**Committee for Risk Assessment**

**RAC**

Annex 2

# Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

# Melamine

**EC Number: 203-615-4**
**CAS Number: 108-78-1**

CLH-O-0000006932-69-01/F

**Adopted**

**10 December 2020**

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON MELAMINE**

**COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION**

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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**Substance name: 1,3,5-triazine-2,4,6-triamine; melamine**
**EC number: 203-615-4**
**CAS number: 108-78-1**
**Dossier submitter: Germany**

**GENERAL COMMENTS**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Germany | Pfleiderer Deutschland GmbH | Company-Downstream user | 1 |
| Comment received | | | | |
| Melamine is one of the most important substances which are necessary for the production of wood based panels (WBP). Beside formaldehyde and urea it is one of the essential substanc-es to produce glues or resins for the production of raw boards as well as decorative boards.<br>Normally for the production of raw boards the glues are consisting of urea-formaldehyde poly-condensates but in the meantime polycondensates also using melamine are getting more and more important (MUF glues). The reason is that melamine is a very reactive molecule, building very easily polymers with formaldehyde which are much more stable against hydrolysis than polymers consisting only of urea and formaldehyde. So by adding melamine very low emitting boards can be produced.<br><br>This is exactly the reason why for decorative laminates only melamine-formaldehyde resins are used at least in the last impregnation step because of course such decorative laminates have to be very hygienic and resistant against the requirements of daily life (e.g. coming into contact with food).<br><br>Because of the fact that melamine is very reactive, the concentration of free melamine which is completely unbounded is very low in the final articles and if unbounded melamine is present in traces it can be regarded as impurity.<br><br>In our company we have two glue/resin plants where we are using pure melamine since dec-ades of years. Melamine is handled in closed systems so there is no direct contact between the worker and melamine. Measurement of worker exposure with respect to dust/melamine are therefore showing results close to the detection limit. Also the reactors in which melamine is mixed together with urea and formaldehyde or only with formaldehyde are closed systems. Only for some procedures regarding quality assurance the worker can come into direct contact with the resin. In this moment the worker is | | | | |

obliged to wear gloves, so no contact to skin is possible.

After this production process of glues/resins the free melamine is bounded and so in the further processing steps (impregnation/gluing) a completely new chemical substance (MF/MUF res-in/glue) is used.
In our company we never had health effects of the workers in our plants regarding melamine.

So the conclusion is that free melamine can only be found in a very small part of the whole production process of WBP and this part is at the very first beginning (the production of res-in/glue).
All further steps of the process (impregnation of paper with resin, gluing of wood, production of raw boards in continuous presses or decorative laminated boards in short cycle presses) are using melamine which is completely polycondensated and no more unbounded.

It is very difficult to say how much unbounded melamine is included in the matrix even if it is clear that, if at all, it must be in very small traces.
The reason for the problem with the analysis of unbounded melamine is that it is insoluble in water and other liquids so if you want to analyse it you must treat it with acids or something else with the consequence that the matrix will be destroyed and therefore the analysis is result-ing in higher amounts of free melamine and so overestimating the real concentration.

Regarding the final article there is a European law which is applicable for plastics coming into contact with food and so it is also applicable for decorative WBP. In this European law it is de-scribed how you have to measure the migration of certain substances out of the matrix and there are limit values which have to be fulfilled. We have uploaded such a certificate of compli-ance regarding our products showing that this European law is fulfilled. You can also find the test report showing that no melamine can be found in this migration test.

So the conclusion is that in the WBP industry melamine is used not as unbounded melamine but in a resin and so it is handled in a safe manner regarding workers and consumers.

The CHL proposal for melamine would not result in more safety for the health of workers and consumers but it would result in perhaps dramatic unintended consequences.
According European law there would be the consequence that if melamine is exceeding 1 % in a mixture (not an article) this mixture would have to be labelled in a complete different way.

What would it mean concretely for the WBP Industry?

During the production of WBP along the described process steps we have different mixtures containing melamine which are generated as waste in the production process.
We have waste of resin, impregnated paper and the waste from processing steps of the final product (dust from cutting, sawing, broken boards, cutting the edges in the short cycle presses …) which would have to be classified as dangerous waste it the content of melamine would exceed 1 %.
As described above the analysis of unbounded melamine is very complicated and if analyses are made the result would probably overestimate the content.

So all this waste would have to be classified as dangerous waste and would have to be

dis-posed with additional enormous costs compared to today.
At the moment this waste can be burned in the own incinerators but this would be no more possible if the waste would be classified as dangerous waste. Further consequences would be that the furniture industry cannot burn the waste from processing the boards in their own incin-erators.
Biomass as a fuel would have to be substituted by fossil energy.

Additionally the recycling of decorative boards or low emitting raw boards would be no more possible because probably the content of free melamine can exceed 1 %. This is completely in contradiction to the European principle of cascade.

Another unintended consequence would be the image of the WBP industry. Customers are not willing to distinguish between melamine and melamine in a polymer. Customers do not want to have carcinogenic substances in the product and therefore there is a huge risk for loss of mar-ket. Of course it can be shown by the mentioned test reports that there is no problem at all for the consumer, but nevertheless the consumer is understanding that a WBP is using a carcino-genic substance in the top of the decorative board which is coming in close contact with food, children …

We have to conclude that the risks of unintended negative consequences of the CHL proposal are much higher than any benefits.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ISEGA Unbedenklichkeitserklärung Pfleiderer.pdf

Dossier Submitter's Response

**RESPONSE #1**

The DS appreciates the comments and acknowledges that it may be difficult for consumers to distinguish between pure melamine and melamine in a polymer. The DS also acknowledges the concern of unintended negative consequences. However, as the protection of human health is a priority, an assessment of potentially harmful substances is important to draw conclusions regarding safe use of chemicals and to provide hazard communication information to those who handle the substance/mixture or those who are exposed to it. As a first step, an evaluation of potential hazardous properties needs to be done.

It is important to stress, however, that CLP is hazard-based and does not take exposure into consideration in arriving at a classification as stated in ECHA's Guidance on the Application of the CLP Criteria (1.1.3). Hence, classification under CLP is exclusively based on hazardous properties of a given substance. Exposure considerations are important elements, which, however, come into play in a subsequent step of risk assessment.
To clarify this further, the Court of Justice of the European Union (Fourth Chamber) did confirm, as part of the judicial decision in the case C-15/10 (Borate substances – Classification as reprotoxic substances in category 2), that, *"an assessment of the hazards linked to the substances' intrinsic properties must not be limited in light of specific circumstances of use, as in the case of a risk assessment, and may be properly carried out regardless of the place where the substance is used, the route by which contact with the substance might arise (by ingestion, by inhalation or by dermal penetration) and the possible levels of exposure to the substance."*
[http://curia.europa.eu/juris/liste.jsf?language=en&num=C-15/10].

For information only, as notified by the Germany Federal Institute for Risk Assessment and others, the use of melamine-containing products gives rise to human exposure [https://www.bfr.bund.de/cm/349/fillable-articles-made-from-melamine-formaldehyde-resin.pdf].

RAC's response

Thank you for your comment. As noted by the dossier submitter, hazard classification does not take into account exposure. Moreover, consideration of the economic impact of a proposed classification for a substance is not within the scope of RAC.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Poland | Grupa Azoty Zakłady Azotowe Puławy S.A. | Company-Manufacturer | 2 |

Comment received

Melamine milk adulteration incident
As an introductory point, Grupa Azoty Zakłady Azotowe Puławy S.A. (ZAP) believes that an unwarranted focus has been given to the old incident involving illegal addition of melamine to powdered milk in China 10 years ago, which has tainted the reputation of melamine and indirectly affected its treatment under EU regulatory system and the CLP system. That crisis received a lot of publicity at the time and has highlighted the worldwide need to improve food quality detection standards for chemical contaminants in foods and efficient exchange of information on international level. However, that crisis should not have affected the classification of melamine under the EU CLP Regulation, when used as intended.
The scandal mostly concerned infants as they are particularly at risk of developing adverse health effects due to consuming melamine tainted milk as their major food. The amount of melamine intake per body weight is much higher than that of adults who consume a variety of foods. For comparison, the human data available in the aftermath of the incident is based on estimated exposure of infants in China to adulterated infant formula that ranged, at median levels of the most affected brand, from 8.6 to 23.4 mg/kg body weight per day. These levels are about 40–120 times the TDI and explain the dramatic health outcomes. (1)

The criminal character of the milk contamination, the young age of the population affected, the wide array of globally distributed contaminated products, led this event to take on exaggerated proportions in the public relations and communications sphere. This incident illustrated the complexity of international trade of food products and food ingredients that required both immediate and continuous actions at international level (as reported to WHO/Food and Agricultural Organization International Food Safety Authorities Network INFOSAN or published on particular country official government web site, 47 countries received melamine-contaminated products).
However, today the world is not the same anymore after 2008 milk crisis. The countries responded through a wide range of actions taking both regulatory and protective steps. Such measures were taken by China, and other countries as well, such as India or the EU. In June 2009, China promulgated Food Safety Law, which prohibits any use of unauthorized food additives. It also established a high-profile central commission to improve inter-state coordination and enforcement of food safety regulation at the national level. In order to consolidate authorities in food and drug safety in March 2013, China Food and Drug Administration (CFDA) was set up as a ministry-level agency. In 2019 China has tightened rules for the sale of overseas infant formula into the country and set a target to be 60 per cent self-sufficient in three years. Chinese National Development

and Reform Commission wanted China to better meet growing demand for infant formula and to improve consumer confidence in the Chinese product. It said a quality and safety traceability platform would be built. China would also inspect formula manufacturing companies in an effort to crack down on illegal adding of non-edible materials, overuse of food additives and tampering with food labels, Chinese media reported. A registration-based management on overseas baby formula manufacturing enterprises would be strengthened to ensure the safety of imported baby formula.(2)
India banned the importation of dairy products from China in 2008. On 6th June 2019, the Indian government further extended the last ban on import of milk and its products, including chocolates from China in light of the need of procedures review. The decision was taken on the recommendation of the FSSAI, the Food Safety and Standard Authority of India. According to the India Directorate General of Foreign Trade (DGFT): "Prohibition on import of milk, milk products (including chocolates, chocolate products, candies/confectionary/food preparations with milk or milk solids as an ingredient) from China is extended until the capacity of all laboratories at ports of entry have been suitably upgraded for testing melamine". Although India does not import milk, milk products from China, it has imposed the ban as a preventive measure.(3)
In 2009, the proficiency testing program was conducted at an international level by the Institute of Materials and Reference Measurements at the European Commission (EC-JRC-IRMM) in Geel, Belgium when milk powder samples were analysed for the presence of melamine. The program covered 114 laboratories - among participants there were 31 countries from around the world, including Canada, Australia, India, New Zealand, USA, China, and 21 countries belonging to the European Union. The cyclical proficiency testing is of predominant importance.

In order to avoid adverse health effects appropriate exposure limits have been established:
- a limit value of exposure for consumers (TDI) of 0.5 mg per kg of body weight per day for melamine to protect consumers health has been set in Europe by European Food Safety Authority (EFSA);
- maximum levels in food – A maximum melamine level of 1 mg/kg for powdered infant formula, a maximum limit of 0.15 mg/kg for melamine in liquid infant milk and 2.5 mg/kg for other foods and animal feed has been set in General Standard for Contaminants and Toxins in Food and Feed (Codex Stan 193-1995, version last revised in 2015,p.58);
- migration limits from polymers to food - The release of melamine substance from these articles is regulated by EU Regulation 10/2011 in which a Specific Migration Limit (SML) for melamine of 2.5 mg/kg food is set (Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food, Official Journal of the European Union, L 12, 15.1.2011, p. 1–89).

Surely still all the parties involved in the food-production chain (both food producers and authorities) are tracking and prevent similar melamine food contamination events leading to possible human health impact.
All the measures adopted (both conventional and innovative detection and measurement methods) elaborated on the international level make the repeat of the analogous scandal not possible. Incidents of a similar dimension have not happened since the 2008 scandal. Taking into account the above, it is more likely that another inexpensive nitrogen-rich adulterant will be chosen to evade detection.

Reasonably expected use vs. criminal use

Moreover, article 9(5) of CLP stipulates that "for the purposes of classification, the manufacturers, … shall consider the forms or physical states in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used".

(4)
ECHA Guidance, Section 1.2.2.states that "reasonably expected use of a substance or mixture" includes "all professional and non-professional uses including reasonably foreseeable accidental exposure, but not abuse such as criminal or suicidal uses".(5)
As abuse is outside the scope of CLP, classification should not take into account criminal use of the substance.
With the above in mind, ZAP believes that it is unjustified to analyze melamine's potential carcinogenicity in light of the Chinese milk incident. That was a criminal and evil act where melamine was used in contravention of its intended and even remotely predictable use, violating all principles of law, common sense and basic human decency. Such an act cannot be attributed to the entire industry and affect a classification of a product that is simply not meant nor used for consumption. This is confirmed not only by common sense, but also by EU law (CLP Regulation and ECHA Guidance).

Scope of limited melamine "widespread use"

The industry produces melamine in specially designed and operated closed systems. It is sold as a commodity chemical. ZAP – or any other known melamine producer- do not sell melamine for food or feed purposes.

It is important to note that the word "melamine" is used both for the chemical compound melamine and the plastic made from this compound. This confusion may lead to erroneous exposure concept, as the use of both products named "melamine" have different properties.

In fact, 95 % of melamine is further transformed. It is chemically converted by industry actors into a new substance at industrial sites. The substance melamine itself does not become part of articles, but it is converted to form melamine-resin is (e.g. laminates, wood adhesives, coating resins and moulding compounds).
Approximately 5% of the production volume of melamine is used directly as an additive i.e. in intumescent coatings and (Polyurethane) foams. Melamine in these products is embedded in a matrix (constrained) and is not released during its service life.

Given the above, "Widespread uses by professional workers" described by REACH can refer to approximately 5% (according to available data) of the melamine volume produced.

Company internal experience

Melamine has been produced by Grupa Azoty Zakłady Azotowe Puławy S.A. since 1977 (over 42 years). Some employees may have been exposed to melamine dust for 40 hours a week for over 20 years. During this long time, there have been no cases of occupational disease or carcinogenicity among workers exposed to melamine. Therefore, ZAP practical experience shows that melamine does not increase the probability of cancer, even among persons exposed to it much more than an average user of melamine products.

CLH Report studies reliability

According to article 13 point (4) of REACH Regulation (UE no 1907/2006):
"Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable".

According to point (31) of preamble of CLP (UE no 1272/2008) Regulation:
"If tests are performed, they should comply where appropriate with the relevant requirements for the protection of laboratory animals, set out in Directive 86/609/EEC, and, in the case of ecotoxicological and toxicological tests, good laboratory practice, set out in Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests on chemical substances".
Based on the analysis of the key studies listed as reliable in CLH report, below are the examples of tests that are non-compliant with Good Laboratory Practice standards:
1. Ogasawara et al., 1995 test should not be considered reliable - deviations to OECD TG 451: reduced exposure time, only males, reduced number of animals, limited number of tissues examined (focused exclusively on urinary system) - no GLP standard.
2. Okumura et al., 1992 test also should not be considered reliable - deviations to OECD TG 451: reduced exposure time, only males, reduced number of animals, limited number of tissues examined (focused exclusively on urinary system), description of experimental procedures less detailed - no GLP standard.
The above confirms that the reliability of the studies used in the CLH report is not sufficient to be used in the melamine evaluation.

References:
1.The Melamine Incident: Implications for International Food and Feed Safety, Céline Marie-Elise Gossner,* Jørgen Schlundt, Peter Ben Embarek, Susan Hird, Danilo Lo-Fo-Wong, Jose Javier Ocampo Beltran, Keng Ngee Teoh, and Angelika Tritscher; World Health Organization, Department of Food Safety and Zoonoses, Geneva, Switzerland; Environmental Health Perspectives, December 2009
2.https://www.farmonline.com.au/story/6201044/china-tightens-formula-rules/
3.https://economictimes.indiatimes.com/news/economy/foreign-trade/govt-extends-ban-on-import-of-milk-products-from-china/articleshow/69013338.cms
4. Regulation (EC) no 1272/2008 of the European Parliament and of the council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
5. Guidance on the Application of the CLP Criteria, Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, ECHA, July 2017

ECHA note – An attachment was submitted with the comment above. Refer to public attachment GA Puławy position on Melamine Classification_Feb 6th 2020_non-confidential.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment GA Puławy position on Melamine Classification_Feb 6th 2020.pdf

Dossier Submitter's Response

**RESPONSE #2**

The DS appreciates the comments raised by the organisation with the following response to the main points.

**(1) Unwarranted focus given to the melamine milk adulteration incident**

It cannot be emphasised strongly enough that the current proposal allocating melamine in Category 2 of the hazard class carcinogenicity is primarily based on sufficient evidence of carcinogenicity in experimental animals.
The commonly accepted association between melamine exposure and urolithiasis in humans as unprecedentedly revealed during the milk adulteration incident 2008 in China provides sufficient evidence indicating relevance to human carcinogenicity. Given that these data constitute valuable evidence regarding the effects of melamine in humans, they cannot be ignored and have to be considered in the discussion (CLH dossier, section 10.11.2, page 126): *"The large body of data derived from the melamine adulteration incident as a whole can be considered reliable and good quality evidence for the following reasons: (a) high level of consistency regarding the reported outcomes (calculi mostly in the renal pelvis/calyx, nephrotoxicity, melamine stones composed of melamine and uric acid clearly distinguishable from common calcium-oxalate calculi), (b) the existence of a dose-response relationship, albeit not quantitative (prevalence of urolithiasis depending on exposure level), (c) conformity with experimental animal data, (d) the specificity of the nature of adverse health effects (mode of action; see 10.8.2, section (k) ), (d) the biological plausibility based on observations in experimental animals, (e) no significant confounding factor could be identified.".*
As described in detail in section 10.8.2 (k) *"mode of action and its relevance for humans"*, the available data derived from the melamine adulteration incident together with additional epidemiological information can be considered strong evidence for a consistent mode of action in experimental animals and humans. Thus, urinary tract cancer as a consequence of melamine-mediated urolithiasis should be considered relevant to humans.

As stipulated in section 3.6.1.1 of the CLP Regulation (EC) No 1272/2008, *"Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans."*. The DS wants to emphasise that in case of melamine, strong evidence that the mechanism of tumour formation is not relevant for humans does not exist. It is rather all to the contrary as set out in the CLH dossier.

**(2) Reasonably expected use vs. criminal use**

Article 9(5) of CLP indeed stipulates that information used to determine health hazards shall be related *"to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used."* Melamine is produced as a powdery/particulate solid. The available hazard information from experimental animals and human experience had been generated following oral administration of solid melamine powder, either added to the diet of experimental animal or to milk and powdered infant formula.

Furthermore, ECHA's Guidance on the Application of the CLP Criteria (1.2.2) states:
*"Reasonably expected use summarises all physical forms and states of a substance or mixture that may occur during intended use or reasonably foreseeable conditions of misuse.*
*Reasonably expected use of a substance or mixture is as follows:*

- *Any process, including production, handling, maintenance, storage, transport or disposal.*
- *All technical operations/manufacturing activities like e.g. spraying, filing, and sawing.*
- *Any putative consumer contact through e.g. do-it-yourself or household chemicals.*
- *All professional and non-professional uses including reasonably foreseeable accidental exposure, but not abuse such as criminal or suicidal uses."*

It is our understanding that this section also refers to the physical form/state of the chemical that shall relate to both, reasonably expected uses and hazard information for the purpose of classification. Data from accidents, intoxications or criminal intents can be used for hazard assessment, if available. Only data generated with physical forms and states which can be excluded to be/come on the market and which are therefore not related to any possible or reasonably expected use may not be relevant for classification purposes. In addition, while adding melamine powder to milk/infant formula was clearly an act of criminal intent, unknowingly feeding children with adulterated products does not fall into this category.

