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EPN Additional Comments on 1,4-Dioxane and HBCD

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The Environmental Protection Network (EPN) is an organization comprised of over 450 U.S. Environmental Protection Agency (EPA) alumni volunteering their time to protect the integrity of EPA, human health and the environment. We harness the expertise of former EPA career staff and confirmation-level appointees to provide an informed and rigorous defense against current Administration efforts to undermine public health and environmental protections.

On July 19, 2019, EPN submitted general comments on the 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD) draft risk evaluations to the Science Advisory Committee on Chemicals (SACC) for their July 29-August 2 meeting. These comments were submitted with the intention of submitting additional, more in-depth comments before the close of the public comment period on August 30.

Before addressing the two risk evaluations, EPN would like to underscore its concern that the SACC meeting at which the risk evaluations were discussed was scheduled prior to the deadline for filing comments. This is a reversal of the way EPA normally does things, is an approach that seems to value an arbitrary deadline over solid decision-making, and appears to be a mechanism to discourage public comment. The amount of time to develop comments before the SACC meeting was extremely compressed,. and we understand that detailed comments submitted after the meeting cannot now be considered by the SACC because it has completed its deliberations. This will deprive the SACC of scientific and policy input that would be valuable in informing its review of the two draft evaluations and greatly reduce the value of the public comment process. In the future, EPN strongly recommends that EPA schedule SACC meetings on draft risk evaluations after the close of the comment period so the SACC has a full opportunity to consider the comments.

EPN is filing these additional comments to expand on some of our earlier concerns and address an important issue we did not address previously—the adequacy of human health toxicity databases for the 1,4-Dioxane and HBCD draft risk evaluations in determining Benchmark Margins of Exposure (MOE) and on making findings on the presence or absence of Unreasonable Risk.

It is becoming clear now with four of the first ten draft Toxic Substance Control Act (TSCA) risk evaluations having been issued for public comment and peer review by the SACC, that adequacy and robustness of the database supporting the characterization of potential human hazard are not critical components of the agency's decision-making process on whether or not a chemical poses an unreasonable risk under TSCA. This became glaringly obvious at the time of the SACC review of Pigment Violet 29 (PV29) in June 2019 when the agency abruptly disavowed and re-characterized as inadequate studies originally thought to be the best potential candidates to serve as the basis for calculating Points of Departure (PODs) and determining the adequacy of Benchmark Margins of Exposure; together with serious limitations in the PV20 database, this reversal left the agency with little data of value on which to base this calculation and, subsequently, to make a risk finding.

EPN commented, in its second round of comments on PV29, that the agency should have followed long-standing agency-wide consensus guidance on determining the adequacy of a toxicity database when

deriving a Reference Dose (RfD) or Reference Concentration (RfC) and/or a POD and MOE. Dr. Stan Barone of EPA's Office of Chemical Safety and Pollution Prevention (OPPT) made a comment during the July 29-August 2 SACC meeting that it is not policy to consider database inadequacies/deficiencies when judging the adequacy of an MOE. If he was ascribing this to agency policy, he is flat out wrong. If he was ascribing it to OPPT, that office is out of compliance with agency-wide consensus guidance. The principles in place for RfD and RfC derivation also apply when characterizing an MOE. As stated in the 2002 EPA document Review of the Reference Dose and Reference Concentration Processes, "The methodology recommended in the RfD document is considered generally applicable to both cancer and noncancer endpoints where dose-response relationships are thought to be either nonlinear or consistent with a threshold. Although the emphasis in this document is on the calculation of RfDs and RfCs, **the same processes and considerations are applicable to the margin of exposure (MOE)** (emphasis added)**……"** (U.S. EPA, 2002, page 1-2).

The 1993 *Reference Dose (RfD): Description and Use in Health Risk Assessments Background Document 1A*) and Barnes and Dourson (1988) summarize the agency consensus guidelines on the use of Uncertainty and Modifying Factors in the derivation of an RfD (or an RfC or a POD or an MOE). At that time, there were four Uncertainty Factors (UF) and one Modifying Factor, which is now also called an Uncertainty Factor (UF_D for data deficiencies). This latter UF is an additional uncertainty factor that is greater than zero and less than or equal to 10. The default value for this UF is one. The magnitude of the UF depends upon the professional assessment of scientific uncertainties in the key study(ies) and the database not explicitly covered by the other four UFs ($UF_{H,}$ Intraspecies-human-to-human variability/uncertainty; $UF_{A,}$ Interspecies-animal-to-human variability/uncertainty; $UF_{S,}$ Subchronic-to-Chronic extrapolation; $UF_{L,}$ LOAEL-to-NOAEL extrapolation). Importantly, it addresses the completeness of the overall database.

