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# Addendum To The Report Of The Pilot Exercise On Classifications For Selected Chemicals
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# ADDENDUM TO THE REPORT OF THE PILOT EXERCISE ON CLASSIFICATION FOR SELECTED CHEMICALS ASSESSED AT COCAM

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## FOREWORD

This document is an Annex to the results of a pilot exercise to suggest classifications according to the Globally Harmonised System for a number of chemicals assessed in the OECD Cooperative Chemicals Assessment Programme (CoCAP). Here, 2-vinyl pyridine is reconsidered, as it was initially addressed in phase two of the exercise in October 2013, but a consensus could not be reached.

The Joint Meeting agreed to the declassification of this addendum to the report in December 2015. This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

**Background**

1. After the conclusion of the pilot classification exercise and publication of the report on the exercise, OECD entered into further discussions with the United Nations Sub-Group of Experts on the GHS (UNSEGHS) about their ongoing project to define the process for evaluating chemicals which should provide insight into the level of effort needed to create and maintain a global classification list. In these discussions, it was decided that it would be mutually beneficial if OECD could organize a final "revisit" of one of the chemicals in the exercise to make one more attempt at consensus, and, if consensus was possible, gauge what level of effort was required to reach it.

2. The secretariat selected 2-vinyl pyridine, based on the assumption that reaching consensus should be easier for this chemical than the others because i) it was not part of a category assessment; ii) in the exercise it was the chemical with the most agreed endpoints; and iii) one cause that had led to a lack of consensus for some endpoints – ambiguity or lack of clarity in the draft SIAR & dossier used in the exercise - was now addressed (by this time the sponsor country, Japan, had submitted final versions of the SIAR and dossier, which are now published; OECD, 2014a).

3. The proposal to look again at endpoints for which classification proposals differed for the substance was put to the six countries that took part in the second phase of the pilot exercise, highlighting that final revised assessment documents were available. Of the six countries, the Netherlands, Switzerland, the Russian Federation, France and Japan were able to take part in this final effort. Unfortunately Denmark was unable to take part this time.

4. The endpoints for which consensus was not reached for 2-vinyl pyridine when it was discussed at CoCAM 5 (second phase of the exercise) were as follows (see table 10 of OECD, 2014b)

- Acute toxicity via the oral route;
- Acute toxicity via the dermal route;
- Eye irritation/corrosion;
- Mutagenicity;
- Reproductive/developmental toxicity;
- Specific target organ toxicity, single exposure (STOT SE);
- Specific target organ toxicity, repeat exposure (STOT RE)

5. Consensus had been reached for classification categories for the endpoints of skin sensitization and skin irritation/corrosion, but no agreement had been reached on sub-categorisation (participants had suggested sub-category A or B, or not suggested sub-categorisation based on insufficient data). As a result it was decided to also look again at these two endpoints to try to resolve this difference.

6. The secretariat produced an informal summary document for this final exercise and a template for the participants to use to submit their amended classifications for these nine endpoints. The summary document included a series of nine tables, one for each endpoint that was to be looked at, that listed the previous classification suggestions and cited the relevant information for the endpoint from the revised versions of the SIAR and dossier, highlighting where changes in the study(ies) descriptions had been made by the sponsors in these documents.

7. The five participating countries submitted revised classification proposals in the lead up to CoCAM 6 (30 September – 3 October 2014).

**Results of the Exercise and Discussion**

8. Based on the information in the revised SIAR/dossier, consensus was reached by the five countries for seven out of the nine endpoints without the need for discussion. These endpoints are listed below against the "agreed" classification. Table 1 lists the original proposals (including those of Denmark, for information), revised proposals and rationales for ease of reference for these endpoints. The rationales for the revised proposals in Table 1 reflect changes made to the SIAR and dossier in producing final versions of these assessment documents.

