Environmental Protection Network

(202) 656-6229
environmentalprotectionnetwork.org
info@environmentalprotectionnetwork.org

EPN Comments for the Public Meeting of the Science Advisory Committee on Chemicals Regarding Draft Methylene Chloride Risk Evaluations Under the TSCA

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The Environmental Protection Network (EPN) is an organization comprised of over 480 U.S. Environmental Protection Agency (EPA) alumni volunteering their time to protect the integrity of the EPA, human health and the environment. We harness the expertise of former EPA career staff and confirmation-level appointees to provide insights into regulations and policies proposed by the current administration that have a serious impact on public health and environmental protections.

EPN is submitting these comments to the Science Advisory Committee on Chemicals (SACC) to aid in their review of the Methylene Chloride (MC) draft risk evaluation during their scheduled December 3-4, 2019, meeting.

In addition to these comments, EPN recently sent letters to EPA Administrator Andrew Wheeler to express concern about the serious health risks demonstrated in EPA's draft risk evaluation of the chemical MC, and to the Chairs and Ranking Members of the House Committee on Energy and Commerce and the Senate Committee on Environment and Public Works, urging their support in expressing concern to EPA and asking for immediate action.

MC is one of a group of organochlorine chemicals classified as Volatile Organic Compounds (VOC(s)), based on its ability to easily transition from a liquid state to a vapor or gas. It is a high-volume production and use chemical with a wide range of commercial and consumer uses. A large number of subcategories of use and disposal are the subject of this draft risk evaluation.

On October 29, 2019, EPA published a Federal Register notice announcing the availability of documents and dates for the scientific peer review of the draft risk evaluation for MC. While the official comment period on this draft risk evaluation is open until December 30, 2019, any commenters who wish for their comments to be considered by the SACC during their public meeting scheduled for December 3-4, 2019, must submit their comments by November 26, 2019. While comments submitted after the November 26, 2019, deadline will still be provided to the SACC, they will not be able to contribute to any public dialogue. EPN may prepare additional comments on this draft risk evaluation by the December 30, 2019, deadline; we are concerned, however, that the SACC will have concluded their review before the public comment period closes.

Once again, the agency is implementing a schedule for review that is inconsistent with best management practices. As EPN stated in its July 19, 2019, and August 30, 2019, comments on the 1,4-Dioxane, HBCD draft risk evaluations and in comments on the 1-Bromopropane draft risk evaluation, we continue to be concerned that this process deprives the SACC of scientific and policy input that would be valuable in informing its review of the MC (and NMP) draft evaluations and, thus, greatly reduce the value of the public comment process. This repeated action reinforces the view articulated by EPN and other commenters that the current agency approach seems to value meeting a deadline for a decision over the integrity of the information going into the decision. Furthermore, the process appears to be a mechanism to discourage

comments from the stakeholder community that wishes to see a standardized risk evaluation process followed.

EPN is focusing these initial comments on some of the most critical policy issues that affect not only MC but all past and future chemical risk evaluations under the Toxic Substances Control Act (TSCA).

1. Systematic Review: As in the past, the agency is not using the best available tools by continuing to use the non-peer-reviewed, flawed draft guidance document entitled "Application of Systematic Review in TSCA Risk Evaluations" to identify, sort, select, and exclude studies and other information to be used in the MC risk evaluation and, then, to grade their quality and acceptability for inclusion in the assessment.

   In comments submitted on August 16, 2018, and on several occasions since, EPN and other scientific groups have presented detailed criticisms of that draft systematic review process. Our comments documented EPA's failure to follow its own required internal and external peer-review procedures in developing this process, described serious flaws permeating the entire TSCA systematic review process, and noted critical flaws in evaluating individual studies for use in toxicity assessments (such as failure to assess for bias). This draft guidance remains inconsistent with best practices in systematic review and should not be used for any purpose until peer reviewed and revised in accordance with the feedback received.

