Fertilisers Efficiency Enhancers

Brussels, 13 October 2023

Fertilisers Efficiency Enhancers comments on the proposal for the Harmonised Classifications and Labelling of 3,4-dimethyl-1H-pyrazol

Fertilisers Efficiency Enhancers, a sector group of Cefic representing the value chain of nitrogen stabilisers and other fertiliser enhancers in Europe, welcomes the opportunity to provide input to the public consultation on the proposals for Harmonised Classification and Labelling of 3,4-dimethyl-1H-pyrazol (CAS: 2820-37-3, hereinafter '3,4 DMP'), submitted by the Belgian Competent Authorities.

As a general remark, we would like to bring ECHA's attention to the need of assessing 3,4-DMP based on a robust weight of evidence methodology.

With regard to the classification proposals by the Dossier Submitter, we would like to note the following:

(1) Carcinogenicity

The Dossier Submitter assessed one animal study (combined chronic toxicity/carcinogenicity study, page 12 to 13 of the Annex XV dossier) to conclude that the classification carcinogenicity category 2 is warranted. In this regard, we would like to quote the ECHA Guidance document on Information Requirements and Chemical Safety Assessment R7a (2017) (hereinafter 'ECHA Guidance' in this document):

> *With respect to carcinogenic potential and potency the most appropriate source of information is directly from human epidemiology studies (e.g. cohort, case control studies). In the absence of human data, animal carcinogenicity tests may be used to differentiate carcinogens from non-carcinogens. However, the results of these studies subsequently have to be extrapolated to humans, both in qualitative as well as quantitative terms. This introduces uncertainty, both with regard to potency for as well as relevance to humans, due to species specific factors such as differences in chemical metabolism and toxicokinetics and difficulties inherent in extrapolating from the high doses used in animal bioassays to those normally experienced by humans.*

Moreover, according to the CLP Regulation (Regulation (EC) No 1272/2008), classification for a substance as a carcinogen is a process that involves two interrelated determinations: evaluation of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories (see 3.6.2.2.2).

In our opinion, the classification proposal by the Dossier Submitter does not meet the criteria described above since it considers carcinogenicity data limited to a single experiment, leaves questions regarding the adequacy of the design, conduct and interpretation of studies unresolved, and the severity of the effects observed is limited.

Fertilisers Efficiency Enhancers Sector Group
Rue Belliard 40 b.15 B-1040 Brussels Belgium
Tel: +32.2.436.94.64 – Email: mim@cefic.be

In rats, tumour formation was observed only at a dose exceeding the maximum tolerated dose and at doses compromising detoxification process. For this reason they are unlikely to be human relevant.

Therefore, available data justify that 3,4- DMP does not warrant a classification for carcinogenicity. A Carcinogenicity Cat 2. classification could be considered only based on the precautionary principle and worst-case scenario.

(2) Reproductive toxicity

A robust weight of evidence assessment of all available data should be performed in the assessment of 3,4-DMP for reproductive toxicity.

A two-generation reproduction toxicity study according to OECD 416 guidelines (Anonymous, 2021 – page 19 of the Dossier) shows lack of adverse effects on sexual function and fertility. Moreover, the available mechanistic data suggests that detoxification via excretion by the kidneys is more efficient in humans compared to rats, making humans less prone to the toxic effects of the substances.

When considering whether the effects observed in studies regarding the substance are adverse or not, we would like to quote the ECHA Guidance:

> *Although not required by REACH, toxicokinetic studies may be helpful in the evaluation and interpretation of repeated dose toxicity data, for example in relation to accumulation of a substance or its metabolites in certain tissues or organs as well as in relation to mechanistic aspects of repeated dose toxicity and species differences. Toxicokinetic information can also be used in the selection of the dose levels. When conducting repeated dose toxicity studies it is necessary to ensure that the observed treatment-related toxicity is not associated with the administration of excessive high doses causing saturation of absorption and detoxification mechanisms. The results obtained from studies using excessive doses causing saturation of metabolism are often of limited value in defining the risk posed at more relevant and realistic exposure levels where a substance can be readily metabolised and cleared from the body. It is suggested that a key element in designing better repeated dose toxicity studies is to select appropriate dose levels based on results from useful metabolic and toxicokinetic investigations.*

In fact, due to compromised detoxification processes in the reproductive toxicity studies, the resulting internal exposure becomes irrelevant to human hazard assessment because effects occur only under experimental conditions where detoxification by excretion is impaired. Therefore, the observed effects at high doses are disproportionate and do not reflect human hazard potential.

Therefore, based on available data and on a weight of evidence approach, we propose that classification Repro Cat 2 for fertility and for reproductive toxicity as such not be warranted.

(3) STOT RE

Regarding the proposed STOT RE category 2 (nasal cavity), we would like to quote the following provision in the CLP Regulation (Regulation (EC) 1272/2008), Annex I:

3.9.2.8.1. It is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate 'significant' toxicity;

(b) small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;

(c) changes in organ weights with no evidence of organ dysfunction;

(d) adaptive responses that are not considered toxicologically relevant;

(e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification

Based on the above and on the available data, we suggest that 3,4- DMP should not be classified for specific target organ toxicity after repeated exposure because the adverse effects observed in the nasal cavity are not relevant to humans. All other organ effects occurred either above the cut-off limit for classification or are also not considered relevant to humans due to species differences between rodents and humans (salivary gland).

We thank you for your kind attention, and remain at your disposal should you have any further questions.

Your sincerely,

[redacted]

Manager of Fertilisers Efficiency Enhancers