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Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals

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Item 2 (f) of the provisional agenda
Classification criteria and related hazard communication: Practical classification issues

Proposal to address issues from the programme of work for the practical classification issues correspondence group

Transmitted by the expert from the United States of America on behalf of the informal correspondence group on practical classification issues*

Purpose

1. The agreed scope of work for the informal correspondence working group on practical classification issues (PCI) is to clarify application of the GHS criteria through, for example, development of proposals for changes to the GHS document or development of examples illustrating application of criteria and any related hazard communication issues, as needed. By way of this document, the PCI is providing examples illustrating application of GHS criteria.

Background

2. At its twenty-eighth session the Sub-Committee approved the PCI program of work[1] which included an item to consider developing guidance in the form of example(s) to illustrate how to interpret both the specific target organ toxicity single and repeated exposure general considerations (i.e. paragraphs 3.8.1.1 and 3.9.1.1, respectively) that effects covered in other health hazard chapters (i.e.,, chapters 3.1 to 3.7 and 3.10) are not included in specific target organ toxicity classification.

3. The first thought starter on this issue was discussed during a PCI working group meeting at the thirty-third session. It took some time for members of the PCI group to develop consensus on the need for the examples. Subsequently, a thought starter with three examples was presented to the PCI working group meeting at the thirty-fifth session. After much

* 2020 (A/74/6 (Sect.20) and Supplementary), Subprogramme 2.

[1] In accordance with the programme of work of the Sub-Committee approved at its 28th session (informal document INF.32) and again at its thirty-second session (informal document INF.39) and thirty-sixth session (informal document INF.39/Rev.1).

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discussion and review of various thought starters over the years the PCI now has five examples being proposed for consideration.

Proposal

4. The correspondence group invites the Sub-Committee to consider the recommended worked examples in the annex.

Annex

Five examples illustrating how to interpret both the specific target organ toxicity (single and repeated exposure) general considerations (i.e. paragraphs 3.8.1.1 and 3.9.1.1, respectively) that effects covered in other health hazard chapters (i.e. chapters 3.1 to 3.7 and 3.10) are not included in specific target organ toxicity classification.

Example 1

This example illustrates the criteria in 3.8.1.1 and 3.8.1.6 that a substance should not be classified into the specific target organ toxicity - single exposure hazard class when the target organ effect(s), following a single exposure, are serious adverse health effects (i.e., lethality) meeting the acute toxicity hazard classification criteria.

Information on substance 1

Data

Acute toxicity animal data

Route	Species	LD_{50} value	Remark
Oral	Rat	275 mg/kg	• Severe lethal damage in kidney in 5 out of 10 animals (macroscopic examination). Mortality in the same 5 out of 10 animals was observed. • No other effects on organs were noted during necropsy.

Answer

Acute oral toxicity, Category 3

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 275 is within the Category 3 range of $50 < ATE \leq 300$ resulting in a Category 3 classification via the oral route.

(b) Specific Target Organ Toxicity – Single Exposure (STOT- SE)

To be classified into STOT-SE the effects on the kidney or another organ system would need to be non-lethal (paragraph 3.8.1.1) (i.e., not meeting the acute toxicity criteria). Given the limited data (i.e., no additional data at lower doses indicating non-lethal effects on the kidney) in this example, that the only noted effect is on the kidney, and the data support classification into the acute toxicity hazard class, the effect is not in scope for consideration in the STOT-SE hazard class (paragraphs 3.8.1.1 and 3.8.1.6) as it would lead to classification for the same effect/mechanism. Thus, there is no STOT-SE classification. However, if there were additional data showing significant non-lethal effects on the kidney at lower dose levels then expert judgement would be needed to determine if a STOT-SE classification would also be warranted.

(End of example 1)

Example 2

This example illustrates the criteria in 3.8.1.1 and 3.8.1.6 when a substance can be classified into both the Specific Target Organ Toxicity – Single Exposure hazard class, for non-lethal effects, and Acute Toxicity hazard class, for lethal effects.

Information on substance 2

Data

Human experience:

Numerous separate instances of accidental exposure involving hundreds of people have been reported over a 30-year period. Severe neurotoxic effects (i.e., mild peripheral neuropathy to permanent paralysis) were observed after single exposures. Data considered robust and reliable.

