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The Massachusetts Toxics Use Reduction Institute (TURI)[1] offers the following comments in response to EPA's proposed rule to add 12 of the 25 chemicals that TURI earlier petitioned the EPA to add to EPCRA section 313, otherwise known as the Toxics Release Inventory or TRI toxic chemicals.

Our comments are provided in the context of our experience implementing the Massachusetts Toxics Use Reduction Act (TURA), in particular our work with the TURA Science Advisory Board. These comments represent only a brief review of some of the relevant information, and are not comprehensive.

TURA requires large-quantity chemical users in Massachusetts to report annually on their use of toxic chemicals, pay an annual fee, and conduct toxic use reduction (TUR) planning every two years. In the TUR planning process, businesses examine opportunities to reduce toxic chemical use by adopting safer processes or inputs.

The TURA List of Toxic or Hazardous Substances is the basis for the reporting, planning and fee requirements. The list was based originally on the Toxics Release Inventory (TRI) and the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) lists and has been updated over time. The statute provides for substances added under TRI to be added under TURA as well. Thus, adding chemicals to TRI also expands the list of substances subject to use reporting in Massachusetts.

Background: 2014 Petition

On May 6, 2014, TURI submitted a petition proposing that EPA consider adding 25 chemicals to TRI. Each of the proposed chemicals met the following criteria:

- The chemical is not currently on the Toxics Release Inventory chemical list;
- The chemical is a U.S. EPA designated High Production Volume (HPV) chemical that is produced or imported into the U.S. in quantities of 1 million pounds or more per year (as of listing revised January 2006);
- The chemical is used for industrial/manufacturing purposes;
- The chemical appears to meet at least one EPCRA Section 313(d)(2) criterion for chemical list additions, based on hazard classification information from one of the following: International Agency for Research on Cancer (IARC): Group 1 (carcinogenic to humans), or Group 2a (possibly carcinogenic to humans); National Toxicology

Program (NTP): Known to be Human Carcinogen or Reasonably Anticipated to be Human Carcinogen; European Union: REACH Candidate List of Substances of Very High Concern for Authorization (SVHC); State of California:: Classified under Proposition 65 as carcinogen as determined by State Qualified Expert; or International Chemical Secretariat (ChemSec): Substitute it Now (SIN) List for substances that meet Candidate List (SVHC) criteria as defined in the REACH Regulation.

General comments

The EPA proposal to add the following twelve chemicals to the TRI list will provide valuable information to businesses and communities, furthering the goal of protecting human health and the environment.

- Dibutyltin dichloride; 683-18-1
- 1,3-Dichloro-2-propanol; 96-23-1
- Formamide; 75-12-7
- 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran; 1222-05-5
- N-Hydroxyethylethylenediamine; 111-41-1
- Nitrilotriacetic acid trisodium salt; 5064-31-3
- p-(1,1,3,3-Tetramethylbutyl)phenol; 140-66-9
- 1,2,3-Trichlorobenzene; 87-61-6
- Triglycidyl isocyanurate; 2451-62-9
- Tris(2-chloroethyl) phosphate; 115-96-8
- Tris(1,3-dichloro-2-propyl) phosphate; 13674-87-8
- Tris(dimethylphenol) phosphate; 25155-23-1

Moving forward on these listings promptly will provide value, even while the comments on the remaining chemicals are being considered, and will be consistent with the mission of TRI to provide timely and useful information on chemical releases. However, excluding the remaining chemicals that were on TURI's original petition represents a missed opportunity to further protect public health and the environment, increase transparency, and promote the adoption of safer alternatives to toxic chemicals.

We recognize that in making listing decisions, EPA considers a variety of factors. However, we would suggest that additional factors or criteria may be useful and appropriate to consider.

For example, while toxicity data are lacking for certain chemicals, substantial information can be gained by considering analogs. Using read-across data may be an appropriate approach in these cases.