As mentioned in RESPONSE #1, the Court of Justice of the European Union confirmed that an assessment of hazardous properties of a *substance "must not be limited in light of specific circumstances of use"* (case C-15/10).

**(3) Company internal experience**

The DS would appreciate if the organisation could provide scientifically sound data to support their claims. It should be noted, though, that according to a Court of Justice of the European Union decision, an assessment of hazardous properties of a substance *"may be properly carried out regardless of the…, route by which contact with the substance might arise (by ingestion, by inhalation or by dermal penetration)"*. Hence, even if melamine exposure may not pose a health hazard risk by inhalation, e.g. due to risk management measures at the workplace, classification (without the indication of the route) on the basis of oral data is still warranted.

**(4) CLH report studies reliability**

As described in section 10.8.1, four key studies have been identified for the purpose of classification. While the NTP study and the study by Hazleton (1983) were performed in accordance with accepted scientific principles with minor deviations from OECD TG 451, the DS acknowledges that the studies by Okumura (1992) and Ogasawara (1995) are of lower quality with regard to a comprehensive evaluation of potential carcinogenic effects in the entire organism in both sexes. Yet, with respect to melamine-induced tumour formation in the urinary tract of male rats, the information provided by these two studies is considered reliable and acceptable key information given that the observed effects are highly consistent with the NTP study. As listed in Table 15 of the CLH dossier (section 10.8.1, page 42), a dose-response relationship can be established based on the results of the four key studies, again, only for melamine-related effects in the urinary tract system. In light of the high consistency of the data concerning carcinogenic effects in the urinary tract attributed to melamine exposure in male rats across the available studies, discounting the results of the two studies by Okumura (1992) and Ogasawara (1995) is unjustified.
Both studies had also been considered in assessments by WHO and IARC. It is worth noting, that according to the strength of evidence analysis in section 10.8.2 of the CLH dossier, classification in Category 1B may be warranted. However, the DS suggests to allocate melamine into Category 2, suspected human carcinogens.

The DS would also like to refer to response #7, bullet point (3) and (4).

RAC's response

Thank you for your comment

(1) Unwarranted focus given to the melamine milk adulteration incident

As commented by the DS, the human data are only used to provide evidence that the relevance of the mode of action of tumours induction in human cannot be excluded.

(2) Reasonably expected use vs. criminal use

RAC agrees that according to the ECHA guidance document, criminal use should not be considered as "reasonably expected use". Nevertheless, data available from human accidental exposure may still provide insight on the relevance to human of effects observed in experimental animals.

(3) Widespear use and company internal experience

RAC takes note of the use of the substance. RAC considers that company internal experience, not substanciated by data, cannot be used for classification purposes.

(4) CLH report studies reliability

The reliability of Ogasawara *et al*., 1995 and Okumura *et al*., 1992 are discussed in the RAC opinion. The limitations highlighted compared to OECD TG were taken into account (e.g. lower study duration, number of animals). Moreover, RAC agrees that the top dose may have exceeded the MTD. Nevertheless, RAC agrees with the dossier submitter that the two studies provide reliable evidence of the carcinogenic potential of the substance in the urinary tract system in male rats.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | United Kingdom | | Individual | 3 |

Comment received

Our company manufactures globally thermoset composite materials for use in fire retardant applications for the protection of life in aircraft, trains, marine and civil structures. The melamine is incorporated into a polymer "matrix" which undergoes a non-reversible chemical reaction to form a hardened and bound composite plastic material and therefore the exposure to melamine is limited throughout the lifecycle of the product. We wish to state that we agree with the classification comments submitted by the EMPA (European Melamine Producers Association) and feel that the scientific evidence submitted does not justify the harmonised classification proposed.

To date after over 10 years of detailed research and development in to hundreds of different fire retardant materials we have been unsuccessful in obtaining a material that can out-perform the fire retardant properties of melamine. We believe that the benefit of a good fire retardant material is of more importance in the safeguarding and protection of human life and property than the unfounded evidence that the proposed harmonised classification of melamine poses.

Our uses include the incorporation of melamine into a solid material and although we do not agree with the harmonised classification proposal, any specification to the route of exposure would provide an additional level of detail to downstream users about the hazards present, where the use of melamine is unavoidable.

Further to the classification issues of incorporating melamine into a solid product, the presence of a carcinogenic material within a manufactured article may have adverse consequences with regards to end of life processing (recycling, repurposing, disposal) and may impede any efforts towards a circular economy product. As given in the Waste Framework Directive 2008/98/EC, (Annex III, HP7), the presence of a carcinogenic material in a waste object, classifies the article as hazardous waste.

| Dossier Submitter's Response |
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| **Response #3**<br><br>The DS appreciates the comments and acknowledges the concern of unintended negative consequences. However, as the protection of human health is a priority, an assessment of potentially harmful substances is important to draw conclusions regarding safe use of chemicals and to provide hazard communication information to those who handle the substance/mixture or those who are exposed to it. As a first step, an evaluation of potential hazardous properties needs to be done. |
| RAC's response |
| Thank you for your comment. Consideration of the economic impact of a proposed classification for a substance is not within the scope of RAC. Regards to EMPA comments, please see response to comment number 7. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Netherlands | Hexion | Company-Downstream user | 4 |
| Comment received | | | | |
| • There is only 1 notable study with strong evidence of carcinogenic activity, reported tumors in male rats. This is not 'sufficient evidence' according to the criteria of CLP to classify as carcinogen.<br>• Studies show that formation of calculi in humans poses a toxicity issue at high doses, but does not pose a carcinogenic risk to humans.<br>• Inhalation of particulate (dust) containing melamine is likely the most common exposure scenario<br>• At Hexion stringent procedural and process control technologies are applied that minimize emissions and any resulting exposure to Melamine particulate. | | | | |
| Dossier Submitter's Response | | | | |
| **Response #4**<br><br>The DS appreciates the comments and would like to refer to responses #1 and #2 regarding comments raised on exposure and uses. CLP is hazard-based and does not take exposure into consideration.<br><br>As comprehensively described within the CLH dossier, data from experimental animals together with human evidence indicate a similar mode of action in humans, justifying classification in the hazard class carcinogenicity (CLH dossier, section 10.8.2 and 10.8.3). | | | | |
| RAC's response | | | | |
| Thank you for your comment. As noted by the DS, hazard classification is not based on exposure.<br>RAC considers that based on the evidence in three relevant studies (NTP, 1983; Ogasawara *et al*., 1995 and okumura *et al*., 1992), there is sufficient evidence for carcinogenicity in male rats study and strong evidence of carcinogenic activity, reported tumors in male rats. Additional factors are considered by RAC such as human relevance. The formation of calculi in humans has been associated with melamine accidental exposure. RAC agrees that there are uncertainties whether melamine can induce caluli following low dose exposure. Nevertheless, human data provides evidence that the relevance to human of the MoA for tumour induction (through the formation of caluli) cannot be disregarded. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Norway | <confidential> | Company-Importer | 5 |

Comment received

We have given our input on uses and exposure via the European Melamine Producers Association (EMPA). Our use and exposure are included in the EMEA response to this public consultation, attachment 2: "Questionnaire for the Manufacture and Use of Melamine".

We are supporting the scientific comments given by EMPA and we do not agree with the BAuA proposal for classification as a Category 2 carcinogen and a STOT1 RE (substance with a 'Specific Target Organ Toxicity 1 Repeated Exposure'). We support no classification for mutagenicity.

Our company is a registrant, and act as importer and downstream user of melamine [CAS 108-78-1]. 100% of our melamine is used for manufacture of resins, were melamine acts as monomer in polymers. The major applications for our resins are wood based panels and engineered wood constructions, were specific durability is required. Other applications are paper impregnation for surfacing and wood fiber flooring. In all cases the resins are cured and incorporated into articles during the downstream use, at industrial sites.

Levels of free melamine in resins for various applications have been shared with EMEA (EMEA response to this public consultation, Attachment 2). Our input is part of their study. There are analytical methods available to determine the free melamine in resins. If the new classification (CARC 2 and STOT 1 RE) will apply, the resin industry will be focused on determining free melamine in intermediate products for labelling purposes. Please note that this will not be relevant for the glued articles placed on the market.

The CLP classification proposed by BAuA will have no impact on, nor be relevant for glued articles.

We understand that articles such as tableware, table tops etc. are commonly referred to under the tradename "melamine", but these articles are not made of the substance melamine and this use should not be considered as widespread use of melamine.

We do not understand how it can be justified that ingestion is the major exposure route for melamine.

The major consumption of melamine occurs under industrial conditions. During industrial resin production the melamine powder is handled via closed systems (no exposure) or bag handling where limited contact with dust can occur. Prevention of dust exposure by inhalation is standard procedure in our industry, not only for classified powders.

Dossier Submitter's Response

**Response #5**

The DS appreciates the comments and would like to refer to response #1 and #2 regarding the comments raised on exposure and uses.

RAC's response

Thank you for your comment. Regards to EMPA comments, please see response to comment number 7. Please note that hazard classification is not based on exposure.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Netherlands | OCI Nitrogen | Company-Manufacturer | 6 |

Comment received

The CLH proposal gives incorrect weight to the studies cited and ignores studies provided

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020 01 22 OCIN response to CLH proposal of Melamine FINAL.pdf

Dossier Submitter's Response

**Response #6**

The DS appreciates the comments raised by the organisation with the following response to the main points.

**(1) The CLH proposal gives incorrect weight to the studies cited and ignores studies provided.**

The DS would like to refer to response #2, bullet point (4).

In addition, the organisation mentions recent publications by Cohen and Swaen (Cohen 2018A, Cohen 2018B, Cohen 2019, Swaen 2019) that had not been cited in the CLH dossier. These review papers describe the views and opinions of the corresponding authors. To our best knowledge, however, they do not contain new and relevant data that had not been considered within the CLH dossier. In the conflict of interest section of one publication (Screening for human urinary bladder carcinogens: two-year bioassay is unnecessary. Toxicology Research, 2018), the sole author S.M Cohen declares funding from industry sources and consulting activities for "*various companies, including ones that have had chemicals that produce urothelial changes in rodents."*

**(2) Bladder cancer found in male rats is related to the presence of persistent particles in the bladder and not to the exposure to melamine and (3) Melamine has no intrinsic properties to cause cancer.**

The DS acknowledges the comment raised by the organisation but would respectfully like to disagree with this statement. Forming crystals/calculi in the urinary tract system is considered the mode of action by which melamine confers its intrinsic hazardous property. Available experimental data show that melamine is rapidly absorbed and excreted, forming particles in the urinary tract system.
It is therefore important to stress that unlike substances such as sodium saccharin or sodium ascorbate, melamine induces urolithiasis in both, experimental animals and humans. This is one of the reasons as to why the DS considers the established mode of action in animals relevant to humans. The DS would like to draw attention to section 10.8.2 of the CLH dossier, especially point (a) (tumour type and background incidence).

RAC's response

Thank you for your comment.

(1) RAC takes note of the review papers of Swaen *et al*., 2019, Cohen *et al*., 2018a and Cohen *et al*., 2018b and the position paper from Cohen, 2019.

Cohen *et al*., 2018 review was related to risk assessment and screening of potential urinary bladder carcinogens. For substances acting like melamine it was stated that "*the risk assessment for such chemicals as melamine is not related to its carcinogenicity in the animal model, but to the actual toxicity of the formation of calculi, which can occur in*

*humans. Thus, if urinary solids formation is the mode of action concluded for a particular chemical, the risk assessment is related to the toxicity of urinary solid formation, not to carcinogenicity*". RAC acknowledges that urinary solid formation is a key step in the proposed MoA for tumour induction. The review of Swaen *et al*., 2019 was also mainly focused on risk assessment and considered that none of the available studies provide evidence of increased urolithiasis below the TDI of 0.2 mg/kg. RAC agrees that the available data on melamine do not allow to set the threshold for uroliths formation due to the uncertainties on exposure and more particularly at low dose exposure in the available studies.

In Cohen *et al*., 2018b and Cohen 2019 (attachment 1), potential quantitative differences between human and rodents were discussed (differences in anatomy, lack of persistence of calculi). According to Cohen *et al*., 2018b, an increased risk of developing urothelial tumours would only appear in humans with diverticuli or neurogenic disorders. The increased risk would be due bacterial cystisis which would not be relevant to human. RAC notes that, as stated by the DS, in other publications, increased risk of urinary tract cancer was also seen in absence of urinary tract infection (page 53 of the CLH dossier). The authors also considered that the same type of toxicity would be produced in response to calculi in rats and human (urothelial irriation, proliferation and regenerative proliferation leading to potential renal consequences such as acute pyelonephritis, hydronephrosis and chronic pyelonephritis). RAC agrees that the same type of response to calculi is expected in rats and human, but also quantitative differences are noted. Nevertheless, RAC also considers that the MoA identified in rats for tumour induction could be relevant to human.

Overall, RAC agrees with the DS that there are no information in these publications that were not addressed by the DS in the CLH dossier.

(2)RAC agrees with the DS's response.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 04.02.2020 | Belgium | The European Melamine Producers Association (EMPA) a Sector Group of Cefic and the Melamine Reach Consortium of REACH Centrum | Industry or trade association | 7 |

Comment received

EMPA is of the opinion that no classification as a carcinogen or for STOT RE is required according to the CLP regulation and ECHA Guidance. We agree to the proposed non-classification for mutagenicity in the CLH proposal.
Life cycle - melamine has limited widespread use
In 95% of the produced volume, melamine is chemically converted into a new substance at industrial sites. The substance melamine itself does not become part of articles, but melamine-resin does (e.g. laminates, wood adhesives, coating resins and moulding compounds). The service life stage for articles is therefore not applicable, consequently no 'widespread use of melamine' can be regarded for melamine.
See chapter 2 of the main document Comment to the CLH proposal and Annex 3 and Attachment 2.

Quality of studies used in the CLH proposal and their application for classification
ECHA guidance to MSCAs and manufacturers, importers and downstream users on how to prepare a CLH dossier under the CLP Regulation states that "relevant available information" should be "systematically evaluated". Further, ECHA's supporting guidance on use of weight-of-evidence states that information should be organized "in a structured and organized way" taking into account "the robustness and reliability of the different data sources "and article 3.6.2.2.1 of Annex I of CLP states that only reliable and adequate study results should be used in the classification process. We find that contrary to these requirements the CLH dossier contains 1) significant weaknesses in assigning key studies; 2) lower reliability studies are given more weight than higher reliability studies; 3) available, relevant high-reliability studies were not included; 4) that there exists alternative, more plausible, explanations for the findings relied upon and that these have led as consequence to deficiencies in the overall CLH process. On the basis of the broader literature and following strict application of the standards outlines in ECHA's and EUCOM/SCHEER's guidance on the use of weight-of-evidence we conclude that there is insufficient evidence to justify classification of melamine with respect to Carcinogenicity or STOT RE.
See chapter 3 of the main document Comment to the CLH proposal and Annex 1

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to the CLH-proposal on Melamine.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Comment to the CLH-proposal on Melamine- Attachment 2.pdf

Dossier Submitter's Response

**Response #7**

The DS appreciates the comments raised by the organisation with the following response to the main points.

**(1) No widespread use of melamine**

The DS would like to refer to responses #1 and #2 (The Court of Justice of the European Union (Fourth Chamber) confirmed that an assessment of hazardous properties of a substance *"must not be limited in light of specific circumstances of use"* (case C-15/10)).

**(2) Significant weaknesses in assigning key studies**

The DS would like to refer to response #2, bullet point (4).

It is worth noting, that according to the strength of evidence analysis in section 10.8.2 of the CLH dossier, classification in Category 1B may be justified. However, the DS suggests allocating melamine into Category 2, suspected human carcinogens.

**(3) Quality of the studies**

As mentioned above and in the CLH dossier, the DS acknowledges a lower quality of the studies by Okumura (1992) and Ogasawara (1995) as compared to the respective guideline and to the other two key studies (NTP and Hazleton). Deviations to the respective guideline are indicated within the CLH dossier. Yet, with respect to melamine-induced tumour formation in the urinary tract of male rats, the information provided by these two studies is considered reliable and acceptable key information given that the observed effects are highly consistent with the NTP study. As listed in Table 15 of the CLH dossier (section 10.8.1, page 42), a dose-response relationship can be established based

on the results of the four key studies, again, only for melamine-related effects in the urinary tract system. In light of the high consistency of the data concerning carcinogenic effects in the urinary tract attributed to melamine exposure in male rats, discounting the results of the two studies by Okumura (1992) and Ogasawara (1995) is unjustified. It is the opinion of the DS that the concerns raised regarding the quality of both studies by the organisation (putative confounding toxicity [see bullet point (11)], inconsistencies regarding the urinary volume and the water consumption, number of animals in the control group) are not substantial to devaluate the obtained results.
Both studies had also been considered in assessments by WHO and IARC. It is worth noting, that according to the strength of evidence analysis in section 10.8.2 of the CLH dossier, classification in Category 1B may be justified. However, the DS suggests allocating melamine into Category 2, suspected human carcinogens.

Limitations regarding the quality of supporting studies are indicated in the CLH dossier. For instance, with respect to the study results provided by Cremonezzi et al. (2001), the text in the CLH dossier reads: *"As the authors do not specifically discriminate between dysplasia and CIS, the epithelial abnormalities are regarded as lesions of uncertain neoplastic potential. In addition, the authors reported having randomly distributed mice and rats of both sexes but do not specify their results according to sex. A sex-specific assessment of the results is, therefore, not possible."*

**(4) Lower reliability studies are given more weight than higher reliability studies**

The DS acknowledges the comment raised by the organisation but would respectfully like to disagree with this statement. According to the strength of evidence analysis in section 10.8.2 of the CLH dossier, information regarding melamine-induced tumour formation in the urinary tract of male rats obtained from three key studies (NTP, 1983; Ogasawara et al., 1995; Okumura et al., 1992) provide sufficient evidence of carcinogenicity. The fourth key study suggests that carcinogenic effects require a certain threshold dose (Hazleton, 1983).

The three supporting studies by Hazleton (1953), Cremonezzi et al. (2004), Cremonezzi et al. (2001) provide limited evidence of carcinogenicity, which, however, is consistent with the effects seen in the key studies. This information, thus, is in support of the outcome of the strength of evidence analysis. However, even without this additional supporting information, classification would have been warranted.

**(5) Available, relevant high-reliability studies were not included**

The DS appreciates the expert opinion by S.M. Cohen but would respectfully like to disagree with the related conclusion given by the organisation that reads as follows: *"In conclusion, Cohen is of the opinion that calculi by themselves (including calculi from precipitates of melamine) are not carcinogenic to the human urinary tract."* The DS would like to stress that the publications written by Cohen represent his expert opinion but do not contain additional sufficient information that had not been considered within the CLH dossier. In contrast, tumour formation in adulthood has been hypothesised for melamine-exposed children by others (Vara Messler et al., 2012; Wen et al., 2016; page 51 of the CLH dossier). Long-term follow-up was suggested to detect early-stage neoplastic events that may arise from melamine exposure in childhood (Puschner and Reimschuessel, 2011; Vara Messler et al., 2012; Wen et al., 2016; page 51 of the CLH dossier).