Animal data:

Route	Species	LD_{50} value	Remark
Oral	Rat	1,160 mg/kg	• Liver – Advanced fibrosis was noted during necropsy as the cause of mortality. • Clinical observations: Ataxia was observed in animals at dose levels ≥ 200 mg/kg
Dermal	Rabbit	3,100 mg/kg	• Liver – Fibrosis was noted during necropsy as the cause of mortality. • No other effects on organs were noted during necropsy.

Answer

Acute oral toxicity; Category 4

Acute dermal toxicity; Category 5

Specific target organ toxicity – single exposure; Category 1 (nervous system)

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 1160 is within the Category 4 range of 300 < ATE ≤ 2000 resulting in a Category 4 classification via the oral route.

(b) Acute dermal toxicity

Classification via application of criteria in GHS Table 3.1.1 is possible. The study used the preferred species (i.e., rat or rabbit) as noted in paragraph 3.1.2.3 and the Dermal (Rabbit) LD_{50} of 3100 is within the Category 5 range of 200 < ATE ≤ 5000 resulting in a Category 5 classification via the dermal route.

(c) Specific target organ toxicity – single exposure

The effects seen after human exposure (i.e., mild peripheral neuropathy to permanent paralysis) are non-lethal toxic effects on the central nervous system. Specifically, the Category 1 criteria "(a) reliable and good quality evidence from human cases or epidemiological studies" in Figure 3.8.1 support a Category 1 classification.

In this case, the acute oral and dermal toxicity classifications do not preclude classification into the STOT hazard class since they reflect the lethal effects on a separate target organ (i.e., liver was confirmed as the cause of death during necropsy) via a different mechanism than the non-lethal effects on the central nervous system.

(End of example 2)

Example 3

This example illustrates the criteria in 3.9.1.1 and 3.9.1.6 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.

Information on substance 3

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.

(End of example 3)

Example 4

This example illustrates the criteria in 3.9.1.1 and 3.9.1.6 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.

Information on substance 4

Data

Acute toxicity animal data

Route	Species	LD_{50} /LC_{50} Value	Observations
Oral	Rat	In two OECD 401 studies values were 160 and 273 mg/kg	• Effects were observed in the lungs (haemorragies) and stomach
Dermal	Rat	404 mg/kg	• No observations reported
Inhalation (Dust/Mist)	Rat	In two 4-hour studies the LC_{50} values were 0.115 and 0.139 mg/L	• No observations reported

Specific target organ toxicity – repeated exposure

(a) Study 1: Oral route of exposure

90-day OECD TG 408 equivalent study

30 Sprague Dawley rats (15 male/15 female); Oral dose levels: 0, 1.9, 6, 17.5 mg/kg bw/day

Dose level (mg/kg bw/day)	Observations
17.5	• Death (28 animals died or were sacrificed between days 18 and 34 and remaining animals by day 36) with severe clinical signs of toxicity including o Tremors, convulsions and aggression/hypersensitivity/difficulty when handling o Appeared to be weak, thin and dehydrated o Cold to touch o Lying on their sides and decreased home-age activity levels • Reduced body weight, • Decreased food and water intake, • Blood biochemical changes, • Behavioural effects, • Neuropathological lesions (mild ventricular dilation and moderate neuronal necrosis) • Decrease in absolute and relative thymus weight was observed at the interim sacrifice (week 4) evaluation for the males. • Several preterminal non-perfused animals with small thymus and/or spleen
6	• Death in 1 animal, with abnormal clinical signs limited to: o Tremors, hypersensitivity (difficulty when handled), o Thin dehydrated for the animal that died, o Transitory dehydrated appearance in another animal, and o Hypersensitivity, convulsions and reduced activity for another animal • Reduced body weight (males only) • Decreased food and water intake • Motor activity was reduced (females only), • Neuropathological lesions were observed • Gross pathological findings include smaller absolute and relative thymus and/or spleen weight at the terminal sacrifice • Terminal evaluations indicated possible treatment-related lymphoid atrophy of the thymus
1.9	• No mortality • Findings were limited to: o Reduced food (males only) and water intake o Neuropathological lesions (slight to moderate vacuolization in the brain and spinal cord tissue) • The NOAEL is considered to be less than this dose level.