In addition, is essential to take account of information available from case reports, epidemiological studies, and mechanistic data, even when chronic animal studies are unavailable. This is particularly important in the context of EPA's efforts to minimize use of vertebrate animals for testing. In addition, while TURI recognizes EPA's efforts to minimize animal testing, it is important to continue to recognize the importance of animal testing in some aspects of ensuring adequate chemical safety.

As a general matter, for chemicals that are produced and used in high volumes, it is important to ensure transparency and encourage the use of safer substitutes whenever possible. To the extent that data gaps are present, this may be an important opportunity for EPA to obtain new test data in order to better understand the toxicity of chemicals that are used widely in the economy.

Finally, TURI would like to share its experiences in managing the TURA Science Advisory Board process. When data of concern have been identified for the primary endpoint but questions still remain about whether those data are sufficient, the SAB broadens its examination to consider toxicity data on additional, related endpoints.

Below, we briefly note how these and other considerations may apply to individual chemicals.

Hexahydrophthalic anhydride (HHPA) (CAS #85-42-7) and Methylhexahydrophthalic anhydride (MHHPA) (CAS #25550-51-0)

Evidence of the toxicity of these chemicals is available from case reports and epidemiological studies, as well as mechanistic and animal studies.

Both HHPA and MHHPA are members of EPA's HPV Challenge cyclic anhydrides category, identified as bicyclic anhydrides; EPA considered this grouping acceptable for the purposes of the HPV Challenge Program. In EPA's Screening Level Hazard Characterization Document for the Cyclic anhydrides Category (2009), EPA concluded from a review of the literature that "CASRNs 85-42-7 and 26590-20-5 were respiratory sensitizers in humans."[2]

ACGIH has set a TLV-ceiling for HHPA at 0.005 mg/m3, inhalable fraction and vapor, with a respiratory sensitizer notation based on both human and animal data. ACGIH notes that HHPA is a potent sensitizer that causes IgE- and IgG-mediated disease, including allergic rhinitis, asthma, hemorrhagic rhinitis, and hypersensitivity pneumonitis.

HPPA and MHPPA have EU Harmonized Classification and Labeling as Respiratory Sensitizer 1 and Skin Sensitizer 1.[3]

The WHO CICAD document (2009) summarized the available epidemiological data for several cyclic acid anhydrides. The available data (summarized in table 5 in the WHO document) indicate that HHPA and MHHPA are among the most potent sensitizers in the group of cyclic acid anhydrides and can cause severe and irreversible adverse effects on human health.[4]

Occupational epidemiological studies for HHPA include cross-sectional (e.g., Moller et al 1985 - occupational asthma, and nasal and ocular symptoms), case control (e.g., Nielsen et al 1994 - nasal symptoms and HHPA sensitization), and prospective cohort studies (e.g., Grammer, et al 2002 - occupational asthma).[5]

In addition, there are studies with mixed exposure to HHPA and MHHPA (e.g., Nielsen, et al 2001 - nasal, ocular and lower airway symptoms; Yokota et al 2002 - HHPA specific IgE, rhinitis, conjunctivitis).[6]

In summary, TURI suggests that the substantial information available on these chemicals are sufficient for listing in this case.

N-Methylformamide (CAS #123-39-7)

Under the EU's Harmonized Classification and Labelling, this chemical is listed as Reproductive Toxicity 1B. EPA determined that criterion for toxicity to reproduction was not met due to high maternal toxicity in both the studies cited. However, some of the studies reviewed by EPA do provide evidence of teratogenicity, and additional studies not cited by EPA also support this concern.

In addition, n-methylformamide shares the common formamide structure with N,N-dimethylformamide (DMF) and formamide. DMF is listed under TRI. The liver is the common major systemic target organ upon repeated exposure for these three structurally similar chemicals. Furthermore, N-methylformamide appears to be a major *in vivo* metabolite of N,N-dimethylformamide and may be responsible for the hepatotoxicity of DMF.[7]

Azodicarbonamide or 1,1'-Azobis(formamide) (CAS #123-77-3)

TURI originally suggested addition of this chemical based on its presence on the Candidate List of Substances of Very High Concern for Authorization, meeting the SVHC criteria for "Respiratory Sensitizer Category 1."