In Cohen's position paper (2019), he states the following: *"However, regardless of the substance that produces the calculi, there is no carcinogenic risk to humans (2, 15, 19)."* The corresponding references are (2) IARC. Consensus Report. International Agency for Research on Cancer. IARC Scientific Publications, 1999, 147: 1-32.; (15) IARC. Melamine. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 1999, 73:329-338.; (19) Cohen, S. M., Johansson, S. L., Arnold, L. L., Lawson, T. A. Urinary tract calculi and thresholds in carcinogenesis. Food Chem. Toxicol., 2002, 40(6): 793-799. However, both publications by IARC do not support this claim (see bullet point (6)). It is important to differentiate between substances with sufficient evidence that they only produce calculi in experimental animals (e.g. sodium saccharin and sodium ascorbate) and substances that cause calculi formation in experimental animals which cannot be excluded to occur or (in exceptional cases such as melamine where data are available) have been shown to occur in humans. In addition, melamine is a factory-made chemical and cannot be compared with *"essential ingredients in our diet (calcium, magnesium)".*

Overall, it is the opinion of the DS that the expert opinion by Cohen cannot be considered strong evidence that the mechanism of tumour formation is not relevant to humans, as many of his claims are insufficiently supported by scientifically sound data. Regarding species-specificity, for instance, there are no data showing that a melamine-related calculus does not affect the urothelium of the human urinary tract. In contrast, as particularise in the CLH dossier (section 10.11.1, page 120), *"Macroscopic and microscopic haematuria was described (Gao et al., 2011; Guan et al., 2009; Shang et al., 2012; Shen et al., 2011b; Sun et al., 2010a; Yang et al., 2010b; Zou et al., 2013) and may be a result of stone-related urothelial abrasion/irritation (Schulsinger, 2014; Yang et al., 2010b)."* According to a NEJM review paper, long-term consequences of the Chinese adulteration incident are unknown [Ingelfinger J.R. (2008): Melamine and the global implications of food contamination. New England Journal of Medicine 359 (26), 2745-2748.]. Given that up to now, tumour formation related to melamine exposure has not been observed in humans (respective long-term follow-up studies are not yet available) but the mode of carcinogenic action is plausible, the DS suggests allocating melamine into the suspected human carcinogen category (Cat. 2). This is also supported by IARCs re-evaluation in 2019 and the respective upgrade of the hazard category.

The DS would also like to refer to response #6, bullet point (1).

**(6) The mode of action is not relevant for humans**

The DS acknowledges the comment raised by the organisation but would respectfully like to disagree with this statement. As comprehensively described in section 10.8.2 of the CLH dossier, species-independent key events, common to both, rodents and humans exist, indicating possible melamine-induced carcinogenic effects in humans. Species-specific anatomical and physiological differences between rats and humans may influence the susceptibility to calculi-mediated carcinogenic effects. However, this theoretical assumption is insufficiently supported by data and cannot be included with certainty in the assessment. For instance, it had been suggested that rodents retain bladder stones for a long time due to their horizontal body posture, consequently developing chronic irritation. However, ceasing melamine treatment in mice results in rapid calculi discharge, suggesting that the horizontal body posture may not prevent the passing of stones in rodents (Ren et al., 2012; Sun et al., 2014). The available epidemiological data, which show an association between urolithiasis and increased cancer risk in the urinary tract, strongly suggests that a tumour risk from melamine-induced stones is plausible.

That the mode of action established for melamine (tumour formation as a result of urolithiasis) cannot be considered to be species-specific had been concluded by IARC in

its 1999 assessment. As ECHAs Guidance on the Application of the CLP Criteria states, that "Urinary bladder tumours due to crystals in the bladder" is a mechanism of tumour formation considered not relevant for humans (section 3.6.2.3.2. [k]), the DS acknowledges the confusion. However, IARCs assessment suggested that the mode of action can only be considered a rat-specific phenomenon for specific sodium salts such as sodium saccharin or sodium ascorbate.

As this is an important point, the DS would like to refer to the CLH dossier (section 10.8.2 (a), page 44/45): *"According to ECHAs Guidance on the Application of the CLP Criteria (3.6.2.3.2.; section a) "By default, carcinogenic effects in experimental animals are considered relevant to humans and are considered for classification as carcinogens". However, certain types of tumours may not be considered for classification if sufficient evidence shows no relevance to humans. According to the recommendations of the ECHA Guidance on the Application of the CLP Criteria (3.6.2.3.2.; section k), based on an assessment by IARC (IARC, 1999b), urinary bladder tumours due to crystals in the bladder are considered not relevant to humans. However, the consensus section of the corresponding IARC report states: "For chemicals producing bladder neoplasms in rats and mice as a result of calculus formation in the urinary bladder, the response cannot be considered to be species-specific; thus, the tumour response is relevant to an evaluation of carcinogenicity to humans. There are quantitative differences in response between species and sexes. Calculus formation is dependent on the attainment in the urine of critical concentrations of constituent chemicals which form the calculus; therefore, the biological effects are dependent on reaching threshold concentrations for calculus formation."(IARC, 1999b)*
*Accordingly, IARC did not exclude a carcinogenic response to chemical-mediated calculi in humans. It was rather discussed whether species have the ability to produce certain calculi based on specific chemical and physical conditions of the urine. Only the effect of sodium salts (e.g. saccharin or ascorbate) in terms of urinary precipitation followed by tumourigenic effects was considered a rat-specific phenomenon. Hereby, urinary precipitation is based on the presence of extraordinarily high urinary concentrations of alpha-2 (α2u) globulin and albumin. The interacting of these proteins with sodium salts deems necessary to form urinary precipitates in rats. Unlike rats, humans have a much lower urinary protein content (100-1000 times lower) and α2u-globulin or a similar protein does not occur (IARC, 1999b). It is worth noting that administration of saccharin leads to precipitation in rats but not in non-human primates, whereas melamine exposure causes calculi/crystal formation in rodents, non-human primates and humans (Early et al., 2013; IARC, 1999b; Lam et al., 2009; Takayama et al., 1998). In addition, several lines of evidence, explicitly discussed in section (k), suggest that melamine-related urinary stone formation may nevertheless pose a carcinogenic risk to humans. Concerning the classification of melamine, dismissing this tumour type may, therefore, not be justified.".* Again, it is important to differentiate between substances with sufficient evidence that they only produce calculi in experimental animals (e.g. sodium saccharin and sodium ascorbate) and substances that cause calculi formation in experimental animals which cannot be excluded to occur or (in exceptional cases such as melamine where data are available) have been shown to occur in humans.

Following a recent reassessment by IARC, the classification of melamine was upgraded from Category 3 to Category 2B (IARC, 2019).

It is also worth noting that the mechanisms presumably not relevant for humans listed in section 3.6.2.3.2. (k) of ECHAs Guidance on the Application of the CLP Criteria are currently under revision. In particular, this includes the mechanism "urinary bladder tumours due to crystals in the bladder".

**(7) MoA - Comparison of the steps of the MoA**

The DS agrees with the statement that the "mode of action of tumour formation for male rats could - in principle - be relevant for humans: I.e. the precipitation in the urine and the formation of uroliths if a threshold exposure level is exceeded."

**(8) No differentiation between stones originated from melamine or other origins and melamine stones are not persistent**

The prevalence of general, i.e. not related to melamine exposure, paediatric urolithiasis is considerably lower as compared to the occurrence of urinary calculi in adults (prevalence: ca. 0.3 % vs. ca. 6 % , respectively (Wang et al., 2009; Yang et al., 2010a; Wang et al., 2017)). Numerous observational studies have clearly established a causative role of melamine in the increased occurrence of urinary precipitation and nephrotoxicity in Chinese children (Dalal and Goldfarb, 2011; Wen et al., 2016; WHO / FAO, 2009). It is commonly accepted that the consumption of high-dose melamine can result in urolithiasis in children.
At hospital admission following the announcement of the outbreak, paediatric patients presented with melamine-related calculi (MRC) that were described as radiographical and ultrasonographically distinguishable from common calcium stones (when compared to calcium stones, melamine-related calculi are: (1) radiolucent on conventional radiographs; (2) lesions less echogenic, more "sandy" appearance, structurally less dense and associated with a feeble or absent acoustic shadow when examined by ultrasonography) (Dalal and Goldfarb, 2011; He et al., 2009). MRC themselves showed, when analysed, a morphology that was sand-like and less dense as compared to calcium oxalate stone (Yang et al., 2010b). Melamine and uric acid were commonly identified as major stone components and considered the main aetiological factors involved in the formation of MRC (Chang et al., 2012; Grases et al., 2009; Sun et al., 2010b; Sun et al., 2009; Sun et al., 2010c; Wang et al., 2011).
The majority of paediatric patients passed their MRC spontaneously or in response to conservative treatment (hydration and urinary alkalinisation) (Wen et al., 2016). However, a number of MRC had been resistant to conservative management (Jia et al., 2009); especially when MRC had a large size (> 10 mm) (Sun et al., 2010a). Several follow-up studies indicate consistently that melamine-related nephrolithiasis persisted in approximately 8 – 10 % of the patients (Chang et al., 2017; Gao et al., 2011; Shen et al., 2011; Wang et al., 2013; Zou et al., 2013). In some cases, the stone size increased in 8 % of the study participants during a 12 months follow-up (Dai et al., 2012).
There is uncertainty regarding the question as of why a fraction of MRC exhibits long-standing occurrence following ineffective conservative treatment. While there are no data suggesting that persistent MRC are unrelated to melamine exposure, a number of studies suggest an interaction of melamine with other lithogenic substances such as calcium oxalate or calcium phosphate. Several *in vitro* studies have shown that melamine promotes the formation of calcium crystals (Gombedza et al., 2019; Poon et al., 2012; Thanasekaran et al., 2012). Consistently, it has been hypothesised that melamine serves as a nidus that subsequently promotes the growth of calcium-related urinary stones *in vivo* (Liu et al., 2011; Wu et al., 2010). The study by Liu et al. (2011) uncovered a strong association between urinary melamine concentrations and the risk of calcium urolithiasis in adults. All analysed stones in the study contained melamine. Moreover, it has been suggested that MRC, found in Chinese paediatric patients, may change their chemical characteristics. Accordingly, the authors of the study by Sun et al. (2010a) hypothesized that large conservative therapy-resistant MRC may undergo calcification. In a study by Wen et al. (2011), it was uncovered that residual MRC, while remaining in the same location, changed their radiographic features from being radiolucent at the time of hospital discharge to radio-opaque at follow-up. The analysis of the residual MRC that

became radio-opaque revealed melamine as the major component of the core enclosed within a calcium/calcium oxalate dehydrate-containing shell, resembling common calcium stones. In addition, some studies have found that MRC contain a certain level of calcium oxalate, which inversely correlated with the effectiveness of conservative treatment (Li et al., 2011; Li et al., 2012). It had also been suggested that predisposing lithogenic factors may determine the development, the composition, and the persistence of stones. The commonly observed elevated male-to-female ratio in the exposed paediatric population, for instance, may be explained by hormonal differences, which can have an impact on urinary saturation of calcium oxalate (Heller et al., 2002; Lu et al., 2011).

In conclusion, in the absence of data showing that persistent stones in Chinese children are unquestionably stones unrelated to melamine exposure, persistent stones described in numerous follow-up studies cannot be discounted based on an assumption that they are completely melamine-independent. The available data consistently show that about 8-10 % of the affected Chinese children had persistent stones. As these stones remained in the urinary tract system of the Chinese paediatric patients for a considerably long period of time, they obviously did not obstruct the urinary tract, as this would cause severe symptoms. There is no evidence that these stones have formed independently of melamine exposure. Given that the abovementioned data are derived from *in vitro* studies and other epidemiological studies of limited quality, the information concerning the interaction of melamine with other lithogenic factors is regarded as insufficient to draw a final conclusion.


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## (9) Uroliths of melamine origin do not form at low exposure

Section 10.11.1 of the CLH dossier also addresses environmental chronic low-dose exposure and its potential impact on the formation of calculi and subsequent health hazards. It is, though, important to stress that due to significant uncertainties concerning the relevance and validity of these data regarding low dose response, a final conclusion cannot be reached at this point (section 10.11.1, page 123).

## (10) Different sites of lesions

The carcinogenic mechanism following oral melamine administration is based on repeated damage to the urothelium due to melamine-induced stones. Damage to the urothelium primarily occurs at the locus where the stone resides (CLH dossier, section 10.8.2 (k), page 53: *"Most notably, as shown by a population-based cohort study, neoplasms tended to occur at the same location within the urinary tract where the respective stone was found (Chow et al., 1997)"*). In the male rat, stones are predominantly found in the urinary bladder where they damage the urothelium, ultimately leading to the formation of bladder tumours. In Chinese paediatric patients, melamine-induced stones were found predominantly in the kidney (renal pelvis), but also in the ureter and bladder. The urothelium in these areas of the urinary tract is therefore susceptible to stone-mediated irritation and damage.

**(11) Confounding toxicity**

According to section 10.8.2 (j) of the CLH dossier, confounding effects of excessive toxicity at test doses were not identified by the DS. Justification is provided by the fact that tumour formation had already been seen at concentrations that did not induce excessive toxicity (page 47). For example, in the study by Ogasawara et al. (1995), papillomas were found in the low-dose group (8/19 (42 %) at 350 mg/kg bw/d) with a calculated statistical significance (Fisher exact test: P = 0.0265) as confirmed by IARCs reassessment (2019).

**(12) Interaction with cyanuric acid**

The interaction of melamine and cyanuric acid is briefly addressed in the CLH dossier (section 10.8.2 (k), page 49). However, for the purpose of classification, this interaction did not play a role. The DS wants to stress that study results obtained from co-exposure experiments (combined administration of melamine and cyanuric acid) were not considered in arriving at a classification for both carcinogenicity and STOT RE.

As pointed out by the organisation, contamination with cyanuric acid may be a potential confounding factor. However, it is unlikely that the concentration of putative cyanuric acid contamination (e.g. traces in drinking water supplied to experimental animals) was high enough to substantially affect the experimental study result on melamine. Cyanuric acid alone does not form crystals or induce kidney toxicity up to high doses (approximately 150 mg/ kg bw/d). As reported by different laboratories, a combined administration of melamine and cyanuric acid causes severe renal toxicity, which is tremendously worse as compared to effects of melamine exposure alone. It would have been noted if study results obtained from the administration of melamine alone and confounded by cyanuric acid contamination had reported effects comparable to co-exposure (for studies on co-exposure, the DS would like to refer to the CLH dossier, table 19). In the study by Cong *et al.* (2014), the composition of stones following 4 weeks oral treatment with melamine alone was analysed. The melamine content of the calculi was 98.6–99.5 %. Cyanuric acid was not found as a stone component. Interestingly and most importantly, the authors detected similar levels of cyanuric acid in the urine of control animals and melamine exposed animals of all dose groups without being statistically different. In addition, while melamine levels in the urine strongly correlated with the applied melamine dose, there was no correlation between melamine doses and urinary cyanuric acid. The authors of the study suggested that "cyanuric acid should not be derived from melamine and involved in melamine-induced stone formation." [Cong X., Gu X., Xu Y., Sun X., and Shen L. (2014): The true stone composition and abnormality of urinary metabolic lithogenic factors of rats fed diets containing melamine. Urolithiasis 42 (3), 227-232.].Ogasawara et al. (1995) reported calculi composed of equimolar amounts of melamine and uric acid (total

combined content 61 – 81 %). Melamine was also considered the principal component in the study by Research Triangle Institute (1982). On the other hand, in co-exposure experiment (i.e. melamine together with cyanuric acid), crystals showed the presence of cyanuric acid [Reimschuessel R., Gieseker C.M., Miller R.A., Ward J., Boehmer J., Rummel N., Heller D.N., Nochetto C., de Alwis G.K., Bataller N., Andersen W.C., Turnipseed S.B., Karbiwnyk C.M., Satzger R.D., Crowe J.B., Wilber N.R., Reinhard M.K., Roberts J.F., and Witkowski M.R. (2008): Evaluation of the renal effects of experimental feeding of melamine and cyanuric acid to fish and pigs. American Journal of Veterinary Research 69 (9), 1217-1228]. Dalal et al., 2011, notes, *"…when melamine is present but cyanuric acid is not, the melamine complexes with uric acid in the urine to form melamine–uric acid stones. When both melamine and cyanuric acid are present, however, these chemicals preferentially combine to form melamine–cyanuric acid stones."*

In addition, it has been suggested (as also mentioned by the organisation) that gut bacteria may metabolise melamine to form cyanuric acid, resulting in potential (internal) co-exposure. Hence, while traces of cyanuric acid may be present either due to contamination of the drinking water, impurities, or internal formation resulting from bacterial metabolisms in the gut; it appears highly unlikely that this would be of toxicological significance.

It is important to note that unlike the application of pure melamine in experimental animal studies selected for the purpose of classification in the CLH dossier, a mixture of several triazines (especially melamine and cyanuric acid but also ammeline and ammelide) was found in the animal feed on the market, leading to numerous fatalities among dogs and cats in 2007. It has been frequently reported that a combined exposure of melamine and cyanuric acid is extremely nephrotoxic, characterised by high mortality among exposed animals [Dalal R.P. and Goldfarb D.S. (2011): Melamine-related kidney stones and renal toxicity. Nat Rev Nephrol 7 (5), 267-274.].

As stated in the CLH dossier (section 10.8.2 (k), page 50), uroliths in paediatric patients were mainly composed of melamine and uric acid. Other triazines were not found relevant for stone formation in humans, suggesting that cyanuric acid did not play a significant role in the aetiology of urolithiasis in Chinese children. Dalal *et al.*, 2011, notes, *"The concomitant presence of cyanuric acid does not seem to be necessary to produce melamine related adverse effects in humans.".* According to a WHO assessment report, affected children were exposed to melamine with a considerably high purity and only insignificant traces of other triazine compounds: *"These human data are different from what has been described for the outbreaks in pets in 2004 and 2007. From all data reported to date, infants were exposed primarily to melamine alone or to very low levels of cyanuric acid when melamine was present at very high concentrations, whereas pets were exposed to melamine and cyanuric acid and possibly to ammeline and ammelide."* and *"The melamine added to adulterated milk for at least some of the infant formula produced in China that caused renal illnesses during the 2008 incident appeared to be relatively pure. Chinese infant formula reportedly contained levels of cyanuric acid, ammeline and ammelide that were only about 0.1% of the melamine levels. They were also much lower than levels present in contaminated wheat gluten and rice protein concentrate ingredients that were used in the production of pet foods during the 2007 melamine contamination incident in the USA, Canada and South Africa."* [WHO / FAO (2009): Toxicological and health aspects of melamine and cyanuric acid. WHO Library Cataloguing-in-Publication Data. ISBN: 978 92 4 159795 1.]

It is important to stress that findings from animal studies conducted exclusively with melamine are consistent with effects seen in Chinese children and distinct from

observations in pets exposed to melamine and cyanuric acid (Hard et al., 2009, Bhat et al., 2010)

**(13) There exists alternative, more plausible, explanations for the findings relied upon and that these have led as consequence to deficiencies in the overall CLH process**

The DS acknowledges the comment raised by the organisation but would respectfully like to disagree with this statement. The DS would like to refer to section 10.8.2 of the CLH dossier. According to a comparative analysis of key events (section 10.8.2 (k), page 54), tumour formation in the urinary tract of humans attributed to melamine-induced urolithiasis is plausible. The scientific arguments presented by the organisation and responded to herein by the DS as well as the expert opinion elaborated within the review and position papers cannot be considered strong evidence that the mechanism of tumour formation is not relevant to humans. It is for this very reason that according to the CLP regulation (3.6.1.1.), classification is warranted. It is the opinion of the DS that allocating melamine in Category 2, a suspected human carcinogen, is appropriate.

RAC's response

Thank you for your comments. RAC taked into account the comment and attachments provided.

**(1) Widespread use**

RAC agrees with the DS that hazard classification is not based on exposure.

**(2) Significant weaknesses in assigning key studies**

The weaknesses highlighted for the key studies are noted.

**(3) Quality of studies**

RAC acknowledges the limitations in the Okumura *et al*., 1992 and Ogasawara *et al*. 1995 but agrees with the DS that disregarding these studies on this basis for classification would be unjustified. Regards to Cremmonezzi *et al*., 2001, RAC agrees that the study had major limitations due to missing information (e.g. no information on the distribution of animals between sexes, observation of doubtful neoplastic relevance).
RAC agrees that Early *et al*., 2013, 14-day study was not performed according to OECD TG but considered that the results of the study can still be considered reliable.
RAC acknowledges that exposure levels in human studies were in the majority of the studies uncertain. Nevertheless, the human data provide evidence of an association between melamine accidental exposure in children and uroliths formation.