(b) Study 2: Oral route of exposure

90-day Oral OECD TG 408 Study

16 Wistar rats (8 male/8 female); Oral dose levels: 0, 0.07, 0.4, 1.0 and 17 mg/kg bw/day

Dose Level (mg/kg bw)	Result
17	• Death in 3 animals during the first month and most remaining animals showed severe neurological and neurobehavioral signs, including tremors, convulsions and increased footsplay. All remaining animals of this group were sacrificed. • Mean body weights for males were significantly lower • Upon microscopic examination, changes were observed in the brain, the kidneys and thymus. o Females had increased incidence of corticomedullary haemorrhage in the thymus and most showed cortical lymphoid depletion in the thymus o All animals showed decreased accumulation of brown pigment in the spleen. o Pronounced neuronal death in a number of areas of the cerebellum was more pronounced in females. The areas with predominant lesions were the hippocampal region, the piriform, entorhinal and perirhinal cortices and amygdala, the olfactory nuclei and the tenia tecta. Also, a slight increase in swollen axons in the spinal cord was observed.
1.0	• No clinical signs • Microscopic examination revealed no changes compared to the control group • The NOAEL is placed at this level.
0.4	• No clinical signs
0.07	• No clinical signs

Answer

Acute oral toxicity, Category 3

Acute dermal toxicity, Category 3

Acute inhalation toxicity, category 2

Specific target organ toxicity – Repeated exposure, Category 1

(Target organs: Nervous system, thymus)

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 2 Oral (rat) LD_{50} between 160 and 273 mg/kg are both within the Category 3 range of $50 < ATE \leq 300$ resulting in a Category 3 classification via the oral route.

(b) Acute dermal toxicity

Classification via application of criteria in GHS Table 3.1.1 is possible. The study used a preferred test species (i.e., rat or rabbit) as noted in paragraph 3.1.2.3 and the Dermal (Rat) LD_{50} of 404 mg/kg is within the Category 3 range of $200 < ATE \leq 1000$ resulting in a Category 3 classification via the dermal route.

(c) 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 two 4-hour inhalation (dust/mist) (Rat) LC_{50} values of 0.115 and 0.139 mg/L are within the Category 2 range of $0.05 < ATE \leq 0.5$ resulting in a Category 2 classification via inhalation.

(d) Specific target organ toxicity – Repeated exposure

Oral route

Together, these two oral 90-day studies indicate that the main target organ is the nervous system. Deaths and severe neurological signs occurred from 6 mg/kg bw/day in Study 1 and at 17 mg/kg bw/day in Study 2. In Study 1, neuropathological lesions were observed from the lowest dose at 1.9 mg/kg bw/day as evidenced by moderate vacuolization in the brain and spinal cord tissue as well as ventricular dilation and neuronal necrosis at the highest dose (17.5 mg/kg bw/day).

The absolute and relative weights of the thymus were reduced in the 6 mg/kg bw/day dose level in Study 1 and there were indications of possible treatment-related lymphoid atrophy of the thymus. In Study 2, females had an increased incidence of corticomedullary haemorrhage in the thymus and most of these high-dose females also showed cortical lymphoid depletion in the thymus at the 17.5 mg/kg bw/day dose level. Thus, both studies support including the immune system as a target organ.

Classification via application of criteria using the guidance values provided in GHS Tables 3.9.1 and 3.9.2 is possible for the nervous and immune system effects. The guidance dose value for a Category 1 classification in an oral rat 90 day study is ≤ 10 mg/kg bw/day. The effects seen in the thymus (and to a lesser extent in the spleen) as well as in the nervous system in the two rat 90-day studies (i.e., 6 mg/kg bw/day) justify classification in STOT RE Category 1 according to the GHS criteria with the central nervous system and the immune system as the specific target organs/systems.

(End of example 4)

Example 5

This example illustrates the 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 5

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 (assumed to be secondary to systemic effects) 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.

(End of example 5)