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HEAL comments - SVHC identification proposal for Melamine: 1,3,5-triazine-2,4,6-triamine

Reasons for proposing:

- **Equivalent level of concern having probable serious effects on the environment (Article 57f)**
- **Equivalent level of concern having probable serious effects on human health (Article 57f)**

The Health and Environment Alliance (HEAL) thanks the German competent authority for the proposal to identify melamine as a substance of very high concern (SVHC) under REACH article 57(f). We fully support this proposal. Our detailed comments can be found below.

Melamine is a high-volume substance (registered at 100,000-1,000,000 tonnes/annum), which is used in a multitude of different industrial and consumer products. Melamine is used in products including building materials (flooring walls, plywood, adhesives, paints, coatings, flame retardants etc), textiles, fertilisers, cosmetics, personal care products, stain and water resistant clothing, detergents, fragrances, electrical and household appliances, and plastic products including reusable plastic tableware and toys. [1] Due to the many uses on the market and its persistence in the environment, exposure to workers, the general public, and wildlife is of high concern.

- **Equivalent level of concern having probable serious effects on human health (Article 57f)**

Human Health Hazards:

Carcinogenicity, Reproductive Toxicity, Endocrine Disruption, and Neurotoxicant properties:

The dossier highlights evidence to support identification of melamine as a SVHC due to the potential lifelong, irreversible impacts of exposure. Associated carcinogenic, reprotoxic, endocrine disruption, and neurotoxic effects have been observed in animal and human studies. Details of which are highlighted below.

1) **Carcinogenic properties**
   The supporting dossier notes IARC's warning that melamine may be "possibly carcinogenic to humans" and therefore that IARC classified it as a 2B substance under its classification system in 2019. [2] ECHA also categorised it as a level 2 carcinogen under

CLP. The short and long-term impacts of cancer on individuals and society are devastating and justify classifying melamine as a SVHC.

2) **Reproductive toxicity, endocrine disruption (ED), and neurotoxicant properties**
The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) issued a warning that melamine is suspected of damaging fertility in the foetus. [3] ECHA is also currently assessing melamine as a suspected endocrine disruptor. A scoping review of the literature conducted in 2017 further supports this approach and classification. The review looked at more than forty human, animal, and in vitro studies investigating melamine exposure and identified associated neurological impacts, reproductive function, and anthropometric outcomes. [4]

<u>Renal Toxicity:</u>
Melamine is a well known urinary toxicant, classified by RAC in 2020 as a specific target organ toxicity-repeat exposure (STOT RE 2 urinary tract). The supporting dossier provides ample epidemiological evidence demonstrating the link between oral exposures and acute kidney toxicity. It highlights the epidemiological evidence borne by the scandal that took place in China in 2008, when milk was intentionally contaminated with melamine to boost protein content. This incident led to the diagnosis of kidney stones in 294,000 infants, approximately 50,000 infant hospitalisations, and at least 6 deaths from renal failure. Chinese observational studies during this time found that melamine-contaminated milk was strongly associated with urinary precipitation and nephrotoxicity. [5] Infants, notably neonates, were found to be more highly susceptible to melamine-induced urolithiasis, with prematurity and male gender identified as risk factors in the literature. [6]

The dossier also raises concerns over increased risk of chronic kidney disease and comorbidities, such as cardiovascular disease later in life which have been associated with a history of kidney stones. Studies also suggest that there may be adverse outcomes at low doses, even below the tolerable daily intake (TDI) including increased risk of calculi formation. Thus, RAC recognizes significant uncertainties in this area. The Committee's inability to derive a safe level also makes the case for melamine meeting the ELoC criteria and the substance identification as a SVHC. This devestating incident in China as well as the potential long-term, irreversible, health outcomes associated with exposure underscore the potential human health hazards of melamine and further supports the proposed SVHC identification.