- Acute toxicity via the oral route – category 3
- Acute toxicity via the dermal route – category 2
- Eye irritation/corrosion – category 1
- Mutagenicity – not classified
- Reproductive/developmental toxicity – category 2
- skin irritation/corrosion – category 1B (reconsidered for the purposes of sub-categorisation)
- skin sensitization – category 1 (reconsidered for the purposes of sub-categorisation; consensus that sub-categorisation not possible)

9. This left two endpoints, STOT SE and STOT RE, with one country in each case (Japan and the Russian Federation, respectively) proposing a classification that differed from the other participants in the lead up to CoCAM 6. Table 2 lists the original proposals and revised proposals, with rationales, for STOT SE and STOT RE. Again, the rationales for the revised proposals in the tables reflect changes made to the SIAR and dossier. Further discussion of these endpoints was undertaken at and after CoCAM 6.

10. At CoCAM 6, following discussion amongst participating member countries, Japan revised their classification for STOT SE from cat 3 (i) to not classified, on the basis that evidence was in fact not strong enough that a mechanism other than localized irritation (an effect covered by other proposed classification) was occurring. This revision brought their proposal for STOT SE into accordance with the other participating member countries.

11. The classification expert from the Russian Federation was unable to attend CoCAM 6, but after the meeting the Russian Federation, having reviewed the toxicity data again, informed the Secretariat that they agree with the other participants that the repeat dose effects are related to local irritation, and that therefore the substance should not be classified for STOT RE as proposed by the other participants.

12. Table 3 summarises the final classification proposals for all considered endpoints for 2-vinyl pyridine from the five member countries that participated in this final exercise. Endpoints for which consensus was previously reached are included. Where classification is not proposed for an endpoint, the phrase "no classification proposed" has been used to cover instances where data are sufficient for classification as well as where no data are available (refer to previous tables for this information).

13. In terms of the time or resource taken to reach consensus, this is difficult to quantify. The majority of time taken in reaching classification proposals is in the review of data, so even though some participants did not need to change any of their previous proposals it is likely they spent about the same amount of time in data review as did those participants who revised their proposals.

14. Overall this final exercise has shown that consensus can be achieved, but that reaching consensus may not be straightforward even in what should be simpler cases. Whilst complex endpoints can provide more of a challenge in terms of reaching consensus between a number of experts, interpreting studies where results are equivocal, ambiguous, or do not shed full light on an important aspect for classification purposes (e.g. mode of action) for any endpoint seems a greater issue.

**References**

OECD, 2014a. Cooperative Chemicals Assessment of 2-vinyl pyridine, CAS 100-69-6.
OECD, 2014b. Report of the Pilot Exercise on Classifications for Selected Chemicals Assessed at COCAM. ENV/JM/MONO(2014)31

**Table 1: Revised classifications for 2-vinyl pyridine for which consensus was reached without discussion (seven of the nine considered)**

