Comment to the CLH-proposal on Melamine

Author:

Author is a Melamine Downstream User
.

Issued on: February 6th, 2020

Proposal by German Authorities

The CLH dossier for Melamine (CAS 108-78-1) proposes an entry in CLP Annex VI as Carc. 2, H351 and STOT RE 1, H372.

Conclusions

Authors opinion is that the proposed classification as Carc. 2, H351 and STOT RE 1, H372. fails to meet the justification for classifying because of toxicological- scientific and legal/regulatory reasons, respectively.
Author proposes to remain with non-classification for carcinogenicity and STOT.

Regarding Classification Carc 2

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:

Proteome of Melamine Urinary Bladder Stones and Implication for Stone Formation

(Jian-dong Liu, Jian-jun Liu, Jian-hui Yuan, Gong-hua Tao, De-sheng Wu, Xi-fei Yang, Lin-qing Yang, Hai-yan Huang, Li Zhou, Xin-yun Xu, Jun-jie Hu, Zhi-xiong Zhuang, Toxicol Lett, 212 (3), 307-14) 2012)

Melamine can cause urinary stones related to nephropathy of the kidney and hyperplasia or carcinoma of the bladder, but the mechanism of stone formation is not well understood. In this study, male rats were administered melamine for thirteen weeks to establish melamine bladder stone models and the stones were analysed by Fourier transform infrared (FTIR) spectroscopy, powder X-ray diffraction (XRD), energy dispersive X-ray (EDX) spectroscopy, sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) and western blot, respectively, for the composition and proteome, and to explore the implication of proteins for stone formation. The results showed bladder stones were composed of predominant melamine and a few amount of proteins. The proteins had a wide range of molecular weights and 1051 proteins were identified. Gene Ontology (GO) classification of the identified proteins showed most proteins were from injured cells, involved in various metabolic processes and had binding functions. Of the identified proteins, there were a few inflammatory proteins and urinary proteins. Physicochemical characteristics of the identified proteins

showed that 67.1% proteins' isoelectric points (pI) value was below 7.0, 91.1% proteins' grand average of hydropathicity (GRAVY) scores were below 0 and nearly half of the proteins were stable. Our data indicated proteins might play an important role in melamine bladder stone formation.

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.

Regarding Classification STOT RE1

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.
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.[1]

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:

---

1 J Ding. Kidney Int 75 (8), 780-2. Apr 2009.
YM Chang et al. Zhongguo Dang Dai Er Ke Za Zhi 12 (4), 278-9. Apr 2010.

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.