Toxicological evidence:
Further evidence from animal studies outlined in the supporting dossier warrants melamine's classification as a SVHC. The 2007 melamine-contaminated pet food incident, in which kidney failure and deaths were observed among exposed cats and dogs, provides another instance of acute renal toxicity and melamine's hazardous properties. Animal studies have demonstrated melamine's ability to cross the placental barrier and it has been detected in animal milk. [7] [8] [9] As with humans, adverse effects were observed at lower exposure values of combined exposures to melamine and cyanuric acid in rats, pets, and livestock compared with individual exposure to one substance at a time suggesting the possibility of interaction and worse outcomes at lower

doses from co-exposures. [10] As the dossier points out, this led to the Dutch Competent Authority lowering their drinking water derived limit values. In addition, the dossier presents evidence that points to higher toxicity with co-exposures that are relevant to real world scenarios compared to lab studies of exposure to one chemical at a time. [11] There have also been observed effects on sperm and testis found in a one-generation reproductive toxicity study. Melamine exposure has also been associated with chronic reprotoxicity and neurotoxicity endpoints, in addition to adverse impacts on the gut microbiome and the endocrine system. [12]

Common Co-Exposures and Chemical Mixtures:
Melamine can be metabolised to a group of potentially harmful derivatives including cyanuric acid, (CYA), ammeline (AMN), and ammelide (AMD). Further, research has shown that co-exposures to cyanuric acid and melamine exacerbate kidney toxicity compared to exposure to one compound by itself. Cyanuric acid and other derivatives are often used together with melamine in industrial and consumer products, leading to increased risk of potential harm. Thus, combined exposures are a major concern.

The dossier cites compelling evidence of increased risk in relation to co-exposures to melamine and its derivatives such as the Sathyanarayana et al. study which found statistically significant associations amongst individuals with higher exposures to melamine and cyanuric acid in combination and kidney injury markers. [13] Another study not mentioned in the dossier looked at melamine and cyanuric acid in foodstuffs and estimated daily intakes (EDI). It found children's EDI were 5-10 times higher than in adults, with dairy, meat, and cereal products accounting for over 80% of contaminated dietary exposures. [14] These findings suggest that these substances are ubiquitous in many products and environments and certain vulnerable populations may be exposed at higher levels on a daily basis.

Melamine is also often used in the production of formaldehyde based resins for plastic production, which we believe further supports its identification as a SVHC. Melamine and formaldehyde are classified as category 2 and 1B carcinogen respectively. The uncertainties of combined exposure effects of these two harmful substances commonly used in tandem, add further arguments in favour of the SVHC identification. [15]

- **Equivalent level of concern having probable serious effects on the environment (Article 57f)**

Environmental Hazards:
The supporting dossier provides sufficient evidence to justify SVHC identification based on melamine's very persistent and very mobile (vPvM) intrinsic properties. It has vPvM properties in aquatic environments due to its long half-life (>60 days), high water solubility, low volatility from water and low absorption potential. The dossier further discusses the OECD long-range transport potential tool and melamine's estimated very long range characteristic travel distance (CTD) of 3530 km together with an overall environmental persistence (Pov) of 2181 days. [16] Thus, there is concern of widespread melamine contamination in surface waters and groundwater far beyond the point source of contamination. As a result of the substance's lack of abiotic and biotic

degradation, its persistence, and mobility in aquatic environments, increasing production, use and disposal of melamine has the potential for long-lasting, irreversible global impacts on the environment. [17] ECHA is currently assessing Melamine as a suspected persistent, bioaccumulative and Toxic (PBT) substance as a result of its intrinsic properties, which are well supported by the scientific literature.

Sources and Pathways for Human Exposure:

The current body of scientific literature has found that food contact materials are one of the most significant sources of melamine exposure. However recent research also suggests that diet accounts for approximately 20-25% of exposure, while bottled and tap water contribute to less than 10% of estimated daily intake. [18] Drinking water, house dust, and contamination throughout the food chain are also potential sources of exposure.

Melamine migration into food contact materials is another known source of exposure. Its use in tableware is often marketed towards use for infants and young children because of its durability, increasing the risk for potentially higher cumulative exposures in this biologically and developmentally vulnerable population. A recent Danish investigation found melamine leaching in children's plastic cups at levels that exceeded the 2.5 mg/kg EU legal limit. Another recent study looking at bowls leaching melamine and cyanuric acid found that infants were particularly susceptible to increased exposure with an estimated daily intake (EDI) that was 1.24 times higher than the tolerable daily intake (TDI) established by the European Food Safety Authority (EFSA). In addition, a study that included biomonitoring data and an exposure assessment investigating urinary concentrations in young adults after consuming hot noodle soup from melamine bowls, found an increase in total urinary melamine excretion. This study demonstrated a direct link between exposure due to use and increased urinary biomarkers. [20]

Melamine also poses a significant barrier to the right to clean water, with its very persistent, very mobile properties allowing for contamination of surface and groundwater that is very difficult to remove. Scientists have found that conventional drinking water treatment plants are not able to remove melamine from water due to its relatively low absorption properties. Melamine is also not removed via river bank filtration or soil infiltration and has been detected in groundwater. [21] In addition, researchers have found Hexamethoxymethylmelamine (HMMM), a crosslinker of melamine resins, in municipal wastewater as a result of its high persistence and mobility in the water cycle. [22] The challenges and costs associated with decontamination of water sources and vPvM properties makes the case for an equivalent level of concern having probable serious effects on the human health and the environment under article (Article 57(f)).