2. Adequacy of databases for assessment: As with all chemicals selected for review in the Existing Chemicals Risk Evaluation program, EPN is concerned about the adequacy of the databases available to assess MC's hazard potential to human health and the environment and to characterize the relevant exposure profiles. In these comments, we will focus on the toxicity database used to assess potential for human health hazard. We have previously articulated our views on what constitutes a minimum database with which to estimate high-confidence points of departure (PODs)/reference values/margins of exposure (MOEs.)

   This draft risk evaluation includes the assessment of risk to workers and occupational non-users (ONUs) from acute and chronic inhalation and dermal exposures. EPA also evaluated the risk to consumer products from inhalation and dermal acute and chronic exposures. Life stages from infants to adults were included in the draft evaluation, also comparing the estimated exposures to acute and chronic human health hazards. However, pregnant women and workers considering a family were not specifically addressed.

   What, then, would constitute a database adequate for assessing hazard to these (sub)populations with regard to the identified toxicity endpoints of concern for determination of credible PODs, reference values and Benchmark MOEs? Databases, historically, have been heavily dependent upon whole animal studies in the absence of adequate human data. In this instance, there is also a relatively substantial body of literature on human exposure to MC, both controlled exposure and epidemiologic studies. The database also contains a series of short-term *in vitro* and *in vivo* genotoxicity studies and others that were focused on exploring the characterization of mode(s) of action for several of the observed toxicity endpoints. Increasingly, new assessment methodologies (NAMs) including short-term *in vitro* assays, (Q)SAR, Read-across and other tools are finding a role

in the mix of useful information and do/will have a place as a complement to, or substitute for, animal studies as they are shown to be scientifically sound and validated for purpose.

EPA identified the following endpoints of concern related to MC exposure: acute toxicity, neurotoxicity, liver toxicity, immunotoxicity, reproductive/developmental toxicity, irritation/burns and genotoxicity/carcinogenicity in its hazard assessment. Studies used for dose-response modeling represented a subset of these endpoints: acute toxicity (based on neurotoxicity), non-cancer liver toxicity and genotoxicity/carcinogenicity. Absent fulsome observations in humans, the following types of information are needed in order to conduct a credible hazard assessment and derive useful PODs and appropriate Benchmark MOEs, without having to incorporate an uncertainty factor to accommodate for database deficiencies:

a. Studies that would illuminate the potential for general systemic toxicity over exposure duration(s) commensurate with that/those of the actual exposure scenario(s) under evaluation or, if long term, 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). In this draft risk evaluation, both acute and long-term exposure scenarios are being evaluated.
b. For chronic exposures, studies that would adequately test for carcinogenic potential by the relevant route(s) of exposure or that could be extrapolated to those routes of exposure;
c. For both acute and chronic exposures, at least one developmental toxicity study;
d. For both short-term and chronic exposures, a one- or two-generation reproductive toxicity study, and;
e. If nervous system effects have been observed in exposed humans or animals, a more systematic evaluation of neurotoxicity and developmental neurotoxicity, since the worker population includes women of childbearing age and the general population, which also includes women of childbearing age as well as infants and young children.

In the case of MC, there exists a robust database comprised of a number of controlled human exposure and epidemiology studies as well as animal studies, which evaluate a broad range of endpoints. At first blush, it might appear that all the bases have been covered and, thus, inclusion of an uncertainty factor to account for data deficiencies in deriving Benchmark MOEs is not warranted.

However, there is one area of investigation that remains incomplete. It is very clear that MC produces effects on the nervous system, especially after acute (inhalation) exposure at high levels. Given the profile of (sub)population exposures to MC in both the occupational and consumer use settings, it is important to understand the potential for MC to produce nervous system effects in the developing organism. One such study in animals exists (Bornschein, RL; Hastings, L; Manson, JM. (1980). Behavioral toxicity in the offspring of rats following maternal exposure to dichloromethane. Toxicol Appl Pharmacol 52(1): 29-37). It should be noted that dichloromethane and MC are the same chemical; some of the following studies use differing acronyms.