| | **Country** | | | | | |
|---|---|---|---|---|---|---|
| **Endpoint** | **NL** | **DK**[1] | **CH** | **RO** | **FR** | **JP (HH only)** |
| **Acute Toxicity (oral)** | | | | | | |
| Original proposal | Cat 2 | Cat 2 | Cat 3 | Cat 3 | Cat 3 | Cat 3 |
| rationale | LD50 >50 <300 mg/kg bw (rat) | LD50 >50 <300 mg/kg bw (rat) | LD50 >50 <300 mg/kg bw (rat) | LD50 >50 <300 mg/kg bw (rat) | LD50 >50 <300 mg/kg bw (rat) | LD50 >50 <300 mg/kg bw (rat) |
| Revised Proposal | Cat 3 | - | Cat 3 | unchanged | Unchanged | Unchanged |
| Revised rationale | Based on OECD TG 423 (Annex 2b). After revising the data, it seems that there was an interpretation error on our part when using the GHS. | | LD50 >50 <300 mg/kg bw (rat) | | | |
| **Acute Toxicity (dermal)** | | | | | | |
| Original proposal | Cat 1 | Cat 2 or 3 | Cat 2 | Cat 2 | Cat 1 | Cat 2 |
| Rationale | $LD_{50}$ 160 mg/kg bw (guinea pig) | $LD_{50}$ (rabbit) 640 mg/kg; $LD_{50}$ (guinea pig) 160 mg/kg (inconclusive) | $LD_{50}$ 160 mg/kg bw (guinea pig) | $LD_{50}$ 160 mg/kg bw (guinea pig) | $LD_{50}$ 160 mg/kg bw (guinea pig) | $LD_{50}$ 160 mg/kg bw (guinea pig) |
| Revised Proposal | Cat 2 | - | Cat 2 | unchanged | Cat 2 | Unchanged |
| Revised rationale | A weight of evidence approach is difficult here, since the two LD50 values are so far apart. Why guinea pig more important than rat/rabbit data? When it is unknown which species is more representative of humans, the species showing in the lowest LD50 was chosen. | | $LD_{50}$ 160 mg/kg bw (guinea pig) | | Cat 2 for 50 < ETA ≤ 200 Mistake in the FR initial proposal. | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Eye Irritation** | | | | | | |
| Original proposal | Cat 1 | not classified (Cat 1B indicated from skin data) | Cat 1 | Cat 1 | not classified | not classified (cat 1 or 2 indicated) |
| rationale | based on skin data | data not sufficient (detail lacking for rabbit eye study) | Based on skin data | based on skin data (eye data in rabbits not sufficient) | data not sufficient (no scoring) | data not sufficient (detail lacking for rabbit skin study & eye study) |
| Revised Proposal | Unchanged | - | Unchanged | unchanged | Eye Dam 1 | Cat 1 |
| Revised rationale | | | Based on skin data | based on skin data as giving more severe classification | Based on proposed classification for skin corrosion (in this case, both Skin Corr. 1 and Eye Dam. 1 required). | based on skin data |
| **Skin Irritation/corrosion – for sub-categorisation** | | | | | | |
| Original proposal | Cat 1B | Cat 1B | Cat 1 | Cat 1B | Cat 1B | not classified (Cat 1B indicated) |
| rationale | skin necrosis 48 h after 1h exposure (rabbit) | skin necrosis 48 h after 1h exposure (rabbit) | skin necrosis 48 h after 1h exposure (rabbit) | skin necrosis 48 h after 1h exposure (rabbit) | skin necrosis 48 h after 1h exposure (rabbit) | data not sufficient (detail lacking for rabbit study) |
| Revised Proposal | Unchanged | - | Cat 1B | unchanged | Unchanged | Cat 1B |
| Revised rationale | | | skin necrosis 48 h after 1h exposure (rabbit) | | | skin necrosis 48 h after 1h exposure (rabbit) |
| **Skin Sensitisation – for sub-categorisation** | | | | | | |
| Original proposal | Cat 1 | Cat 1 | Cat 1 | Cat 1B | Cat 1A (or B) | Cat 1 (subcategory not possible) |
| rationale | WoE: LLNA stimulation index >3; human patch test ++ve | WoE: LLNA stimulation index >3; human patch test ++ve; GPMT 80% | WoE: LLNA stimulation index >3; human patch test ++ve; GPMT 80% | data sufficient (GPMT data) | WoE: GPMT 80% (lacking details), human studies | WoE: LLNA stimulation index >3; human patch test ++ve |
| Revised Proposal | Unchanged | - | Cat 1 | Cat 1 | Cat 1 | Unchanged |
| Revised rationale | | | WoE: LLNA stimulation index >3; human patch test ++ve; GPMT 80% | Unchanged + WoE: LLNA stimulation index >3; human patch test +ve; | Subcategory not possible due to lacking details | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Mutagenicity** | | | | | | |
| Original proposal | not classified | not classified | not classified | not classified | not classified | Cat 2 |
| rationale | no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473) | no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473) | no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473) | no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473) | data not sufficient (no in vivo data; equivocal in vitro results) | data sufficient (+ve *in vitro* OECD TG 471, 472 & 473) |
| Revised Proposal | Unchanged | - | not classified | unchanged | Unchanged | Not classified |
| Revised rationale | | | no data (*in vivo*; but +ve *in vitro* OECD TG 471, 472 & 473) | | | No *in vivo* data |
| **Reproductive Toxicity** | | | | | | |
| Original proposal | Cat 2 | Cat 2 (?) | not classified | Cat 2 | Cat 2 | not classified |
| rationale | data sufficient (OECD 421; NOAEL 20 mg/kg bw/day based on dystocia), but possible secondary effect | data sufficient (OECD 421; NOAEL 20 mg/kg bw/day based on dystocia), but possible secondary effect | data not sufficient (unclear if OECD 421 effects are developmental or due to parental toxicity at 20 mg/kg bw/day) | data sufficient (OECD 421; NOAEL 20 mg/kg bw/day based on dystocia) | data sufficient (pup death at 50 mg/kg bw/day) | data not sufficient (effects in pups considered secondary) |
| Revised Proposal | Unchanged | - | Cat 2 | unchanged | Unchanged | Cat 2 |
| Revised rationale | | | data sufficient (OECD 421; NOAEL 20 mg/kg bw/day based on dystocia), but possible secondary effect | | | OECD 421; NOAEL 20 mg/kg bw/day based on dystocia |