Evidence of the substance's growing ubiquity in the environment can be found in monitoring data that detected melamine in groundwater, surface water, drinking water, bottled water, and rain water in many different areas of the world. [23] [24] Melamine and its derivatives have also been found in human breast milk, formula, and food, further suggesting that these substances are posing unacceptable risks to vulnerable populations and are coming from many different sources that are hard to avoid. [25] [26] [27] [28] Irrigation and agricultural waters also contribute to contaminated food. [30] In addition, electronics, household products and even infant clothing containing grease, stain, and water repellents and flame retardants have been found as sources of potential melamine exposure.[1] A recent study detecting melamine in infant clothing provides evidence of melamine's use as a regrettable substitute for PFAS. Studies have also detected melamine and its derivatives in house dust, indicating another pathway for human exposure. [31]

Melamine's extensive use in a broad range of different products, its potential use as a regrettable substitute for other hazardous groups of chemicals including PFAS, its vPvM properties, its growing ubiquity, and its potential irreversible impacts on the environment and human health all provide strong justification for it meeting the ELoC criteria and identifying it as a SVHC on that basis.

In summary, there is well documented evidence supporting the identification of melamine as a SVHC under article 57(f) for its effects on both human health and the environment.

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[1] ECHA. Substance Infocard: Melamine. Substance Information - ECHA (europa.eu).

[2] IARC (June 27, 2019). Some chemicals that cause tumours of the urinary tract in rodents.

[3] S EPA. Comptox. Safety—GHS data.
https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID6020802#safety

[4] Bolden, A.L., Rochester, A.L., and Kwiatkowski, C. (2017). Melamine, beyond the kidney: A ubiquitous endocrine disruptor and neurotoxicant? *Toxicology Letters.* 280:(181-189). Doi: 10.1016/j.toxlet.2017.07.893.

[5] German Competent Authorities. August 2022. Annex XV Report: Proposal for identification of a substance of Very High Concern on the Basis of the Criteria Set Out in Reach Article 57. Pg. 36. 7e0e4a95-b942-350e-ba7d-7cf7aa652ab8 (europa.eu).

[6] Ibid.

[7] Chan J.Y., et al. (2011): Gestational and lactational transfer of melamine following gavage administration of a single dose to rats. *Food Chem Toxicol* 49 (7), 1544-1548. DOI: 10.1016/j.fct.2011.03.046.

[8] Cruywagen C.W., Stander M.A., Adonis M., and Calitz T. (2009): Hot topic: pathway confirmed for the transmission of melamine from feed to cow's milk. Journal of Dairy Science 92 (5), 2046-2050. DOI: 10.3168/jds.2009-2081.

[9] Kim S.H., et al. (2011): Effects of melamine on pregnant dams and embryo-fetal development in rats. *Journal of Applied Toxicology* 31 (6), 506-514. DOI: 10.1002/jat.1703.

[1] Zheng, G. and Kannan, K. (2020). Are Melamine and Its Derivatives the Alternatives for Per- and Polyfluoroalkyl Substance (PFAS) Fabric Treatments in Infant Clothes? *Environ. Sci. Technol.* 54, 16, 10207–10216. Doi: 10.1021/acs.est.0c03035.

[10] German Competent Authorities. August 2022. Annex XV Report: Proposal for identification of a substance of Very High Concern on the Basis of the Criteria Set Out in Reach Article 57. Pg. 8. 7e0e4a95-b942-350e-ba7d-7cf7aa652ab8 (europa.eu).

[11] Ibid. Pg. 37

[12] Zheng, X., et al. (2013). "Melamine-Induced Renal Toxicity Is Mediated by the Gut Microbiota." *Science Translational Medicine.* 5(172): 172ra122. http://stm.sciencemag.org/content/5/172/172ra22.

