years.⁴

The proposed reduction in health costs appears to be based on the assumption that low molecular weight ortho-phthalates such as DEP act as endocrine disruptors. DOE is aware of but apparently ignored the EPA publication, Furr et al. (2014), that showed no effect on fetal testosterone production for DMP and DEP in their screening study. The European Community Rolling Action Plan (CoRAP) conclusion in 2015 for DEP also was ignored; this assessment concluded that no

⁴ IHS Chemical Economics Handbook reports the U.S. production of DEP has decreased from 5 kmt to 0 kmt from 2000 to 2020; consumption was around 2 kmt in 2020 based on import statistics (BASF analysis). Zota, Calafat, Woodruff (2014) showed a corresponding decrease in MEP urinary metabolite levels in human biomonitoring data.



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classification for fertility effects was justified and “existing information on DEP is sufficient to conclude that DEP does not exhibit endocrine disrupting effects in humans similar to those observed with other phthalate diesters.” (ECHA, 2015) A few epidemiological studies have suggested a weak association between DEP and some health effects; however, as noted above, these studies are quite limited in their validity for regulatory determinations and are not suitable for use in justifying regulatory action.

The PRA estimated an aggregate cost of between \$798 and 942 million in lost productivity in Washington due to the use of ortho-phthalates in vinyl flooring and fragrances. We find this estimate highly speculative and, frankly, absurd. This estimate appears to be based on conclusions from one of several questionable publications by Trasande, et al. (2022), common exposure to phthalates in dust and other indoor air sources, the potential impact of phthalates on asthma, and *extrapolation of extrapolated estimates* of the impact of EDC from Europe. This is clearly not a credible analysis of potential costs due to ortho-phthalate exposure. In addition, if established NOAELs and TDIs are considered along with the extensive database from HBM studies, indicating very low exposure levels for the general public including sensitive subpopulations, there are most likely no actual costs to be expected for adverse health effects due to ortho-phthalate exposure, and certainly not due to those that have no hazard classifications with no evidence of anti-androgenic or other effects related to endocrine disruption.

Conclusions

1. **Ortho-phthalates must not be regulated as a class.** This is not supported by the scientific evidence and is inconsistent with conclusions from other relevant government agencies such as US CPSC, Environment Canada and Climate Change, and ECHA.
2. **The full hazard assessments by non-governmental organizations such as SciVera and ToxServices must be made publicly available and subject to scientific scrutiny if they are intended to be part of the basis for regulatory action by the DOE.** These types of assessments are quite helpful to companies such as BASF and our customers; however, if used as part of the regulatory process, transparency is a mandatory requirement. **Once these are available, an extended public comment period should be opened to allow time for review and comment.**
3. **The cost/benefit analysis for ortho-phthalates must be revised or retracted owing to the use of highly speculative publications to support the conclusions by DOE.** DOE might consider a retraction of this analysis altogether based on the circular rationale described in the PRA report:

Ecology determined that a restriction on the use of ortho-phthalates in vinyl flooring would reduce a significant source of ortho-phthalate exposure. Most vinyl flooring no longer contains ortho-phthalates. However, vinyl flooring



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remains a significant source of potential exposure to ortho-phthalates for people using and purchasing vinyl flooring products that contain ortho-phthalates. (PRA, p. 47)

This is a quite strange and circular argument since ortho-phthalates have been largely replaced by alternative plasticizers in vinyl flooring, supporting our suggestion above that this is simply an intellectual exercise.

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