Application of criteria in 3.9.1.1 and 3.9.1.6 showing that a substance can be classified into both specific target organ toxicity (repeated exposure) hazard class, for non-lethal effects, and into the acute toxicity hazard class, for lethal effects

Case 1

Information on substance

Data:

Acute toxicity animal data:

Route	Species	LD_{50} /LC_{50} Value	Observations
Oral	Rat	254 mg/kg	• Direct cause of death was extensive necrosis of the pancreas
Inhalation (Aerosol)	Rat	0.89 mg/l (4 hour)	• Clinical signs: Animals died without displaying specific symptoms. • Gross pathology: Brown discoloration of the lungs.

Specific target organ toxicity – repeated exposure

Oral route of exposure

28-day oral (gavage) Rat doses: 0; 1; 10; 50 mg/kg bw/d

Dose level (mg/kg bw)	Result
50	• Mortality: 6/16 animals – Target organs: liver and kidney toxicity responsible for mortality o Diffuse hepatic necrosis and renal tubular degeneration o Absolute and relative liver weights and relative kidney weights of both sexes was significantly increased. The absolute kidney weights were increased in females only. • Haematology treatment-related effects: o Decrease in red blood cell count of about 10% in males and 11% in females, o Decreased in haematocrit concentration of 5% and haemoglobin of 3% in females, o Elevated reticulocyte count and leukocyte count in both sexes, o Increased total serum protein content in females, o These effects are regarded as “slight haematotoxicity”.
10	LOEL (Lowest Observed Effect Concentration) • Increased liver weight (not statistically significant) • Hepatic and splenic changes (severity not given) • Diminished Red Blood Count (RBC) (no other changes in blood chemistry) • Histopathology: In 5/20 animals swelling of parenchymal cells and increased polymorphism of the hepatocyte and their nuclei. These effects are regarded as not “significant or severe”.
1	NOEL (No Observable Effect Concentration)

The liver and kidney effects at the 50 mg/kg bw dose group are significant effects.

Answer

Acute oral toxicity, Category 3

Acute inhalation toxicity, Category 3

Specific target organ toxicity – Repeated exposure, Category 2

(Target organs: liver, kidney)

Rationale

(a) Acute oral 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 Oral (rat) LD_{50} of 254 is within the Category 3 range of $50 < ATE \leq 300$ resulting in a Category 3 classification via 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 Inhalation (aerosol) (Rat) LC_{50} of 0.89 is within the Category 3 range of $0.5 < ATE \leq 1.0$ resulting in a Category 3 classification via inhalation.

(c) Oral route

Classification via application of criteria using the guidance values provided in GHS Tables 3.9.1 and 3.9.2 is possible for the liver and kidney effect. The liver and kidney effects at the 50 mg/kg bw dose level in a 28-day study fall within the guidance value range of $30 < C \leq 300$ mg/kg bw (i.e., 90-day guidance value of $10 < C \leq 100$ is multiplied by a factor of 3 since the data is for a 28-day study (paragraph 3.9.2.9.4)) resulting in a STOT-RE Category 2 classification with the target organs liver and kidney.

(Reference document: ST/SG/AC.10/C.4/2020/14, example 3)