Interpretation of the criteria in 3.9.1.1 and 3.9.1.6 and 3.8.1.1 and 3.8.1.6 regarding simultaneous classification into specific target organ toxicity (repeated exposure) hazard class, specific target organ toxicity (single exposure) hazard class and into the acute toxicity hazard class, for lethal effects or not

Information on substance

Data

Acute toxicity animal data

Route	Species	LD_{50} /LC_{50} Value	Observations
Oral	Rat	Study 1 (OECD TG 401): 10% mortalities using undiluted substance at 2000 mg/kg bw	• Clinical signs of neurotoxicity
	Rat	Study 2 (Acute neurotoxicity OECD TG 424): 20% mortalities at 100 mg/kg bw using corn oil as vehicle, where the reason for mortality was neurotoxicity.	• 100 mg/kg bw: clinical signs of neurotoxicity • At the lower dose level of 50 mg/kg bw there was less severe neurological effects and only in some animals, no mortality
	Mouse	Study 3 (Sighting study for micronucleus): 20% mortality at 60 mg/kg bw using corn oil as vehicle	• 60 mg/kg bw: tremors • Lower dose levels: no clinical signs
Inhalation (Dust/Mist)	Rat	OECD TG 402 (4 hours using mist): 0.5 mg/L: no mortality 1.0 mg/L: no mortality 2.0 mg/L: 100% mortality	• 0.5 mg/L and above: clinical signs of neurotoxicity

Repeated dose toxicity animal data

(a) Oral route of exposure

Several dietary studies in rats, mice and dogs are available with exposure durations ranging from 28-days to 2-years. The main finding at dose levels within the guidance values for classification for Specific Target Organ Toxicity – Repeated Exposure category 2 were tremors in rats (28-days study at 285/273 mg/kg bw/day) and dogs (90-days study at 100 mg/kg bw/day). However, although detailed information is not available on the timing of the onset of the effects, it was observed in all animals in the first week of the 26-week study before declining until week 4 after which no effect was observed. A similar pattern was observed in the dog studies 2 to 6h after exposure. In addition, no histopathological findings in the nervous system after detailed examination and no functional findings in the Functional Observational Battery (FOB) were reported.

(b) Inhalation route of exposure

28-day inhalation OECD TG 412 Study

20 Sprague Dawley rats (10 male/10 female); mist concentrations 0, 0.01, 0.05, 0.1 and 0.2 mg/L for 6 hours per day

Concentration (mg/L)	Result
0.2	• Treatment-related mortality (7 /10 males, 3/10 females). The 3 females died on days 3, 4 and 5 respectively. The male deaths were distributed throughout the study with 3 on day 4 and 1 on each of days 9, 19, 25 and 27 respectively. • Tremors, observed during or immediately after exposure (5/10 males, 5/10 females)
0.1	• No treatment related changes
0.05	• No treatment related changes
0.01	• No treatment related changes

Answer

Acute oral toxicity, Category 3

Acute inhalation toxicity, category 4

Specific target organ toxicity – Single exposure, Category 1:

(Target organs: Nervous system)

Specific target organ toxicity – Repeated exposure, Category 2

(Target organs: not specified)

Rationale

(a) Acute oral toxicity:

Classification via application of criteria in GHS Table 3.1.1 is possible. The results using the vehicle corn oil are taken into account as corn oil is a relevant vehicle for lipophilic substances. The study used the preferred test species (i.e., rat) as noted in paragraph 3.1.2.3 and other test species (mice) do not indicate a different acute toxicity. The Oral (rat) LD_{50} is estimated to be within the Category 3 range of $50 < ATE \leq 300$, based on 20% mortality at 100 mg/kg bw (study 2). It can be rationalized that the cause of mortality via the oral route is similar to the inhalation route and therefore the dose response relationship is likely to follow a steep slope similar to acute toxicity by inhalation showing no mortality at 1 mg/L and 100% at the next higher dose of 2 mg/L, resulting in a Category 3 classification for the oral route.

(b) Acute inhalation toxicity

Classification via application of criteria in GHS Table 3.1.1 is possible. The study used the preferred test species (i.e., rat) as noted in paragraph 3.1.2.3 and the 4-hour Inhalation (mist) LC_{50} value is between 1.0 and 2.0 mg/L which is within the Category range of $1.0 < ATE \leq 5.0$ resulting in a Category 4 classification for the inhalation route.

(c) Specific target organ toxicity – Single exposure (oral route)

Acute oral exposure induces clinical signs of neurotoxicity at a dose level of 100 mg/kg bw and lower warranting classification in category 1 according to the guidance values in GHS Table 3.8.2. However, these acute neurological effects were generally observed at a dose level that also caused mortality after single exposure at a level justifying classification for acute toxicity. Classification for specific target organ toxicity – Single exposure by the oral route is therefore not appropriate.

(d) Specific Target organ toxicity – Single exposure (inhalation route)

Acute inhalation exposure induces clinical signs of neurotoxicity at concentrations of 0.5 mg/L and above warranting classification in category 1 according to the guidance values in GHS Table 3.8.1 for mists. No mortality was observed at the concentration of 0.5 mg/L that induced clinical signs of neurotoxicity and the LC_{50} was estimated to be significantly higher than 0.5 mg/L which induced neurotoxicity. Therefore, classification as specific target organ toxicity – Single exposure by the inhalation route in Category 1 is justified.

(e) Specific target organ toxicity – Repeated exposure (oral route)

Repeated oral exposure induces clinical signs of neurotoxicity at a dose level of 100 mg/kg bw consistent with criteria for category 2 according to the guidance values in GHS Table 3.9.1. However, these acute neurological effects were observed during or immediately after exposures. Additionally, no histopathological findings in the nervous system after detailed examination and no functional findings in the FOB were reported. Taken together, the information indicates an acute neurotoxic effect relevant for specific target organ toxicity – Single exposure consideration but not specific target organ toxicity – Repeated exposure.

Therefore, classification for specific target organ toxicity – repeated exposure by the oral route is not appropriate.

(f) Specific target organ toxicity – Repeated exposure (inhalation route)

Repeated inhalation in rats induces clinical signs of neurotoxicity at a concentration of 0.2 mg/L warranting classification in category 2 according to the guidance values in GHS Table 3.9.2 for mists after correction for the 28-day exposure duration. However, in the same study, rats died at the concentration of 0.2 mg/L without observation of local or systemic histopathological changes. This effective dose is also relevant for classification STOT RE 2 (range of 0.06-0.6 mg/L/6 h/d for a 28-day study). After acute exposure, the lowest dose that induced mortality was 2 mg/L whereas no deaths were reported at 0.5 mg/L. Deaths after repeated exposure therefore occurred at much lower levels. Furthermore, deaths are distributed throughout the study and are therefore considered distinct from the acute lethal effect. Therefore, classification as specific target organ toxicity – repeated exposure by the inhalation route in category 2 is justified without specifying the target organ.

(Reference document: ST/SG/AC.10/C.4/2020/14, example 5, as amended by informal document INF.32 (39th session)