EPA notes the availability of occupational studies and case reports on the association of this chemical with occupational asthma and contact dermatitis. Despite the availability of human data, EPA determined that the absence of chronic animal studies precludes listing.

In addition to being on the SVHC Candidate list, azodicarbonamide is also recognized as a substance that can cause occupational asthma by the UK Health and Safety Executive.[8] Given the serious burden of occupational asthma and dermatitis, as well as the fact that other authoritative bodies have found that the human data were sufficient for categorization, EPA should consider listing this chemical based on the human health studies.

4-Chlorobenzotrichloride or **p-a,a,a-Tetrachlorotoluene (CAS #5216-25-1)**

This chemical is listed on several authoritative lists based on carcinogenicity; among others, it is included in REACH Annex XVII CMRs - Carcinogen Category 2 - Substances which should be regarded as if they are carcinogenic to man[9], and is listed as a carcinogen under California's Proposition 65.[10]

In addition to the carcinogenicity study cited by EPA, it may be relevant to consider the evidence of mutagenicity noted in the EU registration dossier for this chemical.[11]

It is also worth noting that this chemical could be considered to be an analog of benzotrichloride, although it is not identified as such in EPA's Analog Identification Methodology (AIM). Benzotrichloride is listed under TRI.

Based on analog data as well as the *in vitro* data available from the EU, it would be reasonable for EPA to revisit its conclusion regarding carcinogenicity. Additionally, from a brief review of the information available in CompTox, critical effects included atrophy of olfactory epithelium and aspermatogenesis.[12] These effects may also be worthy of consideration in revisiting the science on this chemical.

N,N-Dimethylacetamide (CAS #127-19-5)

This chemical is included on the Candidate List of Substances of Very High Concern for Authorization (Meets SVHC criteria for Toxic to Reproduction, Category 1B: Presumed Human Reproductive Toxicant). EPA determined that the data were not sufficient for listing based on the doses at which developmental effects occurred as well as presence of toxicity in dams.

It is worth noting that the literature reviewed by EPA does provide evidence of a range of developmental toxicity outcomes. In addition, TURI briefly reviewed the dossier for the Proposal for Harmonized Classification and Labelling developed by the National Institute for Public Health and the Environment (RIVM) in the Netherlands and noted that that document includes additional developmental toxicity studies beyond those noted by EPA. Several of these studies (e.g. BASF 1975, Johannsen 1987, BASF 1989, Klimisch and Hellwig 2000) derive a NOAEL for developmental toxicity that is substantially lower than that for maternal toxicity. This suggests that it may be valuable for EPA to revisit the developmental toxicity literature. In addition, the maternal toxicity could have implications for human health. Finally, additional epidemiological studies are available on chronic human health effects and are worthy of consideration as well.[13]

2,3-Dinitrotoluene (CAS #602-01-7) and 2,5-Dinitrotoluene (CAS #619-15-8)

Both of these chemicals are classified in REACH Annex XVII as CMRs: Carcinogen Category 2 - Substances which should be regarded as if they are carcinogenic to man.[14]

Based on EPA's Analog Identification Methodology (AIM), both of these chemicals are analogs of chemicals that are already listed under TRI and CERCLA (2,4-dinitrotoluene [121-14-2]; 2,6-dinitrotoluene [606-20-2]; *o*-nitrotoluene [88-72-2]; *m*-nitrotoluene [99-08-1]; *p*-nitrotoluene [99-99-0]; dinitrotoluene (mixed isomers) [25321-14-6] as well as two analogs listed under CERCLA (3,4-dinitrotoluene [610-39-9] and nitrotoluenes [1321-12-6]. Therefore, it would be appropriate for EPA to use read-across data as a basis for listing both of these chemicals.

