COMMENTS TO THE CLH PROPOSAL ON MELAMINE CLASSIFICATION

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Grupa Azoty Zakłady Azotowe Puławy S.A. ("ZAP") 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. ZAP agrees with the proposed non-classification for mutagenicity in the CLH proposal.

Melamine milk adulteration incident

As an introductory point, ZAP believes that unwarranted focus has been given to the old incident involving illegal addition of melamine to powdered milk in China 10 years ago,[1] 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

[1] Contamination is believed to have occurred at milk collection centres, where melamine was added to boost apparent protein content as dairy firms judge milk quality mostly by protein content, which they estimate from nitrogen levels. Addition of 1 g of melamine to 1 L of milk falsely increases protein content by 0.4%. When melamine is dissolved at the room temperature, 3.1 g of melamine can be dissolved in water without forming precipitate and protein content will appear to have increased by 1.2%. This could roughly lead to an overestimation of protein content in liquid milk by 30%. In case of milk powder, the amount of melamine added could be greater because of its greater solubility at higher temperature when adding warm water.

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[2], and other countries as well, such as India[3] or the EU.

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:

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[2] 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.

[3] 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.

- 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[4] in which a Specific Migration Limit (SML) for melamine of 2.5 mg/kg food is set.

Surely still all the parties involved in the food-production chain (both food producers and authorities) are tracking and working to 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

[4] 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

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 closed systems designed and operated such that the product is not exposed to the room environment. 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.

Specific target organ toxicity – repeated exposure

According to the position of the German body BauA (6) : "*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 ≤ 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, <u>there is no substantive basis to classify melamine as STOT RE (1 and 2).</u>

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 <u>in compliance with the principles of good laboratory practice</u> 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:

"<u>If tests are performed, they should comply where appropriate with</u> the relevant requirements for the protection of laboratory animals, set out in Directive 86/609/EEC, and, <u>in the case of ecotoxicological and toxicological tests, good laboratory practice</u>, 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.

Carcinogenicity

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.

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.(7)

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. <u>The conclusion of all of these evaluations has been that crystals</u>

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.(8)

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.(9)

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. (10)

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. (11)

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."(12)

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.

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