**(4) Lower reliability studies are given more weight than higher reliability studies**

RAC agrees with the DS that without additional information form Hazelton *et al*., 1953, Cremonezzi *et al*., 2004 and 2001, there is sufficient evidence of a carcinogenic potential in male rats based on three key studies.

**(5) Available, relevant high-reliability studies were not included**

RAC takes note of the review papers of Swaen *et al*., 2019, Cohen *et al*., 2018a and Cohen *et al*., 2018b and the position paper from Cohen, 2019 (attachment 1).
See response to comment no. 6.

RAC agrees with the DS's interpretation regards to IARC, 1999 consensus report. Indeed, in the report, calculi formation induced by substance itself like melamine were

differentiated from substances causing calcium phosphate precipitates in the urine of rats as saccharine or sodium salts, which is not a relevant MoA to human. Although quantitative differences between species were pointed out by IARC, IARC did not considerthe carcinogenic response to urinary baldder calculi induced by substance itself (such as melamine) species-specific.

**(6) MoA - Comparison of the steps of the MoA**
RAC agrees with the DS's reponse.

**(7) No differentiation between stones originated from melamine or other origins and melamine stones are not persistent**

RAC acknowledges that the presence of non-melamine stones may be a potential confounding factor in the epidemiological studies. Nevertheless, RAC agrees with the DS that it is not possible to exclude that persistent stones, described in several follow-up studies, were related to melamine exposure.

**(8) Uroliths of melamine origin do not form at low exposure**
RAC agrees with the DS that a final conclusion cannot be reached on this point.

**(9) Different sites of lesions**
Considering that urothelial irritation and regenerative proliferation is a MoA relevant to human and is expected to occur at the site of the stones, RAC agrees with the DS that differences in location in the urinary tract system does not allow to provide evidence that the MoA would not be relevant to human.

**(10) Confounding toxicity**
RAC agrees with the DS's reponse.

**(11) Interaction with cyanuric acid**

RAC agrees with the DS's reponse.

**(12) There exists alternative, more plausible, explanations for the findings relied upon and that these have led as consequence to deficiencies in the overall CLH process**
RAC agrees with the DS's response.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Czech Republic | Kronospan | Company-Manufacturer | 8 |
| Comment received | | | | |
| Kronospan believes that no classification of melamine (CAS 108-78-1) as a carcinogen cat. 2 or for STOT RE 1 is required according to the CLP regulation and ECHA guidance. We agree to the proposed non-classification for mutagenicity in the CLH proposal.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment REACH-melamine.docx | | | | |
| Dossier Submitter's Response | | | | |
| **Response #8** | | | | |

The DS appreciates the comments raised by the organisation with the following response to the main points.

**(1) Uses, exposure, and occupational exposure**

The DS would like to refer to response #1 and #2.

**(2) Interaction with the DNA**

Section 3.6.1.1 of the CLP Regulation (EC) No 1272/2008 stipulates, *"Carcinogen means a substance or a mixture of substances which induce cancer or increase its incidence."*

A mutagenic mode of action is not a necessity for the purpose of carcinogenicity classification. The DS would like to refer to ECHAs Guidance on the Application of the CLP Criteria section 3.6.2.3.1. (k) and 3.6.2.3.3. (*"Lack of genotoxicity is an indicator that other mechanisms are in operation…"*).

**(3) Interaction with cyanuric acid**

The DS would like to refer to response #7, bullet point (12).

**(4) Relevance for humans**

According to section 10.8.2 of the CLH dossier, species-specific considerations are addressed in detail. As stipulated in section 3.6.1.1 of the CLP Regulation (EC) No 1272/2008, *"Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans."*. The DS would like to emphasise that in the case of melamine, strong evidence that the mechanism of tumour formation is not relevant for humans does not exist. It is rather all the contrary as set out in the CLH dossier (section 10.8.2 (k), page 58: *"a comprehensive analysis of the various key events related to melamine-mediated carcinogenesis was performed with the conclusion that although species-specific anatomical and physiological factors may play a role regarding the response to calculus formation, species-independent key events, common to both, rodents and humans, can be clearly identified. Thus, calculus formation as a consequence of melamine exposure poses a carcinogenic risk to humans."*).

The DS would like to refer to response #2, bullet point (1) and response #7, bullet point (6).

RAC's response

Thank you for your comment. Please see response to comment 1, 2, 7. RAC agrees that a mutagenic mode of action is not a necessity for the purpose of carcinogenicity.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | EFCC (European Federation for Construction Chemicals) | Industry or trade association | 9 |

Comment received

EFCC fully supports both EMPA's Scientific and Regulatory considerations/arguments. See attached EFCC Position Paper on the proposal for Melamine Classification

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EFCC Position Paper on the proposal for Melamine Classification.pdf

Dossier Submitter's Response

**Response #9**

The DS appreciates the comments raised by the organisation and refers to responses #1, #2 and #6 (bullet point (2) and (3)) with regard to the intrinsic property to cause cancer, reasonably expected uses, unintended consequences.

RAC's response

Thank you for your comment. Please see responses no. 1, 2 and 6.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | The Phosphorus, Inorganic and Nitrogen (PIN) Flame Retardants Association (pinfa) a Sector Group of Cefic | Industry or trade association | 10 |

Comment received

The Phosphorus, Inorganic and Nitrogen (PIN) Flame Retardants Association (pinfa) is highly concerned about the proposal of the German Federal Institute for Occupational Safety to classify melamine as a carcinogen Category 2 and a STOT1 RE (substance with a 'Specific Target Organ Toxicity 1 Repeat Exposure'). Such a classification could have negative consequences for the production, marketing and use of all melamine flame retarded products, which could lead to a shift away from the currently used halogen-free flame-retardant solutions.

Unintended downstream consequences
Melamine is an essential and fundamental building block used as an alternative to halogenated flame retardants in many applications where halogenated flame retardants have been used before.
Melamine plays a role in a wide range of flame-resistant materials. These include protective textiles that are used in upholstery (i.e., protecting seats in buses, trains etc.) and clothing such as uniforms worn by firemen. Melamine is also used in the manufacture of thermal liners, heat resistant gloves, and aprons (source: https://thechemco.com/chemical/melamine/).

Melamine is used as a halogen-free alternative to halogenated flame-retardant systems. The proposed classification could potentially deter the increasing use of halogen-free flame-retardant solutions; if as a result, melamine could no longer be used as a building block for in downstream user applications (e.g., fire-safety materials in the building and transport sectors).

Regulatory safety standards for flame retardants
Melamine is used as PIN flame retardants, because they contain nitrogen, which is released to dilute fire gases by releasing nitrous gases, which inhibit flames. These compounds are highly compatible with polymers, as such losses from treated plastics are very low. Additionally, plastic articles containing melamine as FR can be easily recycled, in contrast to other flame-retardant solutions.

The proposed classification could have a negative impact on the increasing use of halogen-free flame retardants. Chemicals used for their flame retardancy in articles are constantly under regulatory scrutiny, which is restricting the possibility for industry to provide materials that fulfill the required safety regulations in Europe and maintain the high standards needed to protect our citizens and the environment.

Pinfa fully supports the scientific arguments presented by the European Melamine Producers Association (EMPA) for this classification proposal.

Pinfa is the Phosphorus, Inorganic and Nitrogen (PIN) Flame Retardants Association and is a Sector Group within Cefic, the European Chemical Industry Council. Pinfa represents the manufacturers and users of non-halogenated phosphorus, inorganic and nitrogen flame retardants (PIN FRs). The members of Pinfa share the common vision of continuously improving the environmental and health profile of their flame-retardant products.

Dossier Submitter's Response

**Response #10**

The DS appreciates the comments raised by the organisation and would like to refer to response #1, with regard to unintended consequences.

RAC's response

Thank you for your comment. Please see response no. 1 and 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Germany | <confidential> | Company-Downstream user | 11 |

Comment received

Comments of Kronospan Lampertswalde GmbH., D 01561 Lampertswalde concerning the proposal to classify (CLH) melamine as Cat 2 carcinogen (H351 suspected carcinogen) STOT RE1 (specific target organ toxicity, H372 urinary tract), based on possible risks from oral intake

Introduction:
These comments are given by Kronospan Lampertswalde GmbH. in the name of the whole Kronospan group. The Kronospan group is a worldwide producer of various wood-based panels (WBP), such as particleboard, MDF, coated boards such as melamine film faced materials (MFC), and laminate flooring.
Kronochem is the chemical part of the Kronospan group, producing among others various types of wood adhesive resins and impregnating resins. Several of these resin types include melamine as raw material, yielding in melamine-formaldehyde (MF) or melamine-urea-formaldehyde resins as adhesive resins as well as impregnating resins. These resins are used for the production of the various WBP as well as for the impregnation of paper as decorative films for the coating of raw boards to produce, among others, furniture boards or laminate flooring.
The Kronochem sites are located in several European countries, in China and in the USA; all in all experience using especially melamine is given at all sites from the very start of any resin production, which sums up to more than 30 years.
Kronospan has contributed also to the comments given by the European Panel Federation

(EPF) in the course of this Public Consultation of ECHA.

General remarks to melamine and melamine based resins
Melamine (CAS 108-78-1) is the one main raw material for all melamine based resins. Melamine reacts chemically with formaldehyde to form melamine-formaldehyde resins (MF) or with urea and formaldehyde to give various versions of melamine-urea-formaldehyde cocondensation resin with different proportion of melamine, from few percent up to more than 20%.
The main point is, that melamine must react with formaldehyde, unless it will not be soluble in water or an aqueous resin solution/dispersion and would precipitate. This means that during the preparation of the MF and MUF melamine must be added in such way, that this reaction and with this the solubility and homogeneous distribution of the melamine is secured by proper reaction between these two components. This is guaranteed by adding melamine always in the first or one of the first steps in the multistep sequence of addition of the raw materials during resin production; this also means that melamine always reacts with a surplus of formaldehyde. Based on this (necessary) reaction more or less no free unreacted melamine is given in adhesive and impregnating MU and MUF resins.
The only analysis method for content of free unreacted melamine in MF and MUF resins is Raman spectroscopy. Scheepers et al. (1995) showed that MF resins with F/M = 1.7 does not contain free unreacted melamine
During the production of wood-based panel (WBP) the MF or MUF resin cure, with increase of the molar mass until three-dimensional crosslinking. This means that also during this processing step never melamine is set free or can be formed by the reactions ongoing during curing. The curing step is from chemical principle the same if we talk about an adhesive resin or a resin within an impregnated paper. The chemical link between melamine and formaldehyde is strong, which is the basis to use such resins for WBP for the use under high moisture content or even impact of exterior climate. Another positive effect of this strong bond is the reduced subsequent formaldehyde emission. Only under very harsh conditions, such as boiling water, hydrolysis can occur, cracking down some chemical links; however, in this reaction only chain scission occurs but no free melamine is liberated. If such hydrolysis occurs, the performance of the WBP suffers and the life time of the WBP for proper application ends.
Based on this experience it is secured that no free melamine can be formed during the application and use of WBP bonded with melamine based adhesives or coated with MF resin impregnated films. Even exposure to various liquids as they are used during the life time use of WBP, such as a MF based surface of a kitchen working table will not create formation or extraction of free unreacted melamine.

Industrial use of melamine
Kronospan/Kronochem works in more than 10 resin plants and partly since decades with melamine when producing MF and MUF resins. Melamine is either handled in closed systems (automatic filling the melamine silo with melamine out of the transport vehicle during delivery; automatic dosage of the melamine powder into the reactor during the resin production), or, in case of deliveries of melamine in bigbags and emptying bigbags during dosage of the melamine, the relevant precaution is taken, including use of personal protection equipment and compliance with the relevant OELs and other worker's protection regulation, avoiding any risk of inhalation, swallowing, or contact with skin. As soon as melamine has reacted, no more free unreacted melamine is given. This situation then remains for the whole chain of further production steps, from application of the adhesive resins onto the wood furnish or the impregnation of paper in the preparation of decorative paper film, up to the hot pressing steps either in the production of the raw WBP themselves or the lamination of boards with decorative films or laminates. Also

further processing of boards by cutting, sawing, milling, or drilling might create dust, but no free unreacted melamine. As far as melamine is part of this dust, it is always in form of chemically bonded into the resin. This statement is also true for all steps after the life time as such of the WBP, such as in form of furniture; any waste material out of furniture, indoor panelling, or any other way of application will contain still the cured MF and MUF resins, but no free melamine. This remains the case also during crushing and diminution of waste material when preparing recycling raw material again for the WBP industry.

Occurrence of free unreacted melamine
As already outlined above, free unreacted melamine is given only in the first step of the production of adhesive or impregnating resins; as soon as melamine is reacted with formaldehyde, no more free melamine is left at the usual industrial compositions of such resins. Evidence of relevant procedures can be found, unless it is proprietary information, in the chemical and technical literature. or
Adverse health effects on basis of an oral intake of melamine can be eliminated from consideration, because no free unreacted melamine is present in the various types of resins and resin bonded or resin impregnated products, including WBP in raw or coated form. Extraction of free melamine from wood based panels by contact with mouth and by salivation can be excluded for several reasons. First, even in children's bedrooms such actions are unlikely; secondly the low solubility of melamine in water (as more or less identical with salive) makes extraction additionally unlikely; and thirdly articles intended to come into contact with food (as synonym for oral contact with WBP and especially decorative surfaces of WBP) are subjected to own legislation with the request for test according to specific migration limit SML; however only articles intended to come into contact with food are regulated regarding melamine release.
As a further statement digestive exposure is very unlikely with WBP, and such oral intake can generally be excluded concerning products made from WBP and by this on basis of melamine based resins. The proposed classification of melamine is related to oral intake, a consequence of criminal addition of melamine to foods or animal foods in the past, especially in China (the nitrogen falsely simulates higher protein content in standard analysis). Additionally no relevant evidence for carcinogenic properties in connection with other exposure routes is given. More detailed information has been summarized and collected by the European Melamine Producers Association (EMPA). Kronospan in this aspect fully underlines and acknowledges these findings, which shall not repeatedly be formulated here.

Waste and recycling
Concerning treatment of waste occurring in the WBP industry and the possibilities for recycling in sight of the industrial cascade use of raw materials with material recycling rather than just burning still valuable raw material we point to details given in the comments of the European Panel Federation, which was prepared also under participation of Kronospan. However anyhow, melamine is given in WBP (irrespective if products under use or as waste or as recycling material) not as free melamine but only in form of chemically bonded melamine in MF and MUF resins.

Dossier Submitter's Response

**Response #11**

The DS appreciates the comments raised by the organisation and would like to refer to responses #1 and #2 with regard to uses and exposure.

RAC's response

Thank you for your comment. Please see response no. 1, 2 and 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | European Panel Federation aisbl (EPF) | Industry or trade association | 12 |

Comment received

Melamine (CAS 108-78-1) is a resin polymer component in binder systems used in the wood-based panels industry for panel and paper laminates production. Melamine is incorporated into binder materials to improve the durability of wood panel products, especially in terms of water resistance and internal bonding.

Melamine-urea-formaldehyde (MUF) adhesive resins or melamine-formaldehyde (MF) impregnation resins are thermosetting polymers, which are made through a condensation reaction of its major constituents. Melamine is part of the polymer; in the case of MF resins, the melamine molecules are linked to each other by formaldehyde; in the case of MUF resins, melamine is linked partly to another melamine or to urea or smaller UF chains by formaldehyde. Based on the necessary and usual chemical procedure when producing such resins, the content of residual free melamine is negligible. In all cases melamine is added in the production procedure in the first or one of the first steps, but never as a final step; this means that there is always a surplus of formaldehyde when melamine is added in order to assure the reaction of all melamine added. This is even more important as melamine has low water solubility and, hence, unreacted melamine might precipitate, hindering the proper application and usage of the resin. Additionally the chemical linkage between melamine and formaldehyde is quite strong (much stronger than between urea and formaldehyde); this means that also during the life time of hardened melamine based resins in their usual application, e.g. as wood adhesive, no melamine can be set free and in case escape from the bonded product. Producing a wood-based panel (WBP) with such a resin in an acidly catalysed, thermosetting process leads to a new polymer with a much higher molecular weight. Also during this hardening reaction no free melamine will be generated.

The raw boards produced are always surface treated (coated) with various finishing systems such as laminates, films, powder coatings and lacquer systems, resulting in an end product intended for the furniture and kitchen markets. Melamine is also the main compound of MF paper laminates. After a three stage thermally driven chemical conversion pathway: MF resin ☐ laminate ☐ board surfacing, the finished "melamine faced chipboard" (MFC) features a surface without free melamine.

WBP produced by use of melamine containing resins with the melamine in such a polymeric matrix as outlined above are raw particleboards, MDF and OSB as well as MFC (melamine resin (MF, MUF) - faced particleboards) and other WBP like MDF and plywood surfaced with such a melamine resin-impregnated decorative paper as well as e.g. plywood bonded with low emission moisture resistant melamine containing (MUF) resins. From these WBP, complex final articles like furniture, construction and packaging materials are manufactured. This includes kitchen furniture, living room furniture and children bedroom furniture, which may result in accidental food contact. It is of greatest importance to stress that the very unlikely digestive exposure is not considered relevant and has not been specified in the CSR (Chemical Safety Report in the REACH Registration dossier).

Due to its high reactivity and the high bonding strength between melamine and formaldehyde on molecular level, cured MF and MUF resins also show low formaldehyde emission when selecting the proper and usual production procedures for the resins as well as for the boards. Additionally, especially melamine-based resins are used for their high

chemical and hydrolytical resistance, yielding WBP for use under influence of higher moisture content and outdoor conditions.

Due to the absence of free unreacted melamine in adhesive and impregnation resins and, hence in WBP (including MFC) it is not present in samples achieved by extraction methods under short time conditions as given during usual application e.g. in kitchens. Melamine as an isolated substance has a very low solubility in cold water (3.2 g/l at 20°C). Under the impact of boiling water over longer times (at least several hours, which is most unlikely during usual application of WBP) a certain hydrolysis of the cured MF or MUF resin can take place; this might destroy the WBP and its performance, but will most likely not deliberate molecular free melamine.

So far only one test method for the detection of free melamine in MF resins is mentioned in the chemical literature and only in one paper: Scheepers, M. L., Meier, R. J., Markwort, L., Gelan, J. M., Vanderzande, D. J., & Kip, B. J. (1995). Determination of free melamine content in melamine-formaldehyde resins by Raman spectroscopy. Vibrational Spectroscopy, 9(2), 139-146. For cured MF resins with a composition as given in today's industrial impregnating resins no free melamine was detected. This Raman spectroscopy test methods does not need any pretreatment of the sample. Until now only cured resin samples had been investigated, but not WBP or decor films. It is essential that during the analysis it can be guaranteed that no change of the substance to be investigated and analysed can occur. Therefore, all other proposed test methods based on extraction methods include the risk that the substance to be analysed is changed. Cured MF and MUF resins are insoluble in all solvents; when partially destroying the chemically hardened network (e.g. by treatment with concentrated sulfuric acid), some raw materials (such as molecular melamine) might be formed again by hydrolysis. Such effects can happen during extraction processes when preparing samples for analysis. But this partial chemical decomposition and cleavage of bonds within the polymers changes the product to be tested immediately during the test, which means that such a pretreatment during the test is not correct in terms of proper investigation and analysis of free melamine.

There are also analysis methods available to determine melamine as such and in not reacted state. These methods, however, are solely applicable when only pure unreacted melamine is present in the sample, because the method does not distinguish between pure unreacted melamine and melamine in reacted form, such as in an MF or MUF resin. Melamine as pure chemical substance added into food (and not undergoing any further chemical reaction) can be determined very precisely; such food analysis is performed e.g. in labs run by authorities. For articles intended to come into contact with food an own legislation exists (basis: white-listed substances with a specific migration limit SML). For articles intended to come into contact with food the finished article has to be tested. This means consumer articles (e.g. kitchen worktops) have to be tested for compliance with the SML's using a method shown in test reports which measures the amount of melamine released from the tested surface. As (i) only articles intended to come into contact with food are regulated regarding melamine release and (ii) the analytics is done with a standardised procedure and method specified by the European Food safety Authority (EFSA), this is a moot issue.

