Minority opinion regarding the classification of epsilon-metofluthrin

by Tiina Santonen, 1.7.2016

This minority opinion on epsilon-metofluthrin concerns the specific target organ toxicity after repeated exposure (STOT RE). RAC has decided to classify epsilon-metoflutrin to STOT RE 2 on the basis of deaths observed in 28-day inhalation study in rats at the air levels of 0.2 mg/L. I 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. For example in occupational context it gives an indication that some target organs might be affected after long term exposure even though exposure remains only at relatively low levels (i.e. at levels that do not induce any significant acute effects/symptoms). In these cases there may be a need to follow up workers for the function of some specific target organs.

According to the CLP regulation (Annex I, 3.9.1.1) STOT RE is defined as follows: *"Specific target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture."* Also CLP guidance states that *"The purpose of STOT-RE is to identify the primary target organ(s) of toxicity for inclusion in the hazard statement."*

Furthermore, CLP regulation (Annex I 3.9.2.1) states that "*Substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement (see 1.1.1), 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)…"* It also states (in Annex I 3.9.2.9.8) that "*The guidance values and ranges mentioned in paragraphs 3.9.2.9.6 and 3.9.2.9.7 are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values."*

Classification to STOT RE categories can be made on the basis of human or animal data. The standard animal studies, which should provide relevant information for STOT RE classification are 28 day, 90 day or lifetime studies (up to 2 years) in rats or mice. According to the testing guidelines (see e.g. OECD 408, repeated dose 90-days study) the highest dose level for these studies should be chosen with the aim to induce toxicity but not death or severe suffering of the animals. This is especially important in the case of substances causing acute toxicity – i.e. those substances causing deaths already at rather low exposure levels (levels close to or even below STOT RE guidance values). In the case of these substances, the dose for repeated dose testing should be selected in order to avoid deaths or suffering caused by acute toxicity but rather to show target organs which are affected after low level long term exposures (resembling e.g. human occupational exposure). In the case of substances causing acute toxicity, if the highest dose selected for the study is too high, it may result in deaths of the animals due to *its acutely toxic properties* at dose levels which are lower than those guidance values given in the CLP guidance for STOT RE.

In the case of epsilon-metofluthrin it is evident that the dose level showing deaths was too high for repeated dose testing since animals were showing severe clinical signs of acute toxicity (tremors and even convulsions) immediately after/during each daily exposure (i.e. it caused acute suffering of the animals). In acute inhalation toxicity test similar signs of toxicity (neurotoxicity manifested as tremors) were observed at all dose levels tested (0.5, 1 and 2 mg/l). In 28-days study these symptoms were particularly evident during the first week of exposure. Also the food and water consumption was reduced during the first week of exposure. Majority (6 out of ten) of the deaths

occurred during the first week of exposure. This clearly indicates that the deaths were rather caused by the repeated insults of acute toxicity compromising animal's health than any specific long term target organ effects caused by low, not acutely toxic, exposure levels. Therefore, the relevance of these findings to human long term exposure is questionable.

CLP regulation (annex I 3.9.2.7.3) emphasizes the assessment of human relevance of the effects as part of expert judgement: "*Consequently all available evidence, and relevance to human health, shall be taken into consideration in the classification process*." In my opinion, these deaths, which has been seen in animals only after repeated exposures to the doses causing severe acute effects, are not relevant to human long term exposures e.g. in occupational context. This is also supported by testing guidelines, which do not support testing of repeated dose toxicity at the doses causing severe acute effects. These effects seen in animals are relevant for acute toxicity/STOT SE classification and the neurotoxic symptoms (convulsions, tremors) seen at doses of 0.2 mg/l immediately after the daily exposures are already covered by STOT SE classification made by RAC (STOT SE 1, nervous system). For these reasons, I consider it inappropriate to classify epsilon-metofluthrin to STOT RE 2 category.