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Metofluthrin: Acute Oral Toxicity Classification

Background:

In the draft CLH report for epsilon-metofluthrin (dated May 2015), a hazard classification of Acute Tox Category 3, with associated risk phrase H301 (Toxic if Swallowed) is proposed. This proposed hazard classification is based on mortality in rats and mice administered metofluthrin in a corn oil vehicle. This is in spite of the finding that the acute oral LD_{50} value for metofluthrin when dosed undiluted to rats is greater than 2000 mg/kg. The applicant, Sumitomo Chemical (UK) PLC, considers this classification to be inappropriate for the reasons outlined below.

Discussion of Data

In a standard acute oral LD_{50} (rat) study conducted to recognised US EPA OPPTS 870.1100 protocol and Japanese Ministry of Health and Welfare, Iyakusin No 655 guidelines (not OECD 401), using undiluted metofluthrin, only one death (female) occurred at the highest dose level of 2000 mg/kg bw/day. Based upon the results of this standard acute oral LD_{50} (rat) study, no acute classification by the oral route would be deemed necessary.

In other supporting acute oral studies utilized for classification in this case by the Member State CA, a "LD_{50}" (*i.e.* death in at least 50% of the animals) was not achieved in either rats or mice, at top doses of 100 mg/kg (rats) or 60 mg/kg (mice). According to the criteria for acute toxicity, classification under the Classification, Labelling and Packaging (CLP) Regulation (1272/2008) requires an LD_{50} value of 300 mg/kg or lower for classification as Acute Tox Category 3, with associated risk phrase H301 (Toxic if Swallowed); with the rat specified as the preferred species.

In mice (dose range-finding study to a micronucleus test: Odawara, 2002), an acute oral dose of 60 mg/kg metofluthrin in corn oil was associated with 2/10 mortalities and evident toxicity. This was a non-regulatory, preliminary study with minimal experimental detail and was (and remains) unsuitable for use as any basis for classification and labeling decisions. In contrast, by dietary administration, mice were able to tolerate intakes of over 500 mg/kg bw/day (in the absence of corn oil) without evident toxicity for periods of up to 13 weeks (Sommer *et al*, 2002). We consider the micronucleus test as well as the above referenced preliminary study to be unsuitable toxicity tests from which to determine a hazard classification because these studies are not designed or intended to arrive at a value for an acute oral LD_{50}. In addition, there is no information on mortality when a dose greater than 60 mg/kg metofluthrin is administered.

In rats (acute neurotoxicity study: York, 2004), 100 mg/kg metofluthrin in corn oil was associated with evident toxicity, and mortality in 3/20 rats of the main study. Evident toxicity was such that a further 4 females were sacrificed 4 to 7 hours after dosing for reasons due both to their poor health conditions and the need to collect neurological tissues for histopathology. The authors noted in the study report that the 4 females may have survived if not sacrificed. Thus, it can be considered appropriate to exclude the sacrificed rats from the evaluation of mortality at the 100 mg/kg dose level. In addition results were inconsistent; a range-finding GLP study at this dose in the same study gave 0/5 mortalities in each sex. The dosing procedures appear highly comparable at the same laboratory and were closely contemporaneous**;** it is therefore appropriate to combine the findings of the pilot and main phases. At 100 mg/kg metofluthrin in rats, mortality figures of 2/15 males and 1/15 females (in total, 3/30) were obtained. This result is consistent with that of another non-GLP study conducted in the same laboratory (1/10 female rat died at a dose level of 100 mg/kg

Metofluthrin in corn oil). The applicant does not dispute the ethical imperative for sacrifice of rats showing evident toxicity; but the decisions were influenced in this case by the need to collect the neurological tissues in the neurotoxicity study. However, since the proposed hazard classification is anticipated to have a significant impact on the marketability of this chemical, a further imperative must be applied: that the criteria for the assessment of hazard classification are applied fairly and consistently between chemicals. The applicant believes that hazard classification decisions are most frequently based on data in studies where sacrifice criteria have been less rigorously applied; results for metofluthrin in rats should be interpreted as "evident toxicity and 10% mortality at 100 mg/kg". Given the mortality, the LD_{50} value is expected to be greater than 300 mg/kg. Therefore, lethality is considered inadequate to classify metofluthrin with Acute Tox 3 (50 mg/kg< acute oral LD_{50} value ≤ 300 mg/kg).

There is an obvious discrepancy between dosing metofluthrin undiluted, and in a corn oil vehicle. Given that a hazard classification should reflect the 'intrinsic" properties of the substance under investigation *i.e.* metofluthrin, the rationale to select the corn oil data in preference to data generated using undiluted metofluthrin is unclear. The CLH report argues (4.2.3, p20):

"There do not appear to be clear methodological reasons to exclude findings from the single oral exposure studies with corn oil vehicle (as it is a standard vehicle)"

but speculates that:

"It is possible there are vehicle dependent differences in toxicokinetics that are revealing an intrinsic hazardous property of Metofluthrin (acute oral toxicity)".

