Minority opinion regarding the classification of trinexapac-ethyl to STOT RE2

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This minority opinion on trinexapac-ethyl concerns the specific target organ toxicity after repeated exposure (STOT RE). RAC has decided to classify trinexapac-ethyl to STOT RE 2 on the basis of two deaths accompanied with stomach mucosal involvement in the rabbit developmental study. We do not agree with this classification on the following reasons.

STOT RE classification is an important hazard class to warn about possible target organ effects which may occur after long term, low level exposure to the substance. According to the CLP regulation (1907/2006) target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. Classification for target organ toxicity (repeated exposure) identifies the substance as being a specific target organ toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it. These adverse health effects include consistent and identifiable toxic effects in humans or in experimental animals, which can be considered relevant for human health.

The CLP regulation states that "Substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement, on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s)." The use of expert judgement and weight of all evidence and relevance to human health is further emphasized later in the CLP regulation.

The guidance values given in the CLP regulation for STOT RE classification are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach. The guidance values refer to effects seen in a standard 90-day toxicity study conducted in rats. Even though they can be extrapolated for toxicity studies of greater or lesser duration using Haber's rule, this assessment shall be done on a case-by-case basis. As mentioned in the CLP regulation, Haber's rule assumes that the effective dose is directly proportional to the exposure concentration and the duration of exposure.

Morbidity or death resulting from repeated or long-term exposure can be taken into account in STOT RE classification. According to CLP regulation morbidity may be relevant at relatively low doses when it is due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites. These cases need, naturally, to be distinguished from the morbidity resulting from short term exposure to high, excessive doses.

In the case of trinexapac-ethyl, there are considerable number of animal data available on its repeated dose effects. The DS summarized altogether 13 repeated dose toxicity studies in different species (rat, dog, rabbit and mice) and of different durations, including sub-acute neurotoxicity, carcinogenicity, developmental and 2-generation toxicity studies in rats, developmental toxicity study in rabbits along with carcinogenicity and immunotoxicity in mice. No effects fulfilling classification criteria were seen in any of the rat, dog and mice studies.

In rabbit dose-finding study for developmental toxicity (by gavage), 4/6 rabbits died at 800 mg/kg, which is a dose clearly above the guidance values for classification. At the lower dose, 400 mg/kg,

there was 1 mortality and transient decreased food consumption and marked weight loss to day 9. In the main developmental study, top dose of 360 mg/kg (by gavage) resulted in 2 mortalities among the 17 treated animals and retarded body weight gain to GD 15. The first death occurred on day 13 (6 days after start of dosing) following suspected convulsions. The stomach of this rabbit was found to be ruptured. The second animal was killed on day 24 due to marked weight loss and was found to have haemorrhagic depressions in the stomach. Although these doses resulting in deaths and GI effects were above the guidance values (GV) given in CLP regulation for classification of substances to STOT RE 2, RAC used Haber's law to extrapolate to lower duration and concluded that the dose was below the adjusted GV of 690 mg/kg. We do not agree that Haber's law should be used in this case to extrapolate these GVs to shorter durations. The local effects seen in these rabbits are, in our opinion, rather dose than time dependent. In addition, it should be noted that in these rabbit studies the substance was administered by gavage resulting in high peak doses at the stomach. Rabbits are also known to be sensitive for gastrointestinal distress. In studies with other species, even at higher doses of trinexapac-ethyl, no effects were seen in the gastrointestinal tract and no mortalities were observed even at doses up to 1000 mg/kg. It should be noted that these other studies included altogether 11 studies with three species (rat, mice, dog) and only studies showing any significant effects is this rabbit developmental study and its dose-finding study in which effects in stomach mucosa and deaths were seen after gavage administration of the substance. In RAC meeting, oral information received from the industry suggested that one of the deaths seen in rabbits was probably due to intubation error further casting doubts for the relevance of these findings seen in rabbit developmental study. Relevance of these local effects on stomach mucosa, seen only at high doses in rabbits, are very unlikely to be relevant for human exposures. Since according to the CLP regulation, the classification for STOT RE should be based on weight of evidence and to consider relevance to humans, classification of trinexapac-ethyl does not, in our opinion, fulfill the CLP criteria for STOT RE2.