PERSONAL OPINION ON THE CLASSIFICATION OF METHANOL AS DEVELOPMENTAL TOXICANT

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SUMMARY

In order to maintain a proper working classification system in Europe that informs on the scientifically observed hazards with a reasonable relevance to humans it is proposed to not classify methanol for developmental effects. The current classification sufficiently informs humans on methanol toxicity and thus enables a proper risk management.

The system of classifying hazards is thought to provide any user or handler of a substance the intrinsic hazard of a substance by appropriate Hazard phrases (H-phrases) without primarily taking into account the risk resulting from an exposure to a substance. Therefore, CLP can be considered, together with triggered Precautionary statements (P Statements), as a part of the risk management system that ensures the proper use of dangerous substances, i.e. it should initiate the next steps necessary to control the risk during every step of the chemicals life stage.

Therefore the expectations to a proper working classification system can be defined:

*It should provide a basis for a concise classification of all substances with all relevant identified hazards but in parallel it should avoid over-classification that may result by losing its origin in the risk management system during handling and use of the substances. In other words the classification of a hazard without any foreseeable risk may be over-done.*

The principle of the relevant hazard can be found in various paragraphs of the EU legislation and also the guidance to CLP:

- REACH Annexes VII and VIII for example suggest to ignore any further acute hazard (skin sensitization, acute oral/dermal/inhalative toxicity) if the substance is known or expected to be corrosive to the skin.
- According to the Guidance to CLP substances showing corrosive effects in acute tests should only be classified for the effects in repeated dose studies if the effect occurs at a dose being half a magnitude lower than in the acute test.

- Maternal or general toxicity should be taken into account when classifying for reproductive hazards.

- Most current OECD guidelines provide an upper dose limit up to which the chemical should be tested for identifying a hazard.

To agree on the relevant intrinsic hazards is therefore the fundamental step in any classification but is most important for the most critical endpoints summarized as CMR categories. To ensure a proper discussion for CMR classification a Europe wide harmonization based on an initially public discussion is foreseen by the legislation, as now done for methanol. For methanol the rapporteur Italy proposes a classification in category 1B for developmental toxicity. Considering the above said for the evaluation of the methanol data a classification with category 1B may be comprehensible based on the effects only but in view of the whole data base it is considered to be overdone.

For the grounds already compiled in the C&L dossier the data available from human exposure cannot be regarded as conclusive for the developmental endpoint, therefore the available data on mice, rat and rabbit as well as in vitro data must be taken into account. This is the first critical point in the assessment as for methanol species specific metabolism and toxicokinetic is known that ironically leads to a human data based classification for severe effects after single exposure. In contrast to rodents, humans have an extremely limited capacity of the folate metabolism leading finally to life threatening acidosis and damage of the optic nerve. Due to these species differences science was able to identify developmental effects in animals at doses that would cause extreme dysfunction in humans and lie beyond the levels normally used in guideline studies for hazard assessment purposes. Not abating the scientific value the data may have it is necessary to discuss its relevance for classification purposes. A classification for developmental toxicity based on the high dose data would be warranted if the same metabolic step is involved in methanol developmental toxicity that makes humans more susceptible for the acute hazards than rodents and other mammalian species. Only in this case one would expect primary developmental effects in humans by scaling the animal experiment to the human case. Otherwise the severe acute hazards can be seen as the relevant unique hazard in humans and the respective classification is sufficiently protective for a developmental hazard that might arise at higher concentrations/doses. Based on the whole database, especially the studies by Fu et al. (1996) and Sakanashi et al. (1996), there is no evidence that the folate-mediated pathway plays a role for the developmental effects observed in rodents. As already concluded in the CLH dossier there is no evidence that humans are more sensitive than other species tested. The need for classification based on the currently available data is therefore more than questionable.

It is therefore proposed to not classify methanol for developmental effects in order to maintain a proper working classification system that informs on the scientifically observed hazards with a reasonable relevance to humans. The current classification sufficiently informs humans on methanol toxicity and thus enables a proper risk management.

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1 Lethal methanol doses in rats and rabbits are 2-3 times higher than those in monkeys, which in turn are 6-10 times higher than those reported in humans (NTP, 2003).
References