A standard toxicology model is that inhalation exposures are extensively (ca. 100%) absorbed. In the acute inhalation study (Deguchi, 2002) an inhalation dose of 2 mg/L metofluthrin was associated with mortality in 10/10 rats; at the 1 mg/L dose level 1/10 rats died. These rats died within approximately 4 hours of commencement of exposure, consistent with extensive and rapid absorption and distribution. Ethical sacrifice of the majority of animals at between 4 to 7 hours post-dosing in the gavage neurotoxicity study suggests absorption by inhalation to be more rapid than from metofluthrin orally administered in corn oil, particularly considering a 4-hour inhalation exposure against a single bolus by gavage. Clinical findings were mostly obscured by the inhalation test apparatus, but those signs which were seen were consistent with oral dose effects. Inhalation characteristics of the aerosol were optimal (analytical concentration within 2% of target concentration, MMAD less than 4 µm; metofluthrin also relatively volatile suggesting not all metofluthrin was associated with droplets). A dose of 1 mg/L for 4 hours corresponds to a systemic dose of about 194 mg/kg. There is no indication (CLH report p19 Table 10) of local lung toxicity. Results are therefore consistent with an intrinsic, systemic LD_{50} above 200 mg/kg following rapid absorption and distribution, relatively unimpaired by first-pass metabolism which is known to be a detoxification pathway of pyrethroids. A more rapid pharmacokinetic "peak height" may be clearly inferred by inhalation relative to ingestion of metofluthrin in corn oil. (A slower C_{max} following oral ingestion would reasonably be expected to be of lower peak height and the corresponding LD_{50} in excess of 300 mg/kg).

In contrast, oral absorption of metofluthrin in corn oil appears slightly prolonged vs. inhalation (peak effect at 4-7 hours, compared to within 4 hours). This time to peak effect is consistent with ADME data following oral dosing in corn oil. Oral doses are also subject to rapid first-pass hepatic metabolism which is known to be a detoxification pathway of pyrethroids. Hepatic metabolism clearly fragments and inactivates the molecule; and is bypassed by inhalation exposure. By comparison with inhalation, a hypothesis of rapid oral absorption from corn oil overwhelming hepatic detoxification is untenable. The results observed are more compatible with corn oil affecting the processes of metabolic detoxification or elimination; it may be an overestimate to conclude that dosing in corn oil reflects the "intrinsic toxicity" of the molecule for acute oral toxicity classification.

Corn oil is neither a component of metofluthrin products, nor of metofluthrin exposure. Indeed, metofluthrin is shipped and supplied to customers as the pure active substance and is not diluted in any vehicle such as corn oil. The effects observed in animals following exposure to metofluthrin dosed in corn oil are therefore irrelevant to human exposure.

In consideration of the above and with reference to the CLP regulation (1272/2008):

"Article 8 (6) *Tests that are carried out for the purposes of this Regulation shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used."*

It is clear that the data obtained from animals exposed to metofluthrin in corn oil do not have any validity for placement on the market or reasonable expectation of use.

Indeed nowhere in the chemicals legislation is it stated that toxicity data obtained in the mouse is a valid basis on which to derive an acute oral LD_{50} value and associated hazard classification for acute exposure by the oral route or indeed any other route. Furthermore, with reference to the CLP regulation (Annex I: 3.1.2.2.1)*:*

"The preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat, …"

The applicant does not support the use of acute oral toxicity data using a corn oil vehicle, and in a non-standard test species, for the derivation of an acute hazard by the oral route.

The "intrinsic" toxicity of metofluthrin at worst may be derived from inhalation data where a greater systemic peak height would be inferred, suggesting an LD_{50} by the oral route in excess of 300 mg/kg in rats. Metofluthrin should be classified no more severely than "Harmful" by the oral route. Indeed, oral dosing of undiluted metofluthrin (an acceptable procedure) indicates no hazard classification to be appropriate by the oral route. Further additional information in support of the low oral toxicity of metofluthrin can be obtained from structure activity relationship data. Pyrethroid insecticides having closely related chemical structures to metofluthrin – including transfluthrin (Bayer) and Sumitomo Chemical Development Number S-1209 have been found in standard acute oral LD_{50} (rat) tests to have values in excess of 2000 mg/kg.

Metofluthrin mixed with corn oil may be considered as a preparation, and it is the toxicity of the preparation that is reflected in corn oil preparations. If metofluthrin preparations are brought to market in future then the acute toxicity is dealt with by considering the actual preparation, so any effects that have been seen due to corn oil or that might arise with any other solvent would be taken in consideration at the product approval stage. Metofluthrin is shipped as the technical grade active material and is not mixed with any other solvent or additive until a product is derived from it, which then has to go through a product evaluation stage.

Conclusion

As described in the document enhanced oral toxicity of metofluthrin prepared in corn oil cannot be attributed to the intrinsic properties of the molecule. However, even under the worst case assumption, the oral LD_{50} value for metofluthrin is expected to be greater than 300 mg/kg. In support of this data, inhalation data also suggest that the estimated LD_{50} value is greater than 300 mg/kg. Furthermore, the acute oral LD_{50} value when dosed undiluted to rats is greater than 2000 mg/kg. Given these results, classification should be deemed as "Acute Tox 4; H302 (Harmful if swallowed)".