EPN noted in its second round of comments on PV29 that agency application of this guidance is predicated upon a determination that, for a chronic exposure scenario, a minimum database on which to estimate a high-confidence POD/reference value/MOE based upon animal studies would consist of chronic dog and rat studies, along with reproductive and developmental bioassays (Dourson et al., 1992; Dourson et al., 1996; U.S. EPA, 2002). As a matter of policy, the composite UF should not exceed 3,000 (U.S. EPA, 2002). Some modification of these requirements may be in order as the regulatory community in the U.S. (i.e., EPA and FDA) and elsewhere has concluded that the chronic dog study is of little added value and can be phased out as a regulatory requirement, and that a subchronic study provides adequate information in this species (e.g., Dellarco et al, 2010). However, it could be argued that, in certain circumstances, additional information on other endpoints of concern would warrant inclusion in the minimal data set to best understand an agent's hazard potential. These endpoints could include immunotoxicity or neurotoxicity.

TSCA Existing Chemical risk evaluations and their associated risk management decisions essentially represent a lifetime regulatory statement given that there are many thousands of commodity chemicals to prioritize and assess (or not) and given that there is no requirement on the part of the agency to revisit these assessments and decisions at any time (unlike the pesticide regulatory program). Therefore, the agency has an obligation to get it right the first time it conducts a risk evaluation because, essentially, it's the only time it

will address the health and environmental effects of a chemical of concern. Judging the completeness and integrity of individual studies and databases and properly selecting PODs/RfDs/RfCs and Benchmark MOEs are key elements of that obligation.

The 2016 Frank R. Lautenberg Chemical Safety for the 21st Century Act (the "new" TSCA) eased the conditions under Section 4 of the Act whereby the agency can issue orders/regulations and enter into consent agreements requiring manufacturers (including importers) or processors to test chemical substances and mixtures. TSCA authorizes this testing ito develop data about health, environmental effects and/or exposure when there are insufficient data to determine whether a chemical substance or mixture presents an unreasonable risk to human health or the environment. The law specifically enables EPA to require testing where necessary for a risk evaluation.

One would expect that the agency would take full advantage of this new authority and conduct a testing/research needs assessment in concert with its prioritization and evaluation programs so that any filling of data gaps would be completed BEFORE a Risk Determination is attempted. To date, there is no evidence of any EPA requests for generation of additional data under TSCA section 4 despite the significant data-gaps on several of the chemicals on which risk evaluations are being conducted. Incorporation of a UF in the calculation of PODs/RfDs/RfCs and/or MOEs should be considered a stopgap measure and not the final solution for data inadequacies.

So what, then, should the UF for data deficiencies be for 1,4-Dioxane and HBCD? And, how would it affect the conclusions concerning unreasonable risk for the various scenarios assessed for these two chemicals?

<u>1,4-Dioxane</u>

1,4-Dioxane is an impurity in a broad range of personal care and cleaning products used by millions of consumers. These "down the drain" products also contribute 1,4-Dioxane to wastewater and surface water and, together with other sources of contamination, account for the widespread presence of 1,4-Dioxane in drinking water. Drinking water contaminated with 1,4-Dioxane has been detected in numerous regions of the US and has prompted significant health concerns in several states and local communities. EPA unjustifiably failed to address these significant sources of exposure and risk to the general population. Had it done so, it presumably would have calculated MOEs for relevant exposure scenarios and, in so doing, applied UFs that reflected inadequacies in the available health effects data for 1,4-Dioxane.

The agency focused its assessment only on worker acute/short-term and chronic dermal and inhalation exposure scenarios in a variety of manufacture, use and disposal settings. Workers were divided into two categories: users and occupational non-users (ONUs). The workers were assumed to be healthy males and females, at least 16 years of age. Both non-cancer and cancer endpoints were assessed and quantified.