[13] Sathyanarayana, S., et al. (2019). Melamine and cyanuric acid exposure and kidney injury in US children. *Environmental Research.* DOI: 10.1016/j.envres.2018.10.038.

[14] Zhu, H., Kannan, K. (2019). Melamine and cyanuric acid in foodstuffs from the United States and their implications for human exposure. *Environ Int.* Doi: 10.1016/j.envint.2019.104950.

[15] ECHA. Substance Information Card - Formaldehyde ECHA (europa.eu)

[16] German Competent Authorities. August 2022. Annex XV Report: Proposal for identification of a substance of Very High Concern on the Basis of the Criteria Set Out in Reach Article 57. Pg. 34. 7e0e4a95-b942-350e-ba7d-7cf7aa652ab8 (europa.eu).

[17] Ibid. Pg. 6-8.

[18] Zhu, H., Kannan, K. (2019). Melamine and cyanuric acid in foodstuffs from the United States and their implications for human exposure. *Environ Int.* Doi: 10.1016/j.envint.2019.104950.

[19] Müller, S.(2022). Melamine Cups: Migration of Unwanted Chemicals.Danish Consumer Council Think Chemicals.

[20] Wu, C., et al. (2013). A crossover study of noodle soup consumption in melamine bowls and total melamine excretion in urine. *JAMA Internal Medicine*: 1-2.

[21] German Competent Authorities. August 2022. Annex XV Report: Proposal for identification of a substance of Very High Concern on the Basis of the Criteria Set Out in Reach Article 57. Pg. 8. 7e0e4a95-b942-350e-ba7d-7cf7aa652ab8 (europa.eu).

[22] Alhelou R. et al. (2019). Hexamethoxymethylmelamine - A precursor of persistent and mobile contaminants in municipal wastewater and the water cycle. *Water Research.* 165, 114973. DOI: 10.1016/j.watres.2019.114973.

[23] Kolkman A.et al. (2021). Assessment of Highly Polar Chemicals in Dutch and Flemish Drinking Water and Its Sources: Presence and Potential Risks. *ACS ES&T Water.* DOI: 10.1021/acsestwater.0c00237

[24] Zhu, H., Kannan, K. 2020. Occurrence and distribution of melamine and its derivatives in surface water, drinking water, precipitation, wastewater, and swimming pool wate. *Environmental Pollution.* (258):113743. DOI: 10.1016/j.envpol.2019.113743.

[25] Zhu, H. and Kannan, K. (2018). Continuing Occurrence of Melamine and Its Derivatives in Infant Formula and Dairy Products from the United States: Implications for Environmental Sources. *Environ. Sci. Technol. Lett.* 2018, 5, 11, 641–648. Doi: 10.1021/acs.estlett.8b00515.

[26] Zhu, H. and Kannan, K. (2019). Occurrence of Melamine and Its Derivatives in Breast Milk from the United States and Its Implications for Exposure in Infants. *Environ. Sci. Technol.* 53(13): 7859–7865. DOI: 10.1021/acs.est.9b02040.

[27] Melough, M. M., et al. (2021). Dietary Sources of Melamine Exposure among US Children and Adults in the National Health and Nutrition Examination Survey 2003–2004. *Nutrients.* DOI: 10.3390/nu12123844.

[28] Melough, M. et al.(2022). Associations of Dietary Intake with Urinary Melamine and Derivative Concentrations among Children in the GAPPS Cohort.*Int. J. Environ. Res. Public Health*. *19*(9), 4964; Doi: 10.3390/ijerph19094964.

[29] German Competent Authorities. August 2022. Annex XV Report: Proposal for identification of a substance of Very High Concern on the Basis of the Criteria Set Out in Reach Article 57. Pg. 9. 7e0e4a95-b942-350e-ba7d-7cf7aa652ab8 (europa.eu).

[30] Zheng, G. and Kannan, K. (2020). Are Melamine and Its Derivatives the Alternatives for Per- and Polyfluoroalkyl Substance (PFAS) Fabric Treatments in Infant Clothes? *Environ. Sci. Technol.* 54, 16, 10207–10216. Doi: 10.1021/acs.est.0c03035.

[31] Zhu, H. and Kannan, K. (2018). Distribution Profiles of Melamine and Its Derivatives in Indoor Dust from 12 Countries and the Implications for Human Exposure. *Environ. Sci. Technol.* (52):21, 12801–12808. Doi: 10.1021/acs.est.8b04154.