Technical review of CLH classifications considered for trihydrogen pentapotassium di (peroxomonosulphate) di(sulphate) ('KMPS'; EC No. 274-778-7)

1. Introduction

Slovenia, the submitter of the CLH report for trihydrogen pentapotassium di (peroxomonosulphate) di(sulphate) ('KMPS'; EC No. 274-778-7) considers classifying KMPS amongst others as STOT RE Category 1 (H372; "Causes damage to organs (eyes) trough prolonged or repeated exposure"). In referral to the CLP criteria, Slovenia supports its consideration for a STOT RE Category (H372) classification based on eye effects observed in a sub-acute inhalation study (head-only exposure)[1].

Based on scientific and regulatory considerations, this document provides a technical argumentation why a STOT RE classifications is not considered to be warranted. It also provides some further comments/clarifications to statements made in the CLH report regarding data relevant for STOT SE and irritation/corrosion classifications.

2. Technical review and comments on selected CLH proposals for KMPS

Consideration to classify KMPS as STOT RE 1 (H372)

Available acute and repeated dose toxicological studies demonstrate that, irrespective of the route of administration, the mode of action of KMPS is characterized by local irritation/corrosion at the site of first contact, presumably triggered by oxidation. No observations indicative for direct treatment-related systemic effects of KPMS were made. In all repeated dose studies after oral (gavage) administration, the first point of contact was the stomach with findings typical for local irritation/corrosion type of effects (e.g., necrotic and inflammatory lesion of the stomach, thickening of the forestomach, oedema, haemorrhage in the mucosal and submucosal areas, epithelial necrosis, ulceration and hyperplasia). Such local effects should not trigger a classification for specific target organ toxicity following repeated exposure ('STOT-RE') according to the CLP classification criteria[2].

Whereas KMPS was dosed in available repeated oral toxicity studies in aqueous solutions, KMPS was dosed as a dust aerosol in an acute and a 14-day inhalation studies. Likewise, KMPS was dosed as neat solid substance in the eye irritation study. Due to its corrosive nature, the effects to the eyes are mediated by a local mode of action because of oxidation and local irritation/corrosion at the site of contact. This effect may be further amplified by mechanical

[1] CLH Report trihydrogen pentapotassium di (peroxomonosulphate) di(sulphate) (EC No. 274-778-7)
[2] ECHA Guidance on the application of the CLP criteria

irritation and injury by the dust particles and partially dissolved KMPS by the lachrymal fluid in the head-only exposure regime. Regarding the latter, it should be noted that lesions were predominantly determined in moist areas such as eyes and eyelids. These observations suggest that the ocular lesions observed in the repeated dose inhalation toxicity study occur as a primary local effect already after the first exposure, as documented in the results of daily observations appended to the study report, and are not a result of repeated exposure. In addition, due to the lack of washing of the eyes after each exposure session in the inhalation study, these effects could not recover or improved after each 6-hour exposure. Thus, the non-reversibility of ocular lesions is a consequence of sustained irritation of the eyes by a corrosive substance.

It should further be noted that in the 14-day inhalation study no local effects were observed in the respiratory tract at exposure concentrations causing ocular effects. This contrasts with the rabbit eye irritation study where after single ocular instillation of the solid material, ocular effects were so severe that the study had to be terminated 24 hours after instillation of the substance for animal welfare reasons. This again confirms that local irritation/corrosion on the eyes is to be considered as an acute effect rather than a result of a repeated exposure regime which has been accordingly addressed by a classification of KMPS with both Skin Corr. 1, H314, and Eye Dam. 1, H318.

The absence of a need for a classification with STOT RE 1 (H372) is further supported by the results of a medical surveillance programme of workers in KMPS production (see also chapter "A.3.12. Further Human data" of the CLH report). No specific adverse effects of KMPS on the examined health parameters were observed within a period of 6 years. It can be reasonably assumed that ocular effects like those observed in the 14-day inhalation toxicity study in male rats would have become evident during testing of the worker's vision in the surveillance programme.

From an inhalation exposure point of view, it should be considered that KMPS has a very low vapour pressure (i.e., < 1.7 x 10-4 Pa at 25 ºC (extrapolated)) and intended applications of KMPS do not foresee the application of the solid material by spraying/dusting as such. Inhalation exposure to volatile KMPS or KMPS powders is therefore considered to be negligible or not relevant. All applications and in particular low pressure manual spraying are performed with diluted aqueous solutions at a concentration of max. 8 g/L = 0.8% (see chapter "A.2. Effects against target organisms" of the CLH report). This concentration is below the generic concentration limits for both skin and eye effects and, thus, local irritation of skin and eyes during spraying applications is not expected. For this reason, the potential ocular effects observed in the subacute inhalation toxicity study in male rats are not considered to be relevant

for humans under intended application conditions taking also into account the absence of adverse effects on eyes in a medical surveillance programme of workers.