Test results in the framework of food contact regulations confirm that the release of melamine in accordance with CEN/TS 13130-27:2005-05 shows HPLC results very close to the detection limit. All such reports known to EPF confirm compliance of the tested WBP with food contact regulation requirements. Consequently, there is no migration of melamine from WBPs nor from articles made thereof.

Emission tests as usually performed for volatile substances do not work, because

melamine is not volatile.

Decades of experience with the use of melamine in WBP and related materials and articles have not shown any health problems neither at the workplace in the factories nor with the final articles. In the few operations where free melamine is handled, workers are required to wear appropriate PPE and/or the respective OELs are complied with. Furthermore, eating or drinking is not allowed in any of these places in the factory, so there is no risk of digestive exposure.

Classifying melamine as a carcinogen by ingestion, like in the CLH proposal, would risk tremendous unintended negative consequences for the wood-based industry. Firstly, customers will not distinguish between free unreacted melamine and reacted melamine in a polymeric matrix. Many customers will simply ask for products free of melamine. This will create a colossal image problem for WBP and articles made thereof, aggravated by the fact that there is no substitute for melamine in the huge volumes required due to its variety of applications. Additionally, substitutes that exist for specific niche applications tend to be perceived as more hazardous than melamine (e.g. isocyanates). Consequently, sustainable wood-based panel products made of the naturally renewable raw material wood and with a very low carbon footprint will come under tremendous pressure to be substituted by other materials with a much higher carbon footprint such as oil based plastic materials.

An additional unintended consequence of a classification is that it will jeopardise the circular economy and recycling of wood articles and wastes, with a tremendous increase in the costs of hazardous wood waste treatments including even incineration. Using extraction methods with acids will lead to artificially high and not correct test results and is therefore no possibility, due to the fact that such pretreatments (partially) destroy the matrix thereby freeing some melamine, because these fake results might lead to frequent exceedences of the 1% threshold for carcinogens. Accepting such results based on wrong test methods would lead to very high volumes of wood waste as hazardous wastes, making recycling impossible and even combustion for energy recovery will not be allowed. This will result in very high costs for treating such wrongly classified hazardous wood wastes in dedicated waste incinerators.

Last but not least, a classification of melamine with STOT RE 1 H372 will result in much stricter requirements for storage (e.g. according to TRGS 510 in Germany). Resin producers need to check whether their storage facilities for melamine do include a storage permit for the storage class 6.1 D.

Conclusion:
Both facts, the negligible melamine residue concentration in final wood-based articles and the firm incorporation of the melamine in the resin matrix of these products do not justify a harmonised classification obligation under CLP neither for melamine as a substance nor for articles manufactured from it. Furthermore, a classification of melamine as carcinogenic will jeopardise the recycling of wood articles and of wastes. Therefore, such a classification would be counterproductive as it would hamper the EU's ambitions for moving to a circular economy and for increasing the targets for wood recycling.

About EPF
EPF – the European Panel Federation has members in 25 countries and represents the manufacturers of particleboard, MDF, OSB, hardboard, softboard and plywood. The EU wood panel industry has an annual turnover of about 22 billion Euros, creates over 100,000 jobs directly and counts more than 5,000 enterprises in Europe.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Melamine_CLH_Proposal_EPF_Response_ECHA_Public_Consultation_FINAL.pdf

Dossier Submitter's Response

**Response #12**

The DS appreciates the comments raised by the organisation and would like to refer to responses #1 and #2 with regard to unintended negative consequences, uses, and exposure.

RAC's response

Thank you for your comment. Please see response no. 1, 2.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | Europur | Industry or trade association | 13 |

Comment received

Having read the classification proposal we feel that we have limited knowledge to contribute to the classification discussion itself as it is a discussion about the intrinsic properties of the substance. However, as downstream users of melamine, we would like to describe the use of the substance and assessments performed with regard to risk characterisation in flexible PU foam. We realise that strictly speaking such information is of no direct relevance to the classification discussion itself, but should concerns exist around our use we would prefer to address these.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Melamine PC Submission.zip

Dossier Submitter's Response

**Response #13**

The DS appreciates the comments raised by the organisation and would like to refer to responses #1 and #2 with regard to unintended negative consequences, uses, and exposure.

RAC's response

Thank you for your comment. Please see response no. 1, 2.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Poland | Polish Chamber of Chemical Industry | Industry or trade association | 14 |

Comment received

Polish Chamber of Chemical Industry has the opinion that no classification as a carcinogen or for STOT RE is required according to the CLP regulation and ECHA Guidance. We stand against classification of melamine as proposed in the CLH dossier for Melamine (CAS 108-78-1) and further entry in Annex VI of CLP Regulation as Carc. 2, H 351 and STOT RE1, H372. Details in attached file.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20200207_ECHA public consultation on melamine classification_stanowisko PIPC.pdf

Dossier Submitter's Response

**Response #14**

The DS appreciates the comments raised by the organisation and would like to refer to responses #1 and #2 with regard to unintended negative consequences, uses, and exposure.

**(1) Broad deficiencies in key studies assignment and quality of the studies**

The DS would like to refer to response #2, bullet point (4) and response #7, bullet points (2) and (3).

**(2) Mechanism of tumour formation considered not relevant for humans**

The DS would like to refer to section 10.8.2 (a and k) of the CLH dossier, response #6 (bullet points (2) and (3)), and response #7, bullet point (6).

**(3) Low reliability studies are given more weight than higher reliability studies**

The DS would like to refer to response #7, bullet point (3).

**(4) Available, relevant high-reliability studies were not included**

The DS would like to refer to response #6, bullet point (1) and response #7, bullet point (5).

**(5) Use of data derived from the Chinese adulteration incident**

The DS would like to refer to response #2, bullet point (1) and (2).

**(6) That there exist alternative, more plausible, explanations for the findings relied upon and that these have led as consequence to deficiencies in the overall CLH process**

The DS would like to refer to response #7, bullet point (13).

RAC's response

Thank you for your comment. Please see response no. 1, 2, 6 and 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Germany | Verband der Chemischen Industrie e.V. (VCI) | Industry or trade association | 15 |

Comment received

Conclusion of the general VCI-comment to the Mode of Action (MoA) of stone-induced urinary bladder tumours with species-specific aspects and its relevance for humans:

- Many chemicals are known to form crystals in the bladder, yet are not considered to be intrinsically carcinogenic. Instead, threshold driven risk assessment is appropriate to address the concern of stone builders.

- Calculi dependent bladder tumor formation is a secondary effect dependent only on the physicochemical solubility of a substance that cannot be attributed to an intrinsic toxicity of a substance but requires long-term bladder stone exposure.

- Furthermore, the tumor formation after stone-building seems to be species- and gender-specific (primary male rate) due to anatomical difference between rodents and humans.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 200207_GENERAL VCI-COMMENT TO THE HARMONISED CLASSIFICATION AND LABELLING OF MELAMINE.pdf

Dossier Submitter's Response

**Response #15**

The DS appreciates the comments raised by the organisation with the following response to the main points.

**(1) Many chemicals are known to form crystals in the bladder, yet are not considered to be intrinsically carcinogenic. Instead, threshold driven risk assessment is appropriate to address the concern of stone builders.**

The DS would like to refer to the CLH dossier, section 10.8.2, page 58: *"Melamine-related tumourigenesis in rodents is based on a non-genotoxic mode of action secondary to the formation of calculi. Calculus formation occurs above a certain threshold at considerably high doses."*

**(2) Calculi dependent bladder tumour formation is a secondary effect depending only on the physicochemical solubility of a substance that cannot be attributed to intrinsic toxicity of a substance but requires long-term bladder stone exposure.**

The DS would like to refer to response #6 (bullet points (2) and (3)) and response #7 (bullet point (8): *"The available data consistently show that about 8-10% of the affected Chinese children had persistent stones."*).

**(3) Furthermore, the tumour formation after stone-building seems to be species- and gender-specific (primary male rate) due to the anatomical difference between rodents and humans.**

The DS would like to refer to section 10.8.2 (a and k) of the CLH dossier, response #6 (bullet points (2) and (3)), and response #7, bullet point (6).

RAC's response

Thank you for your comment. Please see response no. 6 and 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 31.01.2020 | Austria | <confidential> | Company-Downstream user | 16 |

Comment received

Observations on the Proposal for Harmonised Classification and Labelling based on Regulation (EC) No 1272/2008 ("CLP") regarding the substance 1,3,5-triazine-2,4,6-

triamine (Melamine; EC: 203-615-4, CAS: 108-78-1) submitted by the Federal Institute for Occupational Safety and Health (BAuA), Germany, Version: 1.0, November 2019 (hereinafter referred to as "Proposal")

Submitted by
Fritz EGGER GmbH & Co. KG
Holzwerkstoffe

I. Scientific and regulatory assessment of the Proposal submitted by EMPA
(1) We support the observations and comments on the Proposal submitted by the European Melamine Producers Association (EMPA). For the avoidance of reiteration, we refer to the details set out in the submission of EMPA during the public consultation and emphasize that we share the views and interpretations prepared by EMPA regarding the scientific assessment of the studies and justifications provided by BAuA in the Proposal.
(2) We are of the opinion that available scientific data as referred to in the Proposal does neither demonstrate sufficient evidence that Melamin fulfils the criteria set out in Annex I to CLP for carcinogenicity, category 2 (Annex I, section 3.6, to CLP) nor the criteria for specific target organ toxicity – repeated exposure (Annex I, section 3.9, to CLP).

II. Additional Observations and Comments
(3) In addition to the observations and comments submitted by EMPA we would like to submit the following details:
1. No need for action at Community level
(4) The Proposal correctly states that Melamine (1,3,5-triazine-2,4,6-triamine) is neither listed in the Annex VI to CLP nor has a proposal for a harmonised classification and labelling previously been submitted for this substance. It is also correct that none of the notifiers and/or registrants has self-classified the substance as STOT RE 1. The Proposal further states that
"data assessed and discussed in the current CLH dossier, however, support classification in category STOT RE 1 (section 10.11). Thus, a justification that action is needed at community level is given due to disagreement of the dossier submitter with the current self-classification by the notifiers and/or registrants".
(5) We submit that this does not constitute a enough justification for a harmonised classification and labelling. The mere fact that available data supports a classification other than the classification notified in accordance with Articles 39 et seqq. CLP does not trigger a need for action at Community level but rather the obligation for notifiers to re-assess their notifications and submit corresponding updates if and to the extent necessary. Otherwise, any new scientific evidence or updated conclusions drawn from available data deviating from previous notifications would constitute a need for action on Community level. Nothing in CLP supports such approach. Moreover, the justification outlined in the Proposal would lead to an inflationary use of harmonized classifications as any opinion of a competent authority deviating from notifications reported in the classification and labelling inventory would be a sufficient basis for a proposal for harmonised classification.
(6) Bearing in mind that Annex VI, Section 2, to CLP states
"For other effects than carcinogenity, mutagenicity, reprotoxicity and respiratory sensitisation a justification shall be provided that there is a need for action demonstrated at Community level"
it goes without saying that a specific need for action needs to be demonstrated. If the EU legislator had considered that a mere deviation between the opinion of a competent authority and notifications reported in the classification and labelling inventory shall constitute a sufficient justification it would have been more than likely that this aspect would already have been included in the regulation.
(7) Furthermore, it needs to be noted that Member States are obliged to introduce

penalties for non-compliance with the provisions of CLP and take all measures necessary to ensure that this Regulation is applied (cf. Article 47 CLP). Therefore, Member States established national legislation which entitles competent authorities to issue administrative orders (e.g. correction orders) or impose sanctions (e.g. administrative fines) in case information according to Article 40(1) CLP is not submitted correctly. Therefore, CLP stipulates that incorrect notifications, i.e. notifications which a competent authority can proof wrong due to its own assessment of available data, as well as omitted notifications despite availability of data supporting a notification requirement are subject to administrative control mechanism and potential sanctions rather than the basis for a harmonised classification.
(8) In addition, we submit that the Proposal does not sufficiently reflect the provision set out in Article 36(1) CLP. According thereto, a
"substance that fulfils the criteria set out in Annex I for the following shall normally be subject to harmonised classification and labelling in accordance with Article 37".
(9) While Annex VI, Section 2, to CLP states that a specific justification needs to be submitted only for other effects than carcinogenity, mutagenicity, reprotoxicity and respiratory sensitisation, it needs to be noted that even a potential classification of a substance as carcinogenic does not automatically constitute a basis for a proposal for harmonised classification. CLP only states that such classification "shall normally be subject to harmonised classification". Thus, any proposal for harmonised classification regarding the aforementioned hazard criteria needs to assess whether there is relevant information available indicating that there is no need for a harmonized classification due to the fact that exceptional circumstances allow for a deviation from the normal process as enshrined in Article 36(1) CLP.
(10) The Proposal does not contain any assessment or even statement as to whether such deviation could be considered in the case at hand and, thus, is lacking an essential requirement.
(11) Moreover, the observations already submitted by EMPA (cf. Section I. above) outline that the life cycle of Melamine does not include a wide-spread use in a way that the proposed classification would have a relevant effect. Given that in 95 % of the volume of Melamine available on the EU market, Melamine is chemically converted into a new substance, any harmonized classification would have only limited effects. This, in particular, holds true as the vast majority of end-uses relate to the production of articles which on the one hand, do not contain any Melamine as such but Melamine resins not subject to classification requirements due to a Melamine content of less than 1 % (cf. Table 3.6.2 of Annex I to CLP) and, on the other, are not subject to classification requirements as such (cf. Article 4(8), (10) CLP).
(12) Given that the vast majority of Melamine uses would not be affected by the proposed harmonized classification due to the chemical conversion of the substance and further given that the articles produced with Melamine resins would not be subject to classification requirements, there is no relevant argument to demonstrate that there is a need for action on EU level regarding the harmonized classification of Melamine.
(13) This also holds true with respect to a potential wide-spread use of Melamine resins also in consumer products as no relevant exposure to Melamine as such is to be expected in relation to such products. In this regard it needs to be noted that the scientific data referred to by the submitter of the Proposal primarily relate to adverse health effects on basis of an oral intake of Melamine. Such oral intake could generally be excluded with respect to articles produced from or on basis of Melamine resins.
(14) Further given that scientific justification has been put forward by the Proposal only with respect to oral intake and due to the fact that there seems to be no relevant evidence for carcinogenic properties in connection with other exposure routes, we submit that a restriction of a harmonized classification to that specific route of exposure would be adequate.
2. Market effects

(15) We submit that Melamine cannot be substituted by other substances that can be used for similar purposes and in the same way as Melamine. Although other options are, in general, technically possible, available substitutes involve higher risk potentials and, therefore, should not be used. We further submit, that Melamine is produced industrially in large quantities and potential market effects of a potential harmonized classification would require a change of production procedures worldwide.
(16) This, inter alia, due to the fact that a classification as STOT RE would require a change of operational practices and permits with respect to storage requirements. Currently, Melamine does not trigger specific storage requirements, e.g. according to the TRGS 510 in Germany or similar provisions. With a mandatory change to STOT RE Melamine would qualify as a hazardous substance with chronic health effect so that other storage categories would apply. This would tremendously affect all operating sites throughout the EU as amendments to existing permits for businesses (operating, building or storage permits, depending on the applicable national regime) would be necessary. To this end, we respectfully submit that the Commission should grant sufficient lead time and transitional periods prior to the entry into force of a harmonized classification, if and to the extent the Proposal is upheld.
(17) We are of the opinion, however, that the Proposal should be withdrawn on the basis of the scientific arguments submitted by EMPA as well as the aforementioned details.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20200131 EGGER statement Melamine CLH_ECHA.pdf

Dossier Submitter's Response

**Response #16**

The DS appreciates the comments raised by the organisation and would like to refer to response #7. In addition, the DS and ECHA are of the opinion that the justification for STOT RE as provided in the CLH dossier is correct. In the process of the accordance check, ECHA made the following remark: *"In this case none of the registrants or notifiers classify for STOT RE 1, and thus "the dossier submitter disagrees with the current self-classification by the notifiers and/or registrants" would apply."*

The DS would also like to refer to responses #1 and #2 (bullet point (2) and (3)) regarding the raised comments on exposure, uses (wide-spread use, specific route of exposure), and market effects.

RAC's response

Thank you for your comment. Please see response no. 1, 2, 6 and 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Austria | Borealis Agrolinz Melamine GmbH, Borealis Agrolinz Melamine Deutschland GmbH | Company-Manufacturer | 17 |

Comment received

Borealis is a manufacturer of melamine with production facilities located in Germany and Austria. As member of the European Melamine Producers Association (EMPA) Borealis contributed to the scientific commenting of the CLH proposal for Harmonised Classification and Labelling and fully supports EMPA's opinion that no classification for melamine as a carcinogen or for STOT RE is required according to the CLP regulation and ECHA Guidance.
In addition to the scientific evaluation of the available substance information, we would

like to share the following observations about [i] scientific deficiencies, [ii] non-observance of impurities and [iii] the national German consultations about the present proposal.

[i] Scientific deficiencies
The dossier submitter itself valued the available studies according to usual scientific standards. Despite many of them were rated as non-reliable (i.e. provided no information of the purity of the substance or lacked other basic standards) their results were partly used for substance evaluation. Meaning that in the present dossier, unproven assumptions were made and presented as facts in an opportunistic manner. In addition, the substance evaluation is highly one-sided; only arguments supporting the present classification proposal are discussed and considered substantiated. Doubts, which are indicated by the evaluation of the underlying studies are not sufficiently discussed.

[ii] Non-observance of impurities
The substance identification of the proposal foresees a purity of 99.8-100%. Nevertheless, studies that use melamine as a test substance with a purity of <99.8% are considered valid and decisive and assessed as key studies without considering the potential effects of present contaminants or impurities. However, it is well known that the solubility of melamine is depended on the extent of impurities or contaminants. (https://www.who.int/foodsafety/fs_management/Melamine.pdf)
Thus, the observed effects on humans due to the illegal and criminal misuse of melamine in China cannot be attributed to the intrinsic properties of melamine. All observed adverse health effects are caused by particle formation; the present dossier leaves the influence of possible impurities on particle formation completely undiscussed.

[iii] National consultation prior to dossier submission
In contrast to the present dossier, the arguments for and against a classification of the substance melamine were discussed in a highly objective manner in various German expert panels prior to the dossier submission to EHCA.
As a German manufacturer of melamine, representatives of Borealis were invited to take part in the consultations as observers. This process latest from the Registry of Intention (ROI) in summer 2017 to the submission of the classification proposal in autumn 2019. As a result of these consultations, no scientific consensus was reached regarding a recommendation for classification as a Cat 2 carcinogen amongst the experts. In particular, doubts about the human relevance of bladder tumors (comparison with other stone builders) as well as species specificity of bladder tumors in the male rat were reasons for this ambiguous expert assessment.

In the light of the above and the underlying scientific justification according to the EMPA submission, Borealis is of the opinion that no classification as a carcinogen or for STOT RE is required according to the CLP regulation and ECHA Guidance. However, we agree to the proposed non-classification for mutagenicity in the CLH proposal.

Dossier Submitter's Response

**Response #17**

The DS appreciates the comments raised by the organisation with the following response to the main points.

**(1) Scientific deficiencies**

The DS would like to refer to response #7.

**(2) Non-observance of impurities**

The DS would like to refer to response #7, bullet point (12). According to a WHO assessment report, affected children were exposed to melamine with considerably high purity and only insignificant traces of other triazine compounds (Bhalla et al., 2009; WHO/FAO, 2009, page 119 of the CLH dossier).

**(3) The national German consultations about the present proposal.**

The DS would respectfully like to disagree with the following statement: "As a result of these consultations, no scientific consensus was reached regarding a recommendation for classification as a Cat 2 carcinogen amongst the experts."