What, then, would constitute a database adequate for assessing hazard to this demographic? Our answer is that, absent observations in humans, the following types of information are needed:

1. Studies that would illuminate the potential for general systemic toxicity over an exposure duration commensurate with that of the actual exposure scenario or that could be extrapolated from shorter-term exposure studies accompanied by the application of an uncertainty factor representing that extrapolation (e.g., acute short-term or subchronic to chronic);
2. For chronic exposures, studies that would adequately test for carcinogenic potential by the relevant route(s) of exposure or could be extrapolated to those routes of exposure;
3. For acute, shorter-term and chronic exposures, at least one developmental toxicity study;
4. For shorter-term and chronic exposures, a one- or two-generation reproductive toxicity study, and;
5. If central nervous system effects are observed in acutely exposed humans and animals, a more systematic evaluation of neurotoxicity and developmental neurotoxicity, since the worker population includes women of child-bearing age.

The database for 1,4-Dioxane meets the criteria for Items #1-3, but is lacking in Items #4 and #5. These are substantial data gaps, warranting an additional UF of tenfold for data deficiencies when determining the Benchmark MOE for both exposure durations and routes. Thus, the Benchmark MOE for acute/short-term inhalation risks should be increased from 300 to 3,000, and the chronic inhalation and dermal Benchmark MOEs from 30 to 300.

Using this revised Benchmark MOE for the acute/short-term inhalation scenarios, there is a shift to unreasonable risk for the following:

1. Manufacturing, Lab Chemicals and Dry Film Lubricant—central tendency, without personal protective equipment (PPE), and high end with respirator;
2. Import/Repackaging (Bottle), Import/Repackaging (Bottle), Industrial Use, and Disposal—both central tendency and high end with respirator;
3. Film Cement—high end with respirator, and;
4. Use of Printing Inks (3D)—central tendency and high end, without PPE.

For the chronic inhalation scenarios, a shift to unreasonable risk would result for the following:

1. Spray Application—both central tendency and high end, without PPE;
2. Manufacturing, Import/Packaging, Lab Chemicals and Disposal—central tendency with respirator, and;
3. Film Cement, Use of Printing Inks (3D) and Dry Film Lubricant—central tendency and high end with respirator.

For the chronic dermal scenarios, a shift to unreasonable risk would result only for film cement—central tendency and high end with respirator.

It should be noted that for most of the worker exposure scenarios EPA addressed in the draft evaluation, it concluded that risks were not unreasonable assuming effective and continuous use of Personal Protective Equipment (PPE) by exposed workers. As EPN has previously maintained, this assumption is not supportable. For 1,4-Dioxane, there are no OSHA standards that require use of PPE and EPA presents no empirical evidence that PPE is widely and effectively used during manufacture and processing of 1,4-Dioxane. Without assuming the use of PPE, most of EPA's calculated MOEs are smaller than than the benchmark and demonstrate unreasonable risks to workers. The above analysis demonstrates that if a proper UF is applied to account for data-base uncertainty, even the MOEs for some PPE scenarios are smaller than the benchmark and thus demonstrate unreasonable risks. This indicates that EPA should be making unreasonable risk determinations for the great majority of exposed workers.

In its June 19 comments, EPN noted that it would follow-up with additional comments with regard to the degree of evidence available to support the characterization of potential mode(s) of action (MOA) by which the liver tumors observed in the rodent bioassays were produced. Both the 2013 IRIS assessment and the OPPT draft Risk Evaluation conclude that the available data are sufficient to rule out a mutagenic mode of action, but they are not sufficient to support a non-linear MOA characterized by cytotoxicity and regenerative hyperplasia. While some of the data appeared to be indicative of such an MOA, they did not all fit properly into the right places, sequence and temporality. Furthermore, there remain some critical data gaps. In addition, there was inadequate information on the MOAs for all the other tumor types observed in multiple animal studies. Thus, we came to the same conclusions as articulated in the IRIS and OPPT documents on data adequacy, and agree that the default linear approach for quantitative assessment remains the appropriate option.

HBCD

In its assessment of HBCD, the agency considered potential exposures resulting from consumer activities and uses, industrial and commercial activities, and environmental releases and wastes. It considered workers and ONUs, which include men and women of reproductive age. Consumer exposure was assessed for various pathways for all age groups, including adults and children. Non-users could be any age group ranging from infants to adults. Also, it considered exposures to the general population for all age groups, as well as additional considerations for other exposed groups.

A variety of acute and chronic exposure scenarios was assessed. Only non-cancer effects were assessed and quantified, as no adequate cancer bioassays have been conducted with HBCD.