The abstract to the Bornschein et al. paper summarizes their research: "Rats divided in four treatment groups were exposed to dichloromethane (DCM) (4500 ppm) or filtered air before and/or during gestation in order to assess the occurrence and extent of toxic effects on developing offspring. The progeny of dams exposed to DCM either prior to and/or during gestation exhibited

altered rates of behavioral habituation to novel environments. No simple relationship between exposure period and behavioral outcome was observed. Each of the treatment groups showed effects as a function of age at testing and the behavioral task used. Treatment effects were detectable in offspring as early as 10 days of age and were still demonstrable in 150-day-old male rats. Treatment effects were observed in rats of both sexes in preweaning tests but were not seen in adult female rats. No effects of subacute DCM exposure were evident in growth rate, long-term food and water consumption, wheel running activity, or avoidance learning. This study, which should be viewed as preliminary, is of interest since altered rates of habituation to novel environments were observed in the absence of overt maternal toxicity, or teratogenicity. The effects cannot be definitely attributed to a direct effect of DCM since elevated maternal carboxyhemoglobin (COHb)- or DCM-induced changes in maternal-litter interactions could have been contributing factors. The findings do suggest that the functional development of progeny of DCM-exposed dams should be further investigated."

EPN agrees with the authors that additional information should be gathered. It would be of value to have the results of an inhalation developmental neurotoxicity study. The key to this would be results of exposure to a series of MC dose levels (in addition to a control),which, importantly, includes at least one dose inducing measurable effects (a lowest-observed-adverse-effect level (LOAEL) or higher) and at least one resulting in none (a no-observed-adverse-effect-level (NOAEL)). These data would be critical in determining whether or not the Hazard Values (PODs) for Acute Exposure Occupational and Consumer Scenarios are adequately protective for the fetus (in the case of exposures to pregnant women) as well as infants and children.

Nursing infants might be exposed through their mothers' milk as there are data indicating that the chemical has been detected in breast milk, supporting the possibility of exposure orally as well as directly through the inhalation and dermal routes. Furthermore, EPA notes that there is evidence that MC may exert neurotoxic effects through modes of action unrelated to the production of carboxyhemoglobin leading to carbon monoxide poisoning, a point made by Bornschein et al. as well (EPA draft risk evaluation p. 241: "Data suggest that increased COHb levels result in CNS depression (Putz et al., 1979) but doesn't fully explain the independent and possible additive effect of methylene chloride because a weaker effect (or no effect) on the nervous system was observed with administration of exogenous CO compared with methylene chloride administration (Putz et al., 1979; Winneke, 1974)."

3. Route-to-route extrapolation: The occupational and consumer conditions of use assessed in the MC draft risk evaluation reflect exposure via the inhalation and dermal routes. The toxicity database is comprised of studies conducted by the inhalation or oral routes. Thus, dermal acute and chronic PODs and the inhalation unit risk (IUR) were extrapolated from the same inhalation studies used to generate the Acute Inhalation non-cancer PODs and the Chronic non-cancer POD and cancer IUR. The same Benchmark MOEs were derived (Acute = 30; Chronic = 10). The same recommendations for modifying each of these MOEs pertains to the dermal assessments. See below for specific recommendations. Analysis of the impact of this change on the acceptability of the dermal exposures from occupational and consumer conditions of use will be summarized in our follow-up comments.

So, where does that leave us with regard to determining the adequacy and appropriateness of the PODs and Benchmark MOEs for both the acute and chronic durations of exposure?