In addition, both of these chemicals are part of a mixture that is already listed under TRI (dinitrotoluene mixed isomers). Thus, adding these two chemicals would support the consistency and completeness of the list.

TURI would suggest that EPA consider analog data as well as revisiting the data on carcinogenicity/mutagenicity.

Conclusions

The information derived from listing these chemicals would provide important additional information to assist communities, businesses, and others in decision making, as well as helping to protect health and the environment and supporting adoption of safer alternatives. Adding these chemicals to TRI would help to prevent regrettable substitutions, as businesses move away from listed chemicals and substitute those that are not listed. Failure to add chemicals to the list could increase the likelihood of regrettable substitutions.

Thank you for considering these comments as you continue your analysis of these chemicals. Please do not hesitate to reach out to us if we can further assist your efforts in this regard.

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[1] TURI was established pursuant to the Massachusetts Toxics Use Reduction Act of 1989, Mass. General Laws Ch. 21I (TURA).

[2] U.S. Environmental Protection Agency September, 2009 Hazard Characterization Document. Screening Level Hazard Characterization: Cyclic Anhydrides Category. Viewed at https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.175.5959&rep=rep1&type=pdf, December 2021.

[3] ECHA. 2012. Support Document for SVHC listing (HHPA). Viewed at https://echa.europa.eu/documents/10162/555606e7-97e2-592e-c100-03f5639a82f4, December 2021; ECHA. 2012. Support Document for SVHC listing (MHHPA). Viewed at https://echa.europa.eu/documents/10162/96184c0e-245a-49a2-8a69-691e156dbaf7, December 2021.

[4] World Health Organization, International Programme on Chemical Safety & Inter-Organization Programme for the Sound Management of Chemicals. (2009). *Cyclic Acid Anhydrides: Human Health Aspects*. World Health Organization. https://apps.who.int/iris/handle/10665/44054

[5] ECHA. 2012. Support Document for SVHC listing (HHPA). Viewed at https://echa.europa.eu/documents/10162/555606e7-97e2-592e-c100-03f5639a82f4, December 2021

[6] ECHA. 2012. Support Document for SVHC listing (HHPA). Viewed at https://echa.europa.eu/documents/10162/555606e7-97e2-592e-c100-03f5639a82f4, December 2021; ECHA. 2012. Support Document for SVHC listing (MHHPA). Viewed at https://echa.europa.eu/documents/10162/96184c0e-245a-49a2-8a69-691e156dbaf7, December 2021.

[7] N-methylformamide: Evaluation of the carcinogenicity and genotoxicity. Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety, a Committee of the Health Council of the Netherlands to: the State Secretary of Social Affairs and Employment No. 2011/02OSH, The Hague, February 18, 2011. Viewed at https://www.healthcouncil.nl/binaries/healthcouncil/documents/advisory-reports/2011/02/18/n-methylformamide/advisory-report-n-methylformamide.pdf , December 2021.

[8] Health and Safety Executive, List of Substances that can Cause Occupational Asthma. Viewed at https://www.hse.gov.uk/asthma/substances.htm, December 2021.

[9] REACH Annex XVII, Appendix 2, viewed at https://echa.europa.eu/substances-restricted-under-reach/-/dislist/details/0b0236e1807e26bf, December 2021.

[10] California Proposition 65 List of Substances. Viewed at The Proposition 65 List - OEHHA (ca.gov) December 2021.

[11] https://echa.europa.eu/registration-dossier/-/registered-dossier/2193/7/7/2

[12] https://comptox.epa.gov/dashboard/chemical/hazard/DTXSID2027593

[13] See, for example: Wang J and Chen G. 2020. "Dimethylacetamide-induced toxic hepatitis in spandex workers: clinical presentation and treatment outcomes." *QJM: An International Journal of Medicine*, 324–329.

[14] REACH Annex XVII, Appendix 2, viewed at https://echa.europa.eu/substances-restricted-under-reach/-/dislist/details/0b0236e1807e26bf, December 2021.