Date: February 5, 2020

Subject: **Regulatory aspects not to classify melamine**

1 Summary

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.

No *substance*- but a *particle*-carcinogenicity is observed for melamine. Only the urinary bladder stones, independent of their chemical composition, are responsible for the bladder tumours due to prolonged irritation, as is known also from other (partly inert) particles, composed of e.g. paraffin, glass beads.

A particle carcinogenicity is not within the scope of CLP carcinogenicity classification, it is restricted to classifying substances and/or mixtures

The substance Melamine is therefore not within the scope of carcinogenicity classification under CLP and should not be classified for carcinogenicity.

2 Scope of carcinogenicity classification in CLP

<u>CLP:</u>

See the following statements in the CLP regulation:

1. Regulation REGULATION (EC) No 1272/2008, page 2, item (10):

*"The objective of this Regulation should be to determine which **properties of substances and mixtures** should lead to a classification as hazardous, in order for the hazards of substances and mixtures to be properly identified and communicated. Such properties should include physical*

hazards as well as hazards to human health and to the environment, including hazards to the ozone layer."

2. Annex I chapter 3.6 Carcinogenicity, page 103:

"3.6.1. Definition

*3.6.1.1. Carcinogen means **a substance or a mixture of substances** which induce cancer or increase its incidence. **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.*

*3.6.2. Classification criteria for **substances***

*3.6.2.1. For the purpose of classification for carcinogenicity, **substances** are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route-specific classification may be warranted, if it can be conclusively proved that no other route of exposure exhibits the hazard"*

See the following statements in the CLP guidance:

1. Chapter 1.1.3. Hazard Classification, page 46:

*"'Classification according to CLP is based on intrinsic hazards, i.e. the basic properties of a **substance or mixture** as determined in standard tests or by other means designed to identify hazards."*

2. Chapter 3.6.2.3 Evaluation of Hazard information, page 378:

*Annex I: 3.6.2.2.1. Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for **substances** which have an **intrinsic property** to cause cancer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.*

*Annex I: 3.6.2.2.2. Classification of a **substance** as a carcinogen is a process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.*

The examples shown above from both the CLP regulation and the CLP guidance clearly refer to either the substance or the mixture. So it is relevant whether the identified hazard or classification is applicable for the substance melamine. In addition a possible classification for carcinogenicity should be based on intrinsic properties of the substance melamine.

Only the particles, formed in the urinary bladder after a precipitation in urine at high doses, are responsible for the tumour development due to prolonged irritation in male rats. This mechanism is only associated with the presence of particles in the urinary bladder, independent from the chemical composition of such particles. No other mechanism of the tumours is known than the MoA starting with the formed urinary bladder stones. Such particle carcinogenicity should not be within the scope of CLP since as already mentioned above, classification should primarily be applicable for substances with an intrinsic activity for carcinogenicity.

Intrinsic properties of melamine:

Melamine has many intrinsic properties, e.g. a low toxicity that enables a high dose and thereby enables exceeding the solubility in urine. Other intrinsic properties of melamine that contribute to a possible crystallisation in urine are e.g.: a high absorption, practically no metabolism, practically only excretion with urine, and solubility in urine. Melamine has therefore various intrinsic properties, as each other substance has too, but these properties cannot be considered specific to cause cancer, such as genotoxicity.

The mode of action of tumour formation by melamine is driven by particles formed from precipitates of melamine in the urine. Cancer is a secondary consequence of the formation of bladder stones. The urinary bladder tumour is independent of the composition of the bladder stones.

Paraffin particles, if implanted in the urinary bladder of rats, are also known to cause bladder tumours. Paraffin being an inert substance has also no known intrinsic property to cause cancer. But still these particles - independent of their chemical composition - are known to cause cancer if long-lasting in the urinary bladder.

No indication is found in the CLP that all possible substances materials of which bladder stone can consist of (such as paraffin, glass, beads) should be classified as carcinogens, or in general to classify particles that cause cancer via formation of precipitates in the urinary tract. Also the experts preparing the ECHA Guidance, came to the conclusion that particle carcinogenicity in the urinary bladder does not qualify for carcinogenicity classification under CLP as stated on page 387: " Some mechanisms of tumour formation considered not relevant for humans: Urinary bladder tumours due to crystals in the bladder (IARC, 1999)" .

In conclusion, melamine is to be excluded from carcinogenicity classification under CLP, because 1) particle carcinogenicity is not within the scope of CLP 2) Melamine has no intrinsic properties to cause cancer.