a. The existing databases are adequate for development of credible PODs (for now). As noted above, it would be helpful to have better information on development neurotoxicity in order to determine if the acute PODs based upon adult data are protective of the fetus, infants and children.
b. For this reason, EPN has concerns about the adequacy of the acute Benchmark MOE. EPA has established an Acute Benchmark MOE of 30 (UF_H=10 x UF_L = 3), where UF_H represents within-human variability and UF_L represents extrapolation of a LOAEL to an NOAEL. EPN would argue that a third UF (UF_D) should be incorporated into the derivation of the MOE to accommodate for the incomplete information on neurodevelopment. This third UF could be set at either 1.5 X or 2X. The resulting MOE would then be either 45 or 60 (10X (UF_H) x 3X (UF_L)x 1.5X (UF_D)=45 or (10X (UF_H) x 3X (UF_L)x 2X (UF_D)=60). Analysis of the impact of these changes on the acceptability of the occupational and consumer conditions of use will be summarized in our follow-up comments.
c. Chronic non-cancer and cancer—EPN generally agrees with the use of the physiologically based pharmacokinetic (PBPK) model and the benchmark dose (BMD) approach for the derivation of the PODs for the non-cancer assessment and the Individual Unit Risk (IUR) for the cancer assessment. With regard to the (non-cancer) Benchmark MOE (i.e., the UF for the HEC_{99}) set at 10, EPN finds the UF_A of 1X to be acceptable. EPN is less comfortable with the UF_H of 3, given that the agency has not provided adequate evidence to show that variability in sensitivity of specific subpopulations (fetuses, workers and consumers engaged in vigorous activity, individuals with higher CYP2E1 enzyme levels, smokers and individuals with heart disease/cardiac patients) is accommodated by the UF_H of 3X. A larger UF_H, perhaps 4.5X, should be applied. This would result in a Chronic non-cancer Benchmark MOE of 15. Analysis of the impact of this change on the acceptability of the occupational and consumer conditions of use will be summarized in our follow-up comments.

4. Worker Exposure and Risk: EPN continues to be concerned about the agency's approach for determining unreasonable risk to workers. It underestimates that risk by assuming workers will use personal protective equipment (PPE) for the entire duration of the work activity throughout their careers, even when such equipment is not required, provided or used. EPA appears to discount the risks to workers by assuming constant use of PPE (e.g., respirators and/or gloves). We would argue that while EPA may assess and characterize worker risk with and without the use of PPE, it should make its unreasonable risk determinations based upon the "no PPE" scenarios. Lacking the guarantee of consistent use of PPE, EPA should focus its regulatory options on mitigating risk to the unprotected individual.

5. Aggregate Risk Assessment: The MC draft risk evaluation presents risk assessments and risk determinations for acute and chronic inhalation and dermal exposures in occupational and consumer product conditions of use. As EPA notes in the draft risk evaluation, it is required to describe whether aggregate or sentinel exposures under the conditions of use were considered and the basis

for their consideration. (The agency defines aggregate exposure as "the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways.")

In all of these scenarios evaluated for MC, it is possible, in fact, most likely that exposure via the inhalation and dermal routes will be occurring simultaneously. As EPA states, "For workplace exposures, inhalation and dermal exposures are assumed to occur simultaneously i.e., both occur at the start of the task and continue through the end of the task, shift, or work day. For household exposures, inhalation and dermal exposures occur at the start of the task and continue through the end of the task." In each case, EPA evaluated the exposures to MC inhalation and dermal contact separately. Then, they provided a feeble excuse for not proceeding with an aggregate assessment by stating that the PBPK models they had used lacked a dermal compartment so they could not aggregate the inhalation and dermal exposures. They argued that aggregating inhalation and dermal exposures without the use of a PBPK model would introduce additional uncertainties. They also chose not to employ simple additivity of exposure pathways within a condition of use "because of the uncertainties present in the current exposure estimation procedures." This is simply a cop-out. Aggregation can be done under these conditions and the uncertainties can be accommodated for. The lack of aggregation leads to an underestimate of exposure and risk and, potentially, the incorrect declaration of "no unreasonable risk" when one actually exists. This situation is further compounded by EPA's refusal to consider concomitant exposures in media/scenarios covered by regulatory measures under other statutes. Other examples of exposures excluded from risk evaluations include MC air emissions, drinking water-related exposures and waste-related exposures. MC air emissions are very significant due to its high volatility and widespread use. Just because an exposure would not be regulated under TSCA does not mean it should not be considered when assessing risks that would be regulated under TSCA.