Following the discussion in the German expert panel, AK CM (expert panel for carcinogenicity and mutagenicity), a consensus statement was developed and agreed including the following conclusions: *"Fragen zur Spezies-Spezifität bzw. Human-Relevanz der Blasenkarzinome werden im CLH-Report detailliert erörtert und in Abgrenzung zur Kat. 1B wurde Melamin der Verdachtskategorie (Kat. 2) zugeordnet. Dieser Schlussfolgerung wird auch seitens des AK CM zugestimmt."* [*Questions regarding the species-specificity or human relevance of bladder carcinomas are discussed in detail in the CLH report and melamine was assigned to the suspected carcinogen category (Cat. 2) in dissociation to Cat. 1B. This conclusion is also agreed upon by AK CM*]; *"Da Steinbildung beim Menschen, jedenfalls nach missbräuchlicher Anwendung, vorgekommen und dies als signifikanter Organschaden zu bewerten ist, wird nach STOT RE1, H372 (Harntrakt) klassifiziert."* [Given that stone formation in humans, at least after misuse, occurs and this can be considered as significant organ damage, classification as STOT RE1, H372 (urinary tract), is applied.]

RAC's response

Thank you for your comment and response to comment.
Please see reponse 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 14.01.2020 | Netherlands | <confidential> | Please select organisation type.. | 18 |

Comment received

We support the scientific position provided by EMPA in each of the hazard classes and endorse EMPA's position

Dossier Submitter's Response

**Response #18**

The DS appreciates the comments raised by the organisation and would like to refer to response #7.

RAC's response

Thank you for your comment.
Please see reponse 7.

## CARCINOGENICITY

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Austria | Metadynea Austria | Company-Downstream user | 19 |

Comment received

It is well known in literature, that Melamine causes urothelial cancer by urothelial stone production (non-genotoxic urinary bladder cancerogen) in male rats.
Diametrically, Melamine is not known to cause urothelial stones and urothelial cancer in female rats, male and female mice, or humans.
The same findings have been revealed decades ago in the authorization as food agent in the case of the artificial sweetener Saccharine. In this case it was shown, that Saccharine is forming urothelial stones with special proteins, which were expressed by male rats only. Also in the saccharine

case, female rats, mice and humans we are not affected and did not show any signs of urothelial stones or cancer.
The incidence of urothelial cancer, caused by precipitation of urothelial stones, is obviously founded by the mode of action of urothelial stone formation.
The mode of action to form an urothelial stone seems to be powered by interaction between Melamine and urinary male-rat specific proteins. These protein-consisting stones are called Proteomes, and in the similar Saccharin case it was shown, that Proteomes consist of intercalation structures between Saccharine and male-rat specific proteins.
Also in the Melamine case there is evidence, that a similar mode of action is also responsible for the incidence of melamine-related stone formation in male rats:

Following literature argumentation and evidence it is clear, that Melamine-caused urothelial bladder cancer, accompanied by urothelial stone formation is a male rat–specific incidence.
Also according to Risk Management implications it would be an undue measure to ground a CLP-Carc 2 reevaluation on test data for male rats only. Hence it is clear, that Melamine does not pose a risk for humans in normal use; hence a reevaluation is not suitable.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to the CLH-proposal on Melamine.pdf

Dossier Submitter's Response

**Response #19**

The DS appreciates the comments raised by the organisation and would like to refer to response #7, bullet point (6) and section 10.8.2 (a) of the CLH dossier: "*Only the effect of sodium salts (e.g. saccharin or ascorbate) in terms of urinary precipitation followed by tumourigenic effects was considered a rat-specific phenomenon. Hereby, urinary precipitation is based on the presence of extraordinarily high urinary concentrations of alpha-2 (α2u) globulin and albumin. The interacting of these proteins with sodium salts deems necessary to form urinary precipitates in rats. Unlike rats, humans have a much lower urinary protein content (100-1000 times lower) and α2u-globulin or a similar protein does not occur (IARC, 1999b). It is worth noting that administration of saccharin leads to precipitation in rats but not in non-human primates, whereas melamine exposure causes calculi/crystal formation in rodents, non-human primates and humans (Early et al., 2013; IARC, 1999b; Lam et al., 2009; Takayama et al., 1998)".*

| RAC's response |
|---|
| Thank you for your comment.<br>Please see reponse 7. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Germany | Pfleiderer Deutschland GmbH | Company-Downstream user | 20 |
| Comment received | | | | |
| See comments of EMPA<br><br>ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ISEGA Unbedenklichkeitserklärung Pfleiderer.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #20**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #7. | | | | |
| RAC's response | | | | |
| Thank you for your comment.<br>Please see reponse 7. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Poland | Grupa Azoty Zakłady Azotowe Puławy S.A. | Company-Manufacturer | 21 |
| Comment received | | | | |
| Grupa Azoty Zakłady Azotowe Puławy S.A. opposes classification of melamine as proposed in the CLH dossier for Melamine (CAS 108-78-1) and further entry in Annex VI of CLP Regulation as Carc. 2, H 351.<br><br>Experts that elaborated ECHA Guidance on the Application of the CLP Criteria in Section 3.6.2.3.2.(k) 3.6.2.3.2. enumerate "urinary bladder tumours due to crystals in the bladder" amongst mechanisms of tumour formation considered not relevant for humans.<br><br>It has been confirmed that the MoA is not relevant to humans. Samuel M. Cohen, M.D., Ph.D., Department of Pathology & Microbiology University of Nebraska Medical Center Omaha, Nebraska, USA - a leading expert on for bladder carcinogens, in his article proves that melamine ingested at high levels can form urinary tract crystals and calculi. However, regardless of the substance that produces the calculi, there is no carcinogenic risk to humans. Because the formation of calculi in humans poses a toxicity issue at high doses, but does not pose a carcinogenic risk to humans.(1)<br><br>Concern has arisen that the demonstration of crystals and calculi in humans in the Chinese infant formula episode changes the risk assessment of the potential carcinogenicity of melamine for humans. However, that is not the case. Urinary tract crystals and calculi can be produced in rodents, pets, and humans by a variety of substances, including the essential ingredients in our diet (calcium, magnesium) a variety of drugs (acetazolamide, sulfonamides, and HIV protease inhibitors), and a variety of chemicals. Many of these substances have produced urinary tract tumors in rodents, especially in rats, so that the risk assessment is entirely on the relationship of urinary | | | | |

solids to tumors, rather than on the specific chemicals, in this case melamine. This issue has been reviewed by a wide variety of agencies, including the International Agency for Research on Cancer, the US Environmental Protection Agency, the European Chemical Agency, European Medicines Agency, Food and Drug Administration, and Health Canada, amongst others. The conclusion of all of these evaluations has been that crystals and calculi pose threshold toxicity concerns for humans, but not carcinogenic risk. This is true regardless of the substance that produced the calculus in the first place.(2)

Lack of tumorigenesis in humans post calculi presence has been justified by a lot of reasons but the most apparent is the anatomy difference between the rodent and the human.

In rodents, calculi can accumulate in the dome of the bladder without complete obstruction of the urinary tract, so that the calculi can remain present in the urinary tract essentially for the lifetime of the animal without complete kidney deterioration. In contrast, in the human urinary tract, calculi produce complete obstruction of the urinary tract. This is partly due to the vertical nature of human stature so that stones cannot accumulate in the bladder, but also because of specific anatomic factors in humans. Specifically, there are several points along the urinary flow which have significant narrowing of the urine passage so that stones can cause obstruction at these sites. These include the site at which the kidney pelvis narrows to become the ureters, secondly, at the point where the ureters cross the pelvic brim, and thirdly, the traversing of the ureter through the urinary bladder muscular wall. If urinary crystals and small calculi form, they will readily be excreted without obstruction, without damage to the urothelium, and will not accumulate in the urinary bladder. Crystalluria in humans does not have the same effect it can have in rodents where cytotoxicity of the urothelium can occur with consequent regenerative proliferation.(3)

Tumors occur in rodents if this (urothelial toxicity and consequent urothelial proliferation) persists for a long period of time. The question is whether these tumorigenic effects occur in all species, whether rodents, pets, or humans. It turns out that the urothelial tumors secondary to urinary crystals or calculi do not predict tumors in other species such as cats, dogs, nonhuman primates, and humans. (4)

Stones in the humans urinary tract (mainly in the kidney) were only observed in children exposed for the limited period of time to criminally adulterated infant formula, therefore permanent exposure above the threshold for stone formation cannot be reasonably assumed in humans. Bladder calculi are more rapidly expelled in humans than in rodents as a result of differences in bladder anatomy between humans and male rats. Even in case of retaining, in humans calculi are present only for short time and tumors do not develop as calculi produce obstructions in the urinary tract causing pain and necessitating medical intervention.

In rodents, the presence of crystals and calculi in the lower urinary tract can lead to chronic irritation of the urothelium and regeneration with the ultimate formation of urothelial tumors (Clayson, Fishbein, and Cohen 1995; Cohen et al.2002). This has been demonstrated not only with melamine but with a large number of other substances, with the rat usually more susceptible than the mouse, and the male rat usually more susceptible than the female rat. (5)

Although on p. 51 of the CLH proposal it is stipulated that: "Persistent urolithiasis (up to 5 years) and chronic renal abnormalities have been reported and linked to potential irreversible damages …. The most recent follow-up analysis reported that 91.4 % of the children (n = 198) expelled their stones after 5 years of their discharge and renal

damages were not found. However, residual stones in the kidney were still observed in 17/198 (8.6 %) subjects (Chang et al., 2017). Another study demonstrated that the size of calculi increased in a small number of patients during a 12 month follow-up period (Dai et al., 2012)" any indication for persistence of melamine stones in humans derived from epidemiological studies is best explained by the background of persistent uroliths of other, non-melamine origin. Melamine bladder stones are not persistent but regress as shown in mice (Ren et al., 2012; Sun et al., 2014). It has been strongly indicated that melamine urolithiasis is reversible and rapid discharge or dissolution of stones occurred after ceasing melamine administration to mice.

Apart from the above, melamine has no intrinsic properties related to its structure, such as genotoxicity, to cause cancer. Abuse and criminal use, which are not 'reasonably expected uses', should not be taken into account for classification according to Article 9(5) of CLP. These observations concern classifications for carcinogenicity as well as for STOT RE1.

IARC classification assessment
IARC on its evaluations on carcinogenicity:
"These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations."(6)
As the following examples show, it is not possible to directly transpose the IARC classification into the CLP classification:

| Carcinogenic chemical | IARC | CLP |
|---|---|---|
| Nitromethane | Group 2B | Not classified |
| Carbon black | Group 2B | Not classified |
| Yperite | Group 2B | Not classified |

What is important, IARC uses the term "agent", whereas the scope of the classification under CLP is confined to substances.

References:
1-3. Evaluation of the Mode of Action of Melamine-induced Urinary Bladder Tumors in Rats and an Assessment of the Human Relevance of its Human Relevance, Samuel M. Cohen
4-5. Crystalluria and Chronic Kidney Disease Toxicologic Pathology 2018, Vol. 46(8) 949-955, Samuel M. Cohen
6. Some chemicals that cause tumours of the urinary tract in rodents, IARC Monographs, Vol 119, 2019

ECHA note – An attachment was submitted with the comment above. Refer to public attachment GA Puławy position on Melamine Classification_Feb 6th 2020_non-confidential.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment GA Puławy position on Melamine Classification_Feb 6th 2020.pdf

Dossier Submitter's Response

**Response #21**

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|---|
| The DS appreciates the comments raised by the organisation and would like to refer to response #6 (bullet points (2) and (3)) and response #7, especially bullet points (6), (8), and (13). |
| RAC's response |
| Thank you for your comment.<br>Please see reponse 6 and 7. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Netherlands | OCI Nitrogen | Company-Manufacturer | 22 |
| Comment received | | | | |
| The argumentation of the CLH-proposal on melamine deviates significantly from the CLH regulation and guidelines, in particular on particle carcinogenicity. Strict application of the CLH regulation and guidelines provide arguments why melamine should not be classified as a carcinogen. This submission focuses on the differences between a substance and a particle.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020 02 05 Regulatory arguments on particle vs substance FINAL.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #22**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #6 (bullet points (2) and (3)) and response #7. The DS would also like to refer to responses #1 and #2 regarding uses (criminal uses, widespread use) and company internal experience. | | | | |
| RAC's response | | | | |
| Thank you for your comment.<br>Please see reponse 1, 2, 6 and 7. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Norway | <confidential> | Company-Importer | 23 |
| Comment received | | | | |
| We do not support the classification proposal of CARC 2. We support the scientific position provided by EMPA. | | | | |
| Dossier Submitter's Response | | | | |
| **Response #23**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #7. | | | | |
| RAC's response | | | | |
| Thank you for your comment.<br>Please see reponse 6 and 7. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Netherlands | OCI Nitrogen | Company-Manufacturer | 24 |
| Comment received | | | | |
| Bladder cancer found in male rats is related to the presence of persistent particles in the bladder and not to the exposure to melamine. | | | | |

Melamine has no intrinsic properties to cause cancer.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020 01 22 OCIN response to CLH proposal of Melamine FINAL.pdf

Dossier Submitter's Response

**Response #24**

The DS appreciates the comments raised by the organisation with the following response to the main points.

**(1) Quality of the studies**

The DS would like to refer to response #2, bullet point (4), and response #7, bullet points (2), (3), and (4).

**(2) Particle effect**

The DS would like to refer to response #6 (bullet point (2) and (3)) and response #7, bullet points (6).

**(3) Intrinsic properties to cause cancer**

The DS would like to refer to response #6 (bullet point (2) and (3)). In addition, the organisation mentions asbestos as an example of a substance that has the intrinsic property to cause cancer. In this case, it is an asbestos fibre, a particle, that causes irritation to the cells in the lung or pleura, ultimately inducing tumour formation in the lung. In the case of melamine, though, particles are formed in the course of internal transformation (i.e. precipitation within the urine). Melamine is not absorbed as a particle by the human body.

RAC's response

Thank you for your comment.
Please see reponse 2, 6 and 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Netherlands | | MemberState | 25 |

Comment received

The NL CA agrees with the classification proposal for Carcinogenicity Cat. 2. There is a clear increase in tumor incidence in male rats and the effects seen in human children during the milk adulteration incident show that this mode of action (formation of calculi within the urinary tract) can be relevant for humans. Further, the correlation between urinary tract calculi and tumor formation in humans further supports the human relevance. For this reason, also category 1B could be supported

We would like to make some remarks on the derivation of the specific concentration limit for carcinogenicity. In the CLH report a T25 is derived from both the 2-year carcinogenicity study and two shorter (36 weeks) repeated exposure studies. It is concluded that melamine should not be considered to have low potency as the T25 values from the 36 week studies fall between 1 and 100 mg/kg bw/d.
We have the following objections against this reasoning:
- In general, the 2-year study should have preference over (much) shorter studies
- In this case this is even more relevant, because as also indicated by the DS, melamine

is a threshold carcinogen. The threshold is probably determined by the dose at which the urinary melamine concentration results in the formation of urinary tract calculi. The actual effective doses during the 36-week studies were around 1000 mg/kg bw/d and the T25 values were derived by extrapolation. It is highly questionable whether this is a valid approach, as the resulting T25 might very well lie under the threshold dose

It would thus have our preference to use the 2-year carcinogenicity study as a starting point. In addition, according to the guidance: "If a NOAEL is identified from the experimental data and the underlying mechanism(s) support a threshold, reference to the NOAEL may be used for setting a specific concentration limit for the carcinogen."
Based on this, an alternative would be to use the NOAEL of 126 mg/kg bw/d for carcinogenicity from the 2-year study by NTP to derive the SCL.
It is noted that this might in fact give the same outcome. As the NOAEL is only slightly above 100 mg/kg bw/d and there are indications humans might be more sensitive than rats as humans have higher urinary uric acid levels, relevant for the formation of melamine-uric acid calculi, we would prefer to take the precautionary route and not derive a specific concentration limit.

Dossier Submitter's Response

**Response #25**

The DS appreciates the comments raised by the Member State. As noted in the CLH dossier (section 10.8.2, page 58), the DS proposes Category 2 rather than 1B for the following reasons:

- *Sufficient evidence of carcinogenicity (benign and malignant tumours) only in the urinary bladder of male rats (key studies in experimental animal studies)*
- *Supporting studies demonstrate the induction of only benign tumours and preneoplastic lesions*
- *Non-genotoxic mode of action*
- *Secondary mechanism of action with a threshold*
- *Sufficient evidence indicating relevance to human carcinogenicity*

With regard to the calculation of the T25, the DS wants to note that the 2-year carcinogenicity study by NTP (1983) was selected as the most relevant study for calculation of a T25.

RAC's response

Thank you for your comment.
RAC agrees that according to EC guidance, a 2-year study should have preference over 36-week exposure studies. The use of a NOAEL instead of the LOAEL could be relevant here but does not change the conclusion on low potency based on the 2-year study. A T25 of 170 mg/kg bw/day is obtained (103/104 x 25/18.4 x 126) using NOAEL and 354 mg/kg using LOAEL. Both T25 points toward a low potency class. RAC agrees that human may be more sensitive to melamine uroliths formation. Nevertheless, due to anatomical differences and the possibility to seek medical advise, human may also be less susceptible. The very short latency period for tumour induction do increase the concern and T25 based on the 36-week studies supporting a medium potency class. All in all, RAC considers that the GCL should be retained for melamine.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 04.02.2020 | Belgium | The European Melamine Producers Association (EMPA) a Sector Group of Cefic and the Melamine Reach Consortium of REACH Centrum | Industry or trade association | 26 |

Comment received

Our objection against classification for carcinogenicity is based on toxicological as well as regulatory arguments.
The mode of action (MoA) for bladder tumour formation in rats by melamine is commonly agreed and may at first sight also be relevant to humans. This mechanism based on precipitation of uroliths followed by chronic irritation and cytotoxicity is specific only for male rats, is reversible and has clearly a threshold. Only the urinary bladder stones, independent of their chemical composition, are responsible for the bladder tumours.
The ECHA Guidance states that urinary bladder tumours due to crystals in the bladder [are] considered not relevant for humans. And this is the MoA applicable to melamine.
The non-relevance of the MoA for humans is supported by experts and bodies, e.g. by SM Cohen (2019) who wrote: ... calculi by themselves are not carcinogenic to the human urinary tract. This is true for melamine ..... The most notably factor for the lack of tumourigenesis in humans is the difference in anatomy between the rodent and the human. The pain and discomfort occurring after a stone has formed will cause humans to seek medical assistance, followed by the removal of the initial cause making cancer development impossible.
Carcinogenicity classification in CLP is intended for substances which have an 'intrinsic property to cause cancer'. Since the chemical composition of the bladder stones plays no role, this MoA is not related to any specific intrinsic property of a substance leading to urinary precipitates. Of course, specific intrinsic properties of melamine enable formation of bladder stones at a threshold exceeding solubility, like low systemic toxicity, no metabolic transformation or low solubility in urine. These properties do not have any direct relation to carcinogenicity and only the dose leading to uroliths is resulting in cancer. Any solid in the urinary bladder like paraffin, glass beads, uracil or thymine may lead to tumour formation and such a particle effect should generally be exempt from classification. This is supported by a variety of publications, e.g. of Cohen and others.
In addition, the different locations of urinary tract stones in rats and humans does not support a direct extrapolation of rat data to humans. To conclude based on these different locations that uroliths may lead to tumours at different sites of the urinary tract in humans is highly speculative.
Of course, it is necessary to decide whether humans can be exposed to melamine above the threshold leading to precipitates for a sufficient time during their life span. Melamine stones have only been observed mainly in China because of criminal adulteration of mainly in infant formula. However, this is the only known event that caused adverse effects in humans and such a criminal use shall be exempted from classification.
The CLH proposal refers to publications from China claiming persistence of melamine stones or their formation after low (environmental) exposures. However, such publications are by far from conclusive as they did not differentiate between melamine stones and those of other origin, like calcium stones. It has been estimated that by the mass screening in China between 6,700 and 134,000 non-melamine urinary stones would have been detected that may erroneously have been interpreted as being caused by melamine. Also, animal studies indicate that melamine precipitates in urine are not

persistent and dissolve after exposure is terminated. In conclusion, although classification does not take into consideration potential exposures, it could only be justified if a situation may exist, apart from criminal abuse of melamine, leading to persistent urinary melamine stones in humans which is not the case.
In addition to classification for carcinogenicity, CLH proposes a classification under the hazard class STOT RE for the first step in the mode of action of tumour formation, i.e. the formation of urinary bladder stones. It can hardly be justified that the first step of the MoA for tumour formation should serve for a double classification in two hazard classes, i.e. STOT RE and carcinogenicity. If consequences by STOT classification are adequately taken into consideration, this will also protect against its secondary effect, cancer. Avoiding uroliths as the primary lesion can be achieved by establishing appropriate exposure limits.
Notwithstanding this basic consideration, the CLP proposal considered STOT classification, primarily STOT RE 1 because in the course of the Chinese incidence, uroliths of melamine led to toxicity in the urinary tract of humans. But these observations were confined to criminal abuse and therefore cannot be used for classification. With regard to STOT RE 2, effective dose levels (EDs) especially from 90d-animal studies leading to toxic effects in target tissues have to be defined. Taking 5 key studies with 14 days up to 2 years duration showed no decrease of the ED with increasing exposure duration. This is explained by the threshold of toxicity with precipitates only being formed if solubility of melamine is exceeded independently from duration of exposure. Therefore, time extrapolation as carried out in the CLH proposal is not justified and for the 5 key studies the EDs are >100 mg/kg bw/d such that STOT RE 2 is not warranted.
See chapter 5 of the main document Comment to the CLH proposal and Annex 2 and Attachments 1.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to the CLH-proposal on Melamine.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Comment to the CLH-proposal on Melamine- Attachment 2.pdf

Dossier Submitter's Response

**Response #26**

The DS appreciates the comments raised by the organisation and would like to refer to response #7.