From a more regulatory point of view, the dossier submitters reference to the CLP guidance needs further considerations with a view to its applicability for KMPS (Section 3.9.2.5.1, p. 470):

"*Substances (or mixtures) classified as corrosive may cause severe toxicological effects following repeated exposure, especially in the lungs following inhalation exposure. In such cases, it has to be evaluated whether the severe effect is a reflection of true repeated exposure toxicity or whether it is in fact just acute toxicity (i.e., corrosivity). One way to distinguish between these possibilities is to consider the dose level which causes the toxicity. If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity. In this case, classification as specific target organ toxicant (repeated exposure) would be warranted even if the substance (or mixture) is also classified as acutely toxic and/or corrosive.* ***In assessing non systemic effects caused by irritating/corrosive substances it should be kept in mind, that the guidance values /criteria for STOT-RE of the CLP were derived from acute toxicity criteria (lethality based) assuming that systemic effects show a time dependent increase of severity due to accumulation of toxicity and taking also adaptive and detoxification processes into account. The effect considered in this context was lethality.*** *This indicates that classification was intended for the presence of severe health damage, only. (see ECBI/67/00, (2000) in EU Commission Summary Record of Meeting of the Commission Working Group on C&L of Dangerous Substances ECBI/44/01)."*

The above guidance for application of the STOT RE criteria refers to the need for a discrimination between true repeated dose toxicity or just acute toxicity. In case of true repeated dose toxicity, effects should only be observed after repeated dosing. Regarding the assessment of non-systemic effects caused by irritating/corrosive substances, the CLP guidance states (bolded in above citation) that the guidance values/STOT RE criteria are based on lethality in acute toxicity studies and are applicable for systemic rather than local effects. The acute nature of the severe local effects on the eyes has been confirmed in the eye irritation study in rabbits.

The data submitter also states in section A.3.7.4.2. Comparison with the CLP criteria of the CLH report that "*The effects in subacute inhalation study were seen at concentration that is 150 lower than the lowest concentration tested in the acute inhalation toxicity study and orders of magnitude lower than the basis for Eye Dam. 1 classification (0.1 g pure substance). Therefore, the classification is warranted also when considering additional considerations set out in CLP Guidance.*"

In the context of the STOT-RE discussion, the direct comparison of the acute inhalation toxicity LOAEC of 1.5 mg/L with the LOAEC of 0.01 mg/L derived from the 14d inhalation toxicity study and thereby deriving a factor of 150 difference is inappropriate and not indicative of a repeated exposure effect. Without having well-defined dose response curves for eye effects as well as LOAECs and NOAECs in both studies, it is impossible to conclude on whether the observed eye effects are of repeated exposure nature.

Moreover, the data submitter's conclusion that the effects in the subacute inhalation study were seen at a concentration which is orders of magnitude lower than that which is the basis for Eye Dam. 1 classification (0.1g pure substance) is not reproducible. Due to the different application/ exposure regimes (inhalation exposure vs. instillation procedure), it is not readily possible without any additional measurement to quantitatively relate the mass of substance getting in contact with the rabbit's eye surface at the LOAEC of 0.01 mg/L in the subacute inhalation study to the dose of 0.1g which was instilled into the rabbit eyes in the eye irritation study. This comparison of two very different exposure metrics and conditions appears inappropriate.

Comments related to discussion on STOT SE 3 C&L (page 50, "A.3.2.5. Specific target organ toxicity – single exposure Category 3 (STOT SE 3)")

The CLH report concludes that KMPS is a respiratory irritant characterized by ocular and nasal discharge observed in the acute inhalation toxicity studies. However, it should be noted that no pathological findings were reported in necropsy. Therefore, in the absence of a pathological manifestation of local irritation/corrosion in the respiratory tract, the effects reported are not considered to be sufficient for a classification of KMPS as STOT SE 3. In addition, the conclusion "As labelling EUH071 'Corrosive to the respiratory tract' is applicable, a classification of STOT SE Cat 3 (H335) is not necessary" is not agreed upon. Labelling with EUH071 can always be assigned alone considering Section 1.2.6. in Annex II of CLP and is not always linked to STOT SE 3, H335. RAC discussions on that endpoint are to be observed.

Comment related to Chapter A.3.3.1. 'Short summary and overall relevance of the provided information on skin corrosion/irritation' (page 55/56)

For reasons of clarity, the sentence "Thus, these studies support the use of the generic concentration limit triggering classification of mixtures as skin irritant (according to Regulation 1272/2008) of 1 % as dermal NOAEC." should rather read "Thus, these studies support the use of the generic concentration limit triggering classification of mixtures **containing skin corrosive substances** as skin irritant (according to Regulation 1272/2008) of 1 % as dermal NOAEC.".

3. Conclusions

The ocular effects observed in the 14-day inhalation toxicity study in male rats result from the acute local irritation/corrosive properties as well as mechanical effects of KMPS dust in animal eyes. Thus, the observed effects are not a result of a repeated exposure regime. This characteristic mode of action of KMPS has been accordingly accounted for by a classification with Skin. Corr. 1, H314, and Eye Dam. 1, H318. An additional classification of KMPS with STOT RE 1, H372 (eyes) is not considered to be warranted.

	Date/Signature
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