Populations of interest and exposure scenarios included the following:

- Workers: Acute-Adult worker (>21 years old) and female workers of reproductive age (>16 year to less than 50 years old) exposed to HBCD for a single 8-hr exposure;

- Chronic-Adult worker: (>21 years old) and female workers of reproductive age (>16 year to less than 50 years old) exposed to HBCD for the entire 8-hr workday for 260 days per year for 40 working years;
- ONU: Acute or Chronic-Adult worker (>21 years old) and female workers of reproductive age (>16 year to less than 50 years old) exposed to HBCD indirectly by being in the same work area of the building;
- General Population (Background Exposure): Acute or Chronic-Infant, Young Toddler, Toddler, Small Child, Child, Teen, Adult, and;
- Highly Exposed Population (NearFacility): Acute or Chronic-Infant, Young Toddler, Toddler, Small Child, Child, Teen, Adult.

What, then, would constitute a database adequate for assessing hazard for these demographics? Our answer is that, absent relevant observations in humans, it would include the following studies:

1. Studies that would illuminate the potential for general systemic toxicity over exposure durations commensurate with those of the actual exposure scenario(s) or that could be extrapolated from shorter-term exposure studies accompanied by the application of an uncertainty factor that represented that extrapolation (e.g., subchronic to chronic);
2. For chronic exposures, studies that would adequately test for carcinogenic potential, particularly given HBCD's potential for persistence and bioaccumulation;
3. For acute and chronic exposures, at least one developmental toxicity study;
4. For chronic exposures, a one- or two-generation reproductive toxicity study in rodents, and;
5. Given inconclusive evidence of thyroid effects in humans but confirmed dose-related effects in animals observed across multiple rat strains, sexes, exposure durations, and study designs, a systematic evaluation of developmental neurotoxicity, as the worker population includes women of child-bearing age, and the general population includes infants and young children.

The database for HBCD meets the criteria for Items #1 and #3-5, but not Item #2 (testing for carcinogenic potential). Given HBCD's polybutylene terephthalate characteristics, this is an important data gap, warranting an additional UF of threefold for data deficiencies when determining the Benchmark MOE for both acute and chronic exposure durations, and for all routes, and for all of the (sub)populations included in the risk evaluation. Thus, the Benchmark MOEs for all exposure scenarios (endpoints, routes and populations) should be increased at least threefold, although one could argue for a tenfold UF as well.

The consequences of this change are plenty, primarily in the occupational sector, assuming an additional UF of threefold.

- **Fourteen (14)** scenarios shift to Unreasonable Risk in the Risk Estimation for Non-Cancer Effects Following Acute Inhalation Exposures, Occupational Scenarios (Table 4-9).

- **Twenty-five (25)** scenarios shift to Unreasonable Risk in the Risk Estimation for Non-Cancer Effects Following Chronic Inhalation Exposures, Occupational Scenarios (Table 4-10).
- **No (0)** scenarios shift to Unreasonable Risk in the Risk Estimation for Non-Cancer Effects Following Acute Dermal Exposures (Table 4-11).
- **Eleven (11)** scenarios shift to Unreasonable Risk in the Risk Estimation for Workers Non-Cancer Effects Following Chronic Dermal Exposures in Occupational Scenarios (Table 4-12).
- **No (0)** scenarios shift to Unreasonable Risk in the Risk Estimation for Non-Cancer Effects – General Population Table 4-13.
- **Four (4)** scenarios shift to Unreasonable Risk in the Risk Estimation for Non-Cancer Effects Following Acute Exposure to Highly Exposed Population (Table 4-14).
- **No (0)** scenarios shift to Unreasonable Risk in the Risk Estimate for Non-Cancer Effects Following Acute Exposure to Highly Exposed Population – Inhalation (Table 4-15).
- **No (0)** scenarios shift to Unreasonable Risk in the Risk Estimate for Non-Cancer Effects Following Acute Exposure to Highly Exposed Populations—Consumer Articles (Table 4-16).
- **Seven (7)** scenarios shift to Unreasonable Risk in the Risk Estimate for Non-Cancer Effects Following Chronic Exposure to Highly Exposed Population (Table 4-17).
- **No (0)** scenarios shift to Unreasonable Risk in the Risk Estimate for Non-Cancer Effects Following Chronic Exposure to Highly Exposed Populations—Consumer Articles (Table 4-18).

Consideration of database adequacy and application of the UF_D when it is not adequate is consequential for the risk evaluations of both 1,4-Dioxane and HBCD. EPA should clearly reconsider its risk evaluations and exercise its "new" TSCA section 4 mandate.

References

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