RAC's response

Thank you for your comment, please see response No 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Czech Republic | Kronospan | Company-Manufacturer | 27 |

Comment received

See attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment REACH-melamine.docx

Dossier Submitter's Response

**Response #27**

The DS appreciates the comments raised by the organisation and would like to refer to response #8.

| RAC's response |
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| Thank you for your comment, please see response No 8. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | EFCC (European Federation for Construction Chemicals) | Industry or trade association | 28 |
| Comment received | | | | |
| See attached EFCC Position Paper on the proposal for Melamine Classification<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment EFCC Position Paper on the proposal for Melamine Classification.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #28**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #9. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response No 9. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | The Phosphorus, Inorganic and Nitrogen (PIN) Flame Retardants Association (pinfa) a Sector Group of Cefic | Industry or trade association | 29 |
| Comment received | | | | |
| Pinfa fully supports the scientific arguments presented by the European Melamine Producers Association (EMPA). | | | | |
| Dossier Submitter's Response | | | | |
| **Response #29**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #7. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response No 7. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Germany | <confidential> | Company-Downstream user | 30 |
| Comment received | | | | |
| Kronospan and Kronochem agree with and support the results of the investigations performed by the European Melamine Producers Association (EMPA) on all aspects of the open hazard classes. In order to avoid duplicity the comments and arguments of the EMPA will be not repeated here. As summary statement we do not see sufficient available | | | | |

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| scientific data and evidence that melamine can be suspected to be classified as carcinogenicity category 2. |
| Dossier Submitter's Response |
| **Response #30**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #7. |
| RAC's response |
| Thank you for your comment, please see response No 7. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | European Panel Federation aisbl (EPF) | Industry or trade association | 31 |
| Comment received | | | | |
| Carcinogenicity: EPF supports the scientific comments of EMPA (European Melamine Producers Association) on this topic. Specifically, EPF questions whether results from studies based on consequences of criminal addition of melamine to milk in China can be considered suitable for a science-based classification of this substance.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Melamine_CLH_Proposal_EPF_Response_ECHA_Public_Consultation_FINAL.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #31**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #12. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response No 12. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | Europur | Industry or trade association | 32 |
| Comment received | | | | |
| Comment with regard to the endpoint included in the attached submission.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Melamine PC Submission.zip | | | | |
| Dossier Submitter's Response | | | | |
| **Response #32**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #13. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response No 13. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | United Kingdom | Vitafoam | Company-Downstream user | 33 |
| Comment received | | | | |
| Vitafoam strongly support the EMPA submission regarding the Reclassification of melamine. In particular, support the viewpoint of the Cohen report Evaluation of the Mode of Action of Melamine-induced Urinary Bladder Tumors in Rats and an Assessment of its Human Relevance<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment melamine submission to ECHA public.docx<br>ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment melamine submission to ECHA Confidential.docx | | | | |
| Dossier Submitter's Response | | | | |
| **Response #33**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #7. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response No 7. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Poland | Polish Chamber of Chemical Industry | Industry or trade association | 34 |
| Comment received | | | | |
| It has been confirmed that the MoA is not relevant to humans. Samuel M. Cohen, M.D., Ph.D., Department of Pathology & Microbiology University of Nebraska Medical Center Omaha, Nebraska, USA - a leading expert on for bladder carcinogens, in his article proves that melamine ingested at high levels can form urinary tract crystals and calculi. However, regardless of the substance that produces the calculi, there is no carcinogenic risk to humans. Because the formation of calculi in humans poses a toxicity issue at high doses, but does not pose a carcinogenic risk to humans.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20200207_ECHA public consultation on melamine classification_stanowisko PIPC.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #34**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #14 and #7. The DS would also like to respectfully disagree with the claim *"It has been confirmed that the MoA is not relevant to humans."*. Given that there are no data proving that the MoA is not relevant to humans, the issue of human relevance cannot be handled as a confirmed fact. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response No 14 and 7. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 31.01.2020 | United States | | Individual | 35 |

Comment received

Melamine administered in the diet increases the incidence of urothelial urinary tract tumors in male rats associated with the induction of urinary tract calculi. Calculi are also produced in female rats and both genders of mice, associated with urothelial hyperplasia but not tumors. Pet feed adulterated with melamine and cyanuric acid produced renal and urinary crystals and calculi in dogs and cats, and adulterated baby formula produced such changes in human infants. In all of these instances, the crystals were composed of melamine with uric acid and/or cyanuric acid. Formation of the crystals and calculi is a physico-chemically based threshold effect. Although CLH presents studies claiming that urinary calculi increase the risk of urinary tract cancer in humans, there are several important anatomic and physiologic differences between rodents and humans that argue against such an association. Furthermore, the studies presented showing an association between calculi and urinary tract cancer have serious methodological issues, most notably confounding and bias because of increased surveillance for urinary tract disease for individuals who develop urinary tract calculi. Also, most individuals with urinary tract calculi also have bacterial cystitis, a known carcinogenic risk factor for urothelial carcinomas, which usually is not adequately assessed in epidemiology studies. Overall, melamine, like numerous pharmaceuticals, essential and non-essential dietary ingredients and endogenously produced chemicals, can produce urinary tract calculi at high exposures with associated toxicity, but does not pose a cancer risk to humans.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Evaluation of the MOA of Melamine 05.29.19 Public Attachment.pdf

Dossier Submitter's Response

**Response #35**

The DS appreciates the comments raised by the individual with the following response to the main points.

**(1) Co-exposure with cyanuric acid**

The DS appreciates the comments and would like to refer to response #7, bullet point (12). According to a WHO assessment report, affected children were exposed to melamine with considerably high purity and only insignificant traces of other triazine compounds (Bhalla et al., 2009; WHO/FAO, 2009, page 119 of the CLH dossier).

**(2) Anatomic and physiologic differences between rodents and humans**

Species-specific anatomical and physiological factors may play a role regarding the response to calculus formation. However, the DS wants to stress that species-independent key events, common to both, rodents and humans, can be clearly identified. According to the comparative analysis of key events (CLH dossier section 10.8.2, page 54-57), there is sufficient evidence that the following key events related to oral melamine exposure can be established in animals and humans: urinary concentration adequate for precipitation, the formation of calculi (regardless of species-specific physiological factors such as protein content in the urine), the persistence of calculi, urothelial irritation/damage, urothelial proliferative lesions. In addition, a considerably large body of evidence from epidemiological studies suggests a significant association between a history of urinary tract stones (unrelated to melamine) and various types of cancer in the urinary tract system. In light of these data, it cannot be concluded that *"the urinary tract of*

*humans is not susceptible to the carcinogenic effect of urinary tract solids"*. The notion that *"calcium is not considered carcinogenic"* while *"calcium-containing salts are the most frequent calculi that form in the human urinary tract"* is misleading since common calcium calculi are (also) associated with an increased risk of urinary tract cancer formation. The claim *"Crystalluria in humans does not have the same effect it can have in rodents where cytotoxicity of the urothelium can occur with consequent regenerative proliferation (11)."* is not supported by data from the publication cited. Accordingly, Dominick *et al.* (2006) rather mentions older epidemiological studies regarding the relationship of calculi in humans and bladder cancer, indicating that *"there is contradictory epidemiologic evidence with respect to the relevance of long-standing bladder calculi in humans to increased risk for bladder cancer"*. However, the CLH dossier lists additional epidemiological studies that were not considered by Dominick *et al.* (2006) with the conclusion that the association between kidney stones and kidney cancer, in particular, is considered strong.

Consequently, tumour formation attribute to melamine in the urinary tract of humans appears plausible. Possible quantitative differences in the carcinogenic response to calculi between species may exist. However, data describing the extent of these differences do not exist. It has rather been suggested that human infants may be more susceptible to the development of melamine-uric acid kidney stones (section 10.8.2 of the CLH dossier, page 50: *"Importantly, as humans lack the enzyme urate oxidase (uricase) that, in most other mammals, converts uric acid to allantoin, uric acid levels are much higher in humans when compared to other mammals such as rats (e.g. 5-fold when comparing human infants to rats) (Alvarez-Lario and Macarron-Vicente, 2010; WHO / FAO, 2009)."*).

The DS would also like to refer to response #7, bullet points (7), (8), and (13).

**(3) Confounding factors in epidemiology studies**

The DS would like to refer to the CLH dossier section 10.8.2 (k), page 53-54. *"Especially for calculi-related induction of bladder cancer, urinary tract infection has been discussed as a potential confounding factor (Burin et al., 1995; McGregor et al., 2010; Meek et al., 2003). Since bacterial infection of the urinary tract is likewise associated with the formation of bladder cancer, identifying the potential cancer-inducing factor is difficult if calculi and infection are simultaneously present (Meek et al., 2003). However, a significantly increased risk of UTC was still observed in patients without a history of urinary tract infections (Chow et al., 1997; Kantor et al., 1984; Sun et al., 2013). Another study reported a statistically significantly increased risk after adjusting for urinary tract infections (Chung et al., 2013a)."* and *"major inherent limitation of an observational epidemiological study, in general, is that it can only describe an association between a potential cause and a given outcome. Causation, however, cannot be established. Several known or unknown confounders and biases may contribute to the outcome of the study. The authors of the two meta-analyses, for instance, discussed a possible surveillance bias, whereas urolithiasis patients may have undergone follow-up examinations that would increase the detection rate of urinary tumours (Cheungpasitporn et al., 2015; Yu et al., 2018). The issue was also discussed in the recent Netherland Cohort Study with the authors concluding that surveillance bias was an unlikely systematic error (van de Pol et al., 2019). In summary, epidemiological studies have established a link between a history of urolithiasis and an increased risk of urinary cancers. The association between kidney stones and kidney cancer, in particular, is considered strong.".*

**Conclusion**

Overall, it is the opinion of the DS that the expert opinion by Cohen cannot be considered strong evidence that the mechanism of tumour formation is not relevant to humans, as many of his claims are insufficiently supported by scientifically sound data. Regarding species-specificity, for instance, there are no data showing that a melamine-related calculus does not affect the urothelium of the urinary tract. In contrast, as particularised in the CLH dossier (section 10.11.1, page 120), *"Macroscopic and microscopic haematuria was described (Gao et al., 2011; Guan et al., 2009; Shang et al., 2012; Shen et al., 2011b; Sun et al., 2010a; Yang et al., 2010b; Zou et al., 2013) and may be a result of stone-related urothelial abrasion/irritation (Schulsinger, 2014; Yang et al., 2010b)."* According to a NEJM review paper, long-term consequences of the Chinese adulteration incident are unknown [Ingelfinger J.R. (2008): Melamine and the global implications of food contamination. New England Journal of Medicine 359 (26), 2745-2748.]. Given that up to now, tumour formation related to melamine exposure has not been observed in humans (respective long-term follow-up studies are not yet available) but the mode of carcinogenic action is plausible, the DS suggests allocating melamine into the suspected human carcinogen category (Cat. 2). This is also supported by IARCs re-evaluation in 2019 and the respective upgrade of the hazard category. In addition, a publication intended to provide guidance for the classification of carcinogens under GHS by McGregor et al. 2010, comes to the following conclusions concerning the carcinogenic potential of melamine: (a) *„In conclusion, although humans appear to be less susceptible to the development of bladder tumours mediated by urinary calculi formation, the established MOA for melamine is considered relevant to humans, in accordance to the comparative analysis of the key events reported in Meek et al (2003)"*, and (b) *„A more conservative classification would consider the unusual situation of the reported abuse of melamine, in which case the MOA described for male rats could have human significance. This different conclusion regarding the human relevance of the MOA leads to a cancer classification Category 2.".*

RAC's response

Thank you for your comment.

**Anatomical and physiological differences**

Due to anatomical differences, human may be less susceptible to calculi retention. Moreover, RAC agrees that in case of complete obstruction, the calculi will be removed by medical treatment or surigery. Nevetheless, RAC notes that calculi may not be always be painful as shown in the epidemiological meta analysis of Wang *et al*., 2013 where 76% of the patients were asymptomatics. RAC considers that although quantitative differences in the response could exist, the MoA is plausible in human.

**Confounding factors**

Regards to cyanuric acid contamination, it is not expected that cyanuric acid was a major confounding factor in the epidemiological human studies as other triazines (such as cyanuric acid) were only found at trace levels in melamine-tainted products. Moreover, in human calculi, cyanuric acid was not found as a component of the stones.
RAC agrees that urinary tract infection may be a confounding factor. Nevertheless, RAC notes that an increased risk was still noted after adjusting for urinary tract infections noted in some studies quoted by the DS.

As noted by IARC, 2019, there is epidemiological evidences that cancer in the urinary tract in human is associated with a history of calculi in the bladder.

Please see also response to comment no.7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Germany | Verband der Chemischen Industrie e.V. (VCI) | Industry or trade association | 36 |
| Comment received | | | | |
| See VCI-Comment attached.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment 200207_GENERAL VCI-COMMENT TO THE HARMONISED CLASSIFICATION AND LABELLING OF MELAMINE.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #36**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #15. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response No 15. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Sweden | chemsec | International NGO | 37 |
| Comment received | | | | |
| ChemSec supports the classification of melamine as a carcinogenic, however, in our opinion the evidence supports a 1b classification "presumed human carcinogen", rather than 2 "suspected human carcinogen".<br><br>The evidence in animals is very extensive, and supported by the existing human studies. We find it speculative to assume that species differences in the urinary tract would make tumor development in humans less likely. In light of the Chinese tainted milk scandal we have learned that the previous assumptions of melamine effects in human were partly wrong. It is to date too early to understand the long-term effects of melamine exposure, and carcinogenicity in humans should not be disregarded. | | | | |
| Dossier Submitter's Response | | | | |
| **Response #37**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #25. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response No 25. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Austria | Borealis Agrolinz Melamine GmbH, Borealis Agrolinz Melamine Deutschland GmbH | Company-Manufacturer | 38 |

| Comment received |
|---|
| We agree to the scientific assessment of EMPA that no classification for melamine as a carcinogen is required according to the CLP regulation and ECHA Guidance. |
| Dossier Submitter's Response |
| **Response #38**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #7. |
| RAC's response |
| Thank you for your comment, please see response No 7. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Sweden | | MemberState | 39 |
| Comment received | | | | |
| The Swedish CA supports classification of Melamine (CAS No. 108-78-1) as at least Carc. Category 2. | | | | |
| Dossier Submitter's Response | | | | |
| **Response #39**<br><br>The DS appreciates the comments raised by the Member State. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | France | | MemberState | 40 |
| Comment received | | | | |
| Mori et al. (2000) study was disregarded by the dossier submitter. The deviations cited as "shorter treatment time, only one dose, only males, low number of animals, limited number of tissues examined" suggest that the study may be not sufficiently sensitive to detect carcinogenic potential of melamine. However, positive effects were reported. Therefore, we consider that this study can be quoted as "supporting study" since adequate conclusion can be reached from this study on the promoting potential of melamine.<br><br>On page 40: Human information: some cohort studies on workers exposed to melamine exist in the literature and can be cited here, even if the evidence was considered as inadequate by the IARC in 2017.<br><br>On page 41, you cite that "There is limited evidence from mice as only two studies address tumourigenesis in this species". The limited evidence from mice should not be based on the number of available studies in mice but rather on the results and quality of these studies: negative result in an adequate 2-year study and some effects reported at very high dose in a non-guideline study.<br><br>On page 45 (b) multi-site response: it is noted that "The incidence of malignant neoplasms was significantly increased in the urinary bladder of male rats (Melnick et al., 1984; NTP, 1983; Ogasawara et al., 1995; Okumura et al., 1992). Papillomas and a single tumour were found in the ureter of male rats (Okumura et al., 1992). D/CIS were reported in the urinary bladder, the ureter, and to a lesser extent in the renal pelvis of | | | | |

mice (Cremonezzi et al., 2001). Preneoplastic lesions such as hyperplasias and metaplasias were observed in the upper urinary tract (kidney, ureter) of rats and mice (Cremonezzi et al., 2004; Cremonezzi et al., 2001; Melnick et al., 1984; NTP, 1983; Ogasawara et al., 1995; Okumura et al., 1992)." It should be noted that examination of the ureters and urethra was not performed in the NTP (1983) study, which is the key study. Therefore, it cannot be excluded that neoplasms can arise at these sites.

The AOP "Urinary bladder calculi leading to urothelial papillomas and carcinomas (in mouse and rat)" is under development (last information dated on January 2018). Do you have some information on the progress of this AOP?

We agree with the proposed classification as Carc. Cat. 2 for melamine.

SCL: 103 weeks refer to the duration of exposure in the NTP study, thus the age of the animals at the start of treatment should not be subtracted in the equation for correction of exposure (in the NTP report, it is specified that the animals were placed on study at 6 weeks and killed at 111 weeks). Same comment applies to the Okumura (1992) and Ogasawara (1995) studies, for which the duration of exposure is 36 weeks and not 30 weeks as noted in the calculations. Nevertheless, this does not affect the conclusion and we agree that no SCL should be proposed for melamine.

Dossier Submitter's Response

**Response #40**

The DS appreciates the comments raised by the Member state. The results by Mori et al. (2000) have to be interpreted in the context of the initial treatment with N-butyl-N-(4-hydroxybutyl)nitrosamine (a known inducer of bladder cancer). The DS is therefore of the opinion that the study is not relevant for classification. The AOP regarding ECHA's guidance is ongoing. Suggestions have been made and are currently under discussion.

RAC's response

Thank you for your comment. Regards to SCL, RAC considers that the obtained T25 based on the NTP, 1983 study is in favour of a low potency class for melamine. Nevertheless due to the very short latency period, studies with lower duration (36-week duration) may provide a relevant basis for melamine T25 calculation and point towards a medium potency class. On this basis, no SCL is considered warranted.