**Table 2: Revised classifications for 2-vinyl pyridine for which consensus was not reached without discussion (two of the nine considered)**

| Endpoint | NL | DK[1] | CH (HH only) | RO | FR | JP (HH only) |
|---|---|---|---|---|---|---|
| **STOT SE** | | | | | | |
| Original proposal | not classified (i, d, o) | not classified (i, d, o) | not classified (i, d, o) | not classified (i, d, o) | not classified (i, d, o) | Cat 3 (i) |
| rationale | no data (i); data not sufficient (d); data sufficient (o) | no data (i, d, o) | no data (i); data not sufficient (d); data sufficient (o) | no data (i, d, o) | WoE: not required based on acute studies | WoE: acute, repeat dose & irritation studies indicate respiratory irritation |
| Revised Proposal | Unchanged | - | not classified (i, d, o) | unchanged | Unchanged | Unchanged |
| Revised rationale | As no mortality is observed in the repeated dose studies in at dose levels inducing dystocia related mortality in the dams, the mortality could be secondary to the dystocia. | | no data (i); data not sufficient (d); data sufficient (o) | | Cat 1 / 2:<br>Inhal: no data<br>Oral: data sufficient<br>Derm: data not sufficient<br>Cat 3: data not sufficient | WoE indicates localized irritation via at least oral exposure |
| **STOT RE (oral)** | | | | | | |
| Original proposal | not classified | not classified | not classified | not classified | not classified | Cat 2 |
| rationale | data sufficient (repeat dose effects related to local irritation) | data sufficient (repeat dose effects related to local irritation) | data sufficient (clinical signs reversible or not substance related) | data not sufficient for classification | data sufficient (repeat dose effects related to local irritation) | data sufficient (92d rat LOAEL 20mg/kg bw/day) |
| Revised Proposal | Unchanged | | not classified | Category 1, but ready to discuss | Unchanged | not classified |
| Revised rationale | Local gastric irritation (mainly protective effect) is normally an acute effect that is reversible (in this case slowly). Irritation/corrosion effects are more dependent on concentration rather than dose. In addition the increase of relative kidney weight without histopathological effects in our view is not sufficient to warrant a classification. | | data sufficient (repeat dose effects related to local irritation) | In case it is assumed that effects are not mainly due to localized irritation, and it is not sufficiently covered by the previous classification proposals, then we should consider the application of category 1 for STOT RE | | Repeat dose effects were related to local irritation. And this suggests the "cat 3" in STOT SE |

[1]Denmark was unable to take part in this final exercise; their original proposals are retained for information only

**Table 3: Final Classification Proposals for all considered endpoints for 2-vinyl pyridine from NL, CH, RO, FR, and JP**

| Endpoint | Classification proposal |
|---|---|
| Aspiration toxicity | no classification proposed |
| Acute Toxicity (inhalation) | no classification proposed |
| Acute Toxicity (oral) | Cat 3 |
| Acute Toxicity (dermal) | Cat 2 |
| Skin Irritation | Cat 1B |
| Skin Sensitisation | Cat 1 (sub-categorisation not possible) |
| Respiratory Sensitisation | no classification proposed |
| Carcinogenicity | no classification proposed |
| Acute Aquatic toxicity | Cat 2 |
| Chronic aquatic toxicity | Cat 2 |
| Eye Irritation | Cat 1 |
| Mutagenicity | no classification proposed |
| Reproductive/developmental Toxicity | Cat 2 |
| STOT SE | no classification proposed (i, d, o) |
| STOT RE (oral)[1] | no classification proposed |

[1]only oral repeat dose toxicity studies available