Memo

Date January 22, 2020

Response to CLH proposal on Melamine

OCI Nitrogen is one of the world-leading melamine producers. In Europe, OCI Nitrogen produces melamine on the Chemelot Industrial site in The Netherlands.

OCI Nitrogen is of the opinion that neither classification of melamine as a carcinogen nor for STOT RE is required, given the available scientific and regulatory arguments.

OCI Nitrogen is member of EMPA – the European Melamine Producers Association. It endorses the extended response of EMPA and the arguments jointly listed by EMPA and the Melamine REACH Consortium.

In this submission references are made to scientific articles (like Swaen (2019)). The reader is referred to the EMPA / Melamine REACH Consortium response for the full reference.

In this submission OCI Nitrogen will address the following subjects:

1. The CLH proposal gives incorrect weight to the studies cited and ignores studies provided.
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.
3. Melamine has no intrinsic properties to cause cancer.

1- Quality of the studies:

OCI Nitrogen supports the objective of ECHA to access the hazards of chemicals irrespective of socio-economic factors. Fulfilment of this objective stands with fact-based debates using high quality studies and data. Therefore, a decision whether to classify a substance should be based on scientific arguments supported by adequate and reliable scientific data. Also, the legislations and regulations used should be applied in a strict and indisputable manner.

ECHA and EUCOM/SCHEER have provided guidance documents how to access scientific studies. The CLH report did not apply this guidance.

In our view in the CLH report, (1) several studies were not properly classified as a "key" or "supportive" study, (2) sometimes "supporting" and "non-reliable" studies were used while "reliable" and "key" studies were available and (3) relevant articles (Cohen 2018, Cohen 2019, Swaen 2019) were (we assume deliberately) not incorporated.

The CLH report when discussing carcinogenicity classifies the articles of Okumura (1992) and Ogasaware (1995) as "key studies" which in our view are, at the most, "supportive studies". For instance, in the Okumura studies tumours in male rates were only observed at extremely high melamine dosages (30.000 ppm), exceeding the maximum tolerated dose.
The Cremonezzi paper (2001) is classified in the CLH report as a study of "lower reliability". However, it is often cited in the CLH report and the outcomes are used as key arguments in the report, while a high quality - NTP - study (Melnick (1984)) is available which provides different arguments.
It is the position of OCI Nitrogen that there is only one key study related to the carcinogenic properties of melamine showing tumours in male rats which is this NTP study.

It is the position of OCI Nitrogen that the data obtained due to criminal abuse (China milk scandal) should not be used in line with the ECHA guidelines. Consequently, a STOT RE 1 classification is unjustified.

In the discussion on STOT RE 2 classification, the CLH report selectively uses data from studies. The CLH report did not argue why two specific articles were preferred of the 5 available. This selection used in the report leads to the incorrect conclusion that a STOT RE 2 classification is required. OCI Nitrogen concluded that considering all studies and properly analysing those, the Effective Dose for melamine is above 100 mg/kg bw/d. This effective dose does not justify a classification as STOT RE2 . Therefore OCI Nitrogen opposes the conclusion of the CLH report on STOT RE 2.

Finally, the CLH report did not refer to and thus did not use relevant articles (Cohen 2018A, Cohen 2018 B, Cohen 2019, Swaen 2019) in their evaluation. We alerted the authors of the CLH report to these articles and the articles were handed over prior to their official publication and the finalization of the CLH report. However, the authors of the CLH proposal choose to fully ignore these relevant studies.

2- Particle effect

In the CLH report a mode of action (MoA) for bladder tumour formation in male rats is proposed. Melamine fed to rats will be taken up into the body and will be excreted via urine. Due to the high levels of melamine administered, there are high levels of melamine present in the urine of the bladder finally resulting in crystallization of melamine. Melamine crystals can sometimes conglomerate into particle – "bladder stones". These particles can irritate the surface layer of the bladder. Prolonged irritation can ultimately result in the formation of bladder tumours.

Key point is that the chronic irritation of the bladder resulting in the formation of tumours is due to prolonged irritation caused by particles present – irrespective of the composition and type - of these particles. Tumour formation is also observed in male rats when particles of diethylene glycol, terephthalic acid, sodium saccharin, sodium ascorbate, thymine and even bladder implants of inert

materials (paraffin, glass beads) are prolonged present in the bladder (IARC (1999), Clayson (1974), Clayson (1995)).

Bladder tumours are formed due to the presence of particles. The CLH report relates the crystallization of melamine in urine and via the particle effect to tumour formation. If this relation would hold, all substances which have a propensity to crystallize in the bladder should be classified as a carcinogen. Examples of such substances are calcium, phosphate, oxalate, etc., etc. Many of these substances are naturally occurring in the body. Relating crystallization in the bladder / urinary track to classification as a carcinogen is in the view of OCIN incorrect and undesired. It would lead to the incorrect classification of many substances.

Therefore, the CLH report incorrectly concludes that melamine is causing tumours in male rats. It are particles that are causing the tumours!

Furthermore, "ECHA guidance" (2017) states that bladder tumour in male rats due to crystals [particles] [are specific and] considered not to be relevant for humans.

3- Intrinsic properties to cause cancer

A prerequisite according to the ECHA guidelines to classify a substance as a carcinogen is that the subject should have the intrinsic property to cause cancer. Ultra-violet light is intrinsically causing cancer – though it is not a substance. Asbestos and benzene possess also the intrinsic property to cause cancer. Even the lowest exposure can initiate the formation of tumours. Melamine does not.

Melamine possesses different intrinsic properties which, in <u>combination and together with</u> the high admission ultimately lead to high levels of melamine in urine and to crystallization. These intrinsic properties of melamine are:

- Low systemic toxicity (acute and chronic)
- High oral absorption
- No metabolism
- Rapid excretion of unmetabolized melamine in urine

Crystallization only will occur above the solubility limit. In other words, the melamine levels in the urine needs to exceed a threshold before crystals *sometimes followed by stone* formation will occur.

One can argue that melamine has an intrinsic property to crystallize in urine if a threshold concentration of melamine in the urine is exceeded.

Melamine has many intrinsic properties, but melamine does not have an intrinsic property to cause cancer. Therefore, OCI Nitrogen opposes to the conclusion of the CLH classification report that melamine is to be classified as a Cat. 2 carcinogen.