**MUTAGENICITY**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | EFCC (European Federation for Construction Chemicals) | Industry or trade association | 41 |

Comment received

See attached EFCC Position Paper

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EFCC Position Paper on the proposal for Melamine Classification.pdf

Dossier Submitter's Response

**Response #41**

The DS appreciates the comments raised by the organisation.

RAC's response

Thank you for your comment.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | The Phosphorus, Inorganic and Nitrogen (PIN) Flame Retardants Association (pinfa) a Sector Group of Cefic | Industry or trade association | 42 |
| Comment received | | | | |
| Pinfa fully supports the scientific arguments presented by the European Melamine Producers Association (EMPA). | | | | |
| Dossier Submitter's Response | | | | |
| **Response #42**<br><br>The DS appreciates the comments raised by the organisation. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Germany | Pfleiderer Deutschland GmbH | Company-Downstream user | 43 |
| Comment received | | | | |
| See comments of EMPA<br><br>ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ISEGA Unbedenklichkeitserklärung Pfleiderer.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #43**<br><br>The DS appreciates the comments raised by the organisation. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Poland | Grupa Azoty Zakłady Azotowe Puławy S.A. | Company-Manufacturer | 44 |
| Comment received | | | | |
| Grupa Azoty Zakłady Azotowe Puławy S.A. agrees with the proposed non-classification for mutagenicity in the CLH proposal.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment GA Puławy position on Melamine Classification_Feb 6th 2020_non-confidential.pdf<br>ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment GA Puławy position on Melamine Classification_Feb 6th 2020.pdf | | | | |

| Dossier Submitter's Response |
|---|
| **Response #44**<br><br>The DS appreciates the comments raised by the organisation. |
| RAC's response |
| Thank you for your comment. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 04.02.2020 | Belgium | The European Melamine Producers Association (EMPA) a Sector Group of Cefic and the Melamine Reach Consortium of REACH Centrum | Industry or trade association | 45 |
| Comment received | | | | |
| The CLH dossier for Melamine (CAS 108-78-1) proposes no classification in a future entry in Annex VI of CLP Regulation for mutagenicity. We agree with this proposal.<br>See chapter 4 of the main document Comment to the CLH proposal.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to the CLH-proposal on Melamine.zip<br>ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Comment to the CLH-proposal on Melamine- Attachment 2.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #45**<br><br>The DS appreciates the comments raised by the organisation. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Netherlands | OCI Nitrogen | Company-Manufacturer | 46 |
| Comment received | | | | |
| We agree with the CLH proposal<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020 01 22 OCIN response to CLH proposal of Melamine FINAL.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #46**<br><br>The DS appreciates the comments raised by the organisation. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Germany | Verband der Chemischen Industrie e.V. (VCI) | Industry or trade association | 47 |
| Comment received | | | | |
| See VCI-Comment attached.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment 200207_GENERAL VCI-COMMENT TO THE HARMONISED CLASSIFICATION AND LABELLING OF MELAMINE.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #47**<br><br>The DS appreciates the comments raised by the organisation. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Norway | <confidential> | Company-Importer | 48 |
| Comment received | | | | |
| We support the classification proposal (Not classified for mutagenicity). | | | | |
| Dossier Submitter's Response | | | | |
| **Response #48**<br><br>The DS appreciates the comments raised by the organisation. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | France | | MemberState | 49 |
| Comment received | | | | |
| FR: we agree that no classification is required for melamine based on the dataset presented in the CLH report. | | | | |
| Dossier Submitter's Response | | | | |
| **Response #49**<br><br>The DS appreciates the comments raised by the Member State. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Austria | Borealis Agrolinz Melamine GmbH, Borealis Agrolinz Melamine Deutschland GmbH | Company-Manufacturer | 50 |
| Comment received | | | | |
| We agree to the proposed non-classification for mutagenicity. | | | | |
| Dossier Submitter's Response | | | | |
| **Response #50**<br><br>The DS appreciates the comments raised by the organisation. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Czech Republic | Kronospan | Company-Manufacturer | 51 |
| Comment received | | | | |
| See attached document.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment REACH-melamine.docx | | | | |
| Dossier Submitter's Response | | | | |
| **Response #51**<br><br>The DS appreciates the comments raised by the organisation. | | | | |
| RAC's response | | | | |
| Thank you for your comment. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Austria | Metadynea Austria | Company-Downstream user | 52 |
| Comment received | | | | |
| It is known in common and peer-reviewed literature, that ingestion of a high amount of Melamine may cause dangerous conditions for the kidney by kidney failure.<br>The case only cited in this respect was an attempt of Chinese criminals to upgrade a low-quality milk-powder to a high quality product in 2008. Since the milk quality is measured by the Nitrogen content (Kjeldahl-Method), the criminals used Melamine, solved in highly watered milk and processed to milk powder, to pretend a high Nitrogen content and hence high quality. Babies and toddlers, who were administered with these milk powder showed a high disposition for kidney failure.<br><br>It is clear, that such criminal attempt is not a reasonably expected use of Melamine according to the premises for evaluation, laid down in Art 9(5) CLP Directive: | | | | |

5. When evaluating the available information for the purposes of classification, the manufacturers, importers and downstream users shall consider the forms or physical states in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used.
Hence it is not in accordance with the good practice of CLP-reevaluation to evaluate unreasonable uses of Melamine. In that case we submit respectful the proposal to refrain from evaluation into STOT RE 1 ground by data based on unreasonable use.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to the CLH-proposal on Melamine.pdf

Dossier Submitter's Response

**Response #52**

The DS appreciates the comments raised by the organisation and would like to refer to responses #1 and #2 regarding data originated from the melamine adulteration incident and reasonably expected use. With regard to STOT RE, the DS agrees with the statement by S.M. Cohen: *"The formation of calculi in humans poses a toxicity issue at high doses but does not lead to increased tumor incidences in humans."* (Cohen, 2019). While constituting a serious concern, the effects of low-dose exposure remain to be elucidated.

RAC's response

Thank you for your comment.
RAC considers that the severity and the adversity of the effects observed in animals at doses relevant for classificaiton does not fulfil the criteria for STOT RE classification.

Regarding human data, similar chronic renal diseases, as seen in animals may be expected in human. Moreover, kidney injuries seen in human that can lead in few cases to acute renal failure, is a severe effect of concern relevant for classification. RAC acknowledge the higher susceptibility of children consuming only tainted-infant formula to kidney failure. Moreover, kidney failure is expected to be seen only following high dose exposure. The acute renal failure recovered following treatment in follow-up patients. Therefore, RAC considers that the classification criteria for STOT RE 2 instead of STOT RE 1 based on human data is appropriate.

Please also see response to comment no. 1 and 2.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Germany | Pfleiderer Deutschland GmbH | Company-Downstream user | 53 |

Comment received

See comments of EMPA

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ISEGA Unbedenklichkeitserklärung Pfleiderer.pdf

Dossier Submitter's Response

**Response #53**

The DS appreciates the comments raised by the organisation and would like to refer to response #7.

RAC's response

Thank you for your comment. Please see response to comment no. 7.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | Poland | Grupa Azoty Zakłady Azotowe Puławy S.A. | Company-Manufacturer | 54 |

Comment received

Grupa Azoty Zakłady Azotowe Puławy S.A. opposes classification of melamine as proposed in the CLH dossier for Melamine (CAS 108-78-1) and further entry in Annex VI of CLP Regulation as Carc. 2, H 351 and STOT RE1, H372.

According to the position of the German body BauA (1) : "Substantial body of evidence concerning melamine-related toxicity following repeated oral exposure exists. Relevant data are derived from both experimental animal studies and observational studies in humans".
The "Chinese incident" is described in the report as well-substantiated human data. However, criminal use of the substance is neither relevant for STOT RE classification nor can be the basis for a reliable toxicological assessment. This contradicts both the CLP regulation and the ECHA guidance.
CLH report presents the results of several studies on rats. Most results of these tests show that oral toxicity dose applied on rats - LD50 is above 100 mg/kg bw/day in a 13 week test (Melnick et al. (1984) and NTP (1983) – p. 70 of CLH report). The CLP Regulation (section 3.9.2.9.6. and Table 3.9.2) requires that the result of an oral test performed in rats indicate a toxic dose is below or equal to 10 mg/kg bw/day in order to be able to classify substances as STOT RE 1.
Moreover, most of these tests do not allow classification as STOT RE 2, because a toxic dose of 10 - 100 mg/kg bw/day is required for such classification (>100 mg/kg bw/day was applied), (acc. to table 3.9.3 of the CLP Regulation). However, here, the dose was much higher.
Therefore, because Chinese milk incident should not be used and tests results definitely show too high levels of toxic doses applied than that required by CLP Regulation, there is no substantive basis to classify melamine as STOT RE (1 and 2).
References:
1. CLH report Proposal for Harmonised Classification and Labelling, Federal Institute for Occupational Safety and Health (BAuA), Version: 1.0, November 2019.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment GA Puławy position on Melamine Classification_Feb 6th 2020_non-confidential.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment GA Puławy position on Melamine Classification_Feb 6th 2020.pdf

Dossier Submitter's Response

**Response #54**

The DS appreciates the comments raised by the organisation and would like to refer to responses #1 and #2 regarding data originated from the melamine adulteration incident and reasonably expected use. In addition, the DS would like to draw attention to section 10.11.2: *"In line with observations in humans, significant adverse effects on the urinary system have been documented following repeated oral exposure to melamine in experimental animals. Based on information derived from key studies, the spectrum of toxic effects considered relevant for classification includes calculus formation in the urinary bladder of male rats (NTP, 1983), dose-related calcareous deposits in the straight segments of the proximal renal tubules in female rats (NTP, 1983), renal crystals in*

| |
|---|
| *female rats (Early et al., 2013), and renal damages in male and female rats (Early et al., 2013). Information derived from supporting studies is consistent with the effects described in the key studies and largely supports the classification as part of the weight of evidence approach. Significant adverse effects on the urinary system were consistently reported at doses close to or below the guidance value of 100 mg/kg bw/d and above 10 mg/kg bw/d (Table 39) which would potentially justify a classification in category 2 (CLP Regulation 1272/2008, 3.9.1.1.; Table 3.9.1).".* |
| RAC's response |
| Thank you for your comment, please see response to comment no. 52. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Norway | <confidential> | Company-Importer | 55 |
| Comment received | | | | |
| We do not support the classification proposal of STOT 1 RE. We support the scientific positition provided by EMPA. | | | | |
| Dossier Submitter's Response | | | | |
| **Response #55**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #7. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response to comment no. 7. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2020 | Netherlands | OCI Nitrogen | Company-Manufacturer | 56 |
| Comment received | | | | |
| A STOT RE 1 or a STOT RE 2 classification is unjustified.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020 01 22 OCIN response to CLH proposal of Melamine FINAL.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #56**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to responses #6 and #7. | | | | |
| RAC's response | | | | |
| Thank you for your comment, please see response to comment no. 1, 2 and 7. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 04.02.2020 | Belgium | The European Melamine Producers Association (EMPA) a Sector Group of Cefic and the Melamine Reach Consortium of REACH Centrum | Industry or trade association | 57 |

| Comment received |
| --- |
| Our objection against classification for STOT RE is based on toxicological as well as regulatory arguments.<br>The mode of action (MoA) for bladder tumour formation in rats by melamine is commonly agreed and may at first sight also be relevant to humans. This mechanism based on precipitation of uroliths followed by chronic irritation and cytotoxicity is specific only for male rats, is reversible and has clearly a threshold.<br>It is necessary to decide whether humans can be exposed to melamine above the threshold leading to precipitates for a sufficient time during their life span. Melamine stones have only been observed mainly in China because of criminal adulteration of mainly in infant formula. However, this is the only known event that caused adverse effects in humans and such a criminal use shall be exempted from classification.<br>The CLH proposal refers to publications from China claiming persistence of melamine stones or their formation after low (environmental) exposures. However, such publications are by far from conclusive as they did not differentiate between melamine stones and those of other origin, like calcium stones. It has been estimated that by the mass screening in China between 6,700 and 134,000 non-melamine urinary stones would have been detected that may erroneously have been interpreted as being caused by melamine. Also, animal studies indicate that melamine precipitates in urine are not persistent and dissolve after exposure is terminated. In conclusion, although classification does not take into consideration potential exposures, it could only be justified if a situation may exist, apart from criminal abuse of melamine, leading to persistent urinary melamine stones in humans which is not the case.<br>Notwithstanding this basic consideration, the CLP proposal considered STOT classification, primarily STOT RE 1 because in the course of the Chinese incidence, uroliths of melamine led to toxicity in the urinary tract of humans. But these observations were confined to criminal abuse and therefore cannot be used for classification. With regard to STOT RE 2, effective dose levels (EDs) especially from 90d-animal studies leading to toxic effects in target tissues have to be defined. Taking 5 key studies with 14 days up to 2 years duration showed no decrease of the ED with increasing exposure duration. This is explained by the threshold of toxicity with precipitates only being formed if solubility of melamine is exceeded independently from duration of exposure. Therefore, time extrapolation as carried out in the CLH proposal is not justified and for the 5 key studies the EDs are >100 mg/kg bw/d such that STOT RE 2 is not warranted.<br>See chapter 6 of the main document Comment of the CLH proposal.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to the CLH-proposal on Melamine.zip<br>ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Comment to the CLH-proposal on Melamine- Attachment 2.pdf |
| Dossier Submitter's Response |
| **Response #57**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #1, #2, and #7. |
| RAC's response |
| Thank you for your comment. RAC agrees that Haber's rule should be used with care in the case of melamine induced toxicity. Please see also response to comment no. 52. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Czech Republic | Kronospan | Company-Manufacturer | 58 |
| Comment received | | | | |
| See attached document.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment REACH-melamine.docx | | | | |
| Dossier Submitter's Response | | | | |
| **Response #58**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #8. | | | | |
| RAC's response | | | | |
| Thank you for your comment. Please see response to comment no. 8. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | EFCC (European Federation for Construction Chemicals) | Industry or trade association | 59 |
| Comment received | | | | |
| See attached EFCC Position Paper on the proposal for Melamine Classification<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment EFCC Position Paper on the proposal for Melamine Classification.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #59**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #9. | | | | |
| RAC's response | | | | |
| Thank you for your comment. Please see response to comment no. 9. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | The Phosphorus, Inorganic and Nitrogen (PIN) Flame Retardants Association (pinfa) a Sector Group of Cefic | Industry or trade association | 60 |
| Comment received | | | | |
| Pinfa fully supports the scientific arguments presented by the European Melamine Producers Association (EMPA). | | | | |
| Dossier Submitter's Response | | | | |
| **Response #60** | | | | |

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| The DS appreciates the comments raised by the organisation and would like to refer to response #7. |
| RAC's response |
| Thank you for your comment. Please see response to comment no. 7. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Belgium | Europur | Industry or trade association | 61 |
| Comment received | | | | |
| Comment with regard to the endpoint included in the attached submission.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Melamine PC Submission.zip | | | | |
| Dossier Submitter's Response | | | | |
| **Response #61**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #13. | | | | |
| RAC's response | | | | |
| Thank you for your comment. Please see response to comment no. 13. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Germany | Verband der Chemischen Industrie e.V. (VCI) | Industry or trade association | 62 |
| Comment received | | | | |
| See VCI-Comment attached.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment 200207_GENERAL VCI-COMMENT TO THE HARMONISED CLASSIFICATION AND LABELLING OF MELAMINE.pdf | | | | |
| Dossier Submitter's Response | | | | |
| **Response #62**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #15. | | | | |
| RAC's response | | | | |
| Thank you for your comment. Please see response to comment 1. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Sweden | chemsec | International NGO | 63 |
| Comment received | | | | |
| ChemSec supports the classification of melamine as STOT RE 1 in the light of the strong and convincing evidence laid out in the dossier. | | | | |
| Dossier Submitter's Response | | | | |
| **Response #63**<br><br>The DS appreciates the comments raised by the organisation. | | | | |

| RAC's response |
|---|
| Thank you for your comment. Please see response to comment 52. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.02.2020 | Austria | Borealis Agrolinz Melamine GmbH, Borealis Agrolinz Melamine Deutschland GmbH | Company-Manufacturer | 64 |

| Comment received |
|---|
| We agree to the scientific assessment of EMPA that no classification for melamine as STOT RE is required according to the CLP regulation and ECHA Guidance. |
| Dossier Submitter's Response |
| **Response #64**<br><br>The DS appreciates the comments raised by the organisation and would like to refer to response #7 and #17. |
| RAC's response |
| Thanl you for your comment. Please see response to comment 7 and 52. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 06.02.2020 | France | | MemberState | 65 |

| Comment received |
|---|
| Animal data:<br>As recommended in the CLP guidance, studies with duration less than 9 days should be considered with caution for classification purpose.<br><br>According to CLP guidance, the ED corresponds to the lowest dose inducing significant/severe target organ toxicity. In the absence of other lesions associated, it can be questioned if "calculus formation" should be considered as a "significant/severe target organ toxicity" for STOT RE classification. If not, a classification as STOT RE is, nevertheless, adequate based on severe lesions in the urinary tract that occur at higher concentrations - fulfilling category 2.<br><br>Human data:<br>Human data are consistent to animal findings. Effects are mainly reported with "high" oral exposure of melamine. Some associations between urinary melamine concentration and renal effects were noted in occupational conditions, but without information on quantitative exposure to melamine.<br><br>In conclusion, we agree that melamine needs to be classified as STOT RE for the urinary tract. Category 1 can be justified based on human data. Indeed, the level of exposure for human is not taken into account for categorisation according to CLP guidance. |
| Dossier Submitter's Response |
| **Response #65**<br><br>The DS appreciates the comments raised by the Member State. |
| RAC's response |
| Thank you for your comment. Please see response to comment 52. |

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON MELAMINE**

PUBLIC ATTACHMENTS
1. REACH-melamine.docx [Please refer to comment No. 8, 27, 51, 58]
2. EFCC Position Paper on the proposal for Melamine Classification.pdf [Please refer to comment No. 9, 28, 41, 59]
3. Melamine_CLH_Proposal_EPF_Response_ECHA_Public_Consultation_FINAL.pdf [Please refer to comment No. 12, 31]
4. Melamine PC Submission.zip [Please refer to comment No. 13, 32, 61]
5. melamine submission to ECHA public.docx [Please refer to comment No. 33]
6. 20200207_ECHA public consultation on melamine classification_stanowisko PIPC.pdf [Please refer to comment No. 14, 34]
7. 200207_GENERAL VCI-COMMENT TO THE HARMONISED CLASSIFICATION AND LABELLING OF MELAMINE.pdf [Please refer to comment No. 15, 36, 47, 62]
8. Comment to the CLH-proposal on Melamine.pdf [Please refer to comment No. 19, 52]
9. GA Puławy position on Melamine Classification_Feb 6th 2020_non-confidential.pdf [Please refer to comment No. 2, 21, 44, 54]
10. 2020 02 05 Regulatory arguments on particle vs substance FINAL.pdf [Please refer to comment No. 22]
11. 2020 01 22 OCIN response to CLH proposal of Melamine FINAL.pdf [Please refer to comment No. 6, 24, 46, 56]
12. Comment to the CLH-proposal on Melamine.zip [Please refer to comment No. 7, 26, 45, 57]
13. Evaluation of the MOA of Melamine 05.29.19 Public Attachment.pdf [Please refer to comment No. 35]
14. 20200131 EGGER statement Melamine CLH_ECHA.pdf [Please refer to comment No. 16]

CONFIDENTIAL ATTACHMENTS
1. melamine submission to ECHA Confidential.docx [Please refer to comment No. 33]
2. ISEGA Unbedenklichkeitserklärung Pfleiderer.pdf [Please refer to comment No. 1, 20, 43, 53]
3. GA Puławy position on Melamine Classification_Feb 6th 2020.pdf [Please refer to comment No. 2, 21, 44, 54]
4. Comment to the CLH-proposal on Melamine- Attachment 2.pdf [Please refer to comment No. 7, 26, 45, 57]