Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Reaction mass of 1,3-dioxan-5-ol and 1,3-dioxolan-4-ylmethanol

EC Number: -
CAS Number: -

CLH-O-0000007209-71-01/F

Adopted

1 December 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON REACTION MASS OF 1,3-DIOXAN-5-OL AND 1,3-DIOXOLAN-4-YLMETHANOL

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: Reaction mass of 1,3-dioxan-5-ol and 1,3-dioxolan-4-ylmethanol
EC number: -
CAS number: -
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
08.04.2022	France		MemberState	1
Comment received				
The classification proposal Repr. 1B; H360Df (with generic concentration limit) is supported by France.				
Dossier Submitter's Response				
Thank you for agreeing with our classification proposal.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.03.2022	Germany		MemberState	2
Comment received				
In chapter 1.2 on page 2 it is stated that „The test substance is glycerol formal in all studies where the test substance was explicitly stated." We wonder, if studies were taken into account for the assessment for which it is not clear which material was tested. Could you please clarify what was meant by the quoted sentence above? Below the table stating the impurities present in the substance three "impurities" are given. However, it seems that these substances are no impurities but additives (as stated on ECHAs dissemination webpage these substances were used as stabilizers). Thus, these substances should be given in table 4 or the report. In Chapter 2 "Proposed harmonized classification and labelling", Table 5 the classification of the substance as Repr. 1B, H360Df is proposed. According to the rules of Regulation (EC) No. 1272/2008 (CLP Regulation), this classification results in a labelling (in coded				

form) with:
GHS08
Dgr
H360Df

Moreover, under "Labelling - Pictogram, Signal Word Code(s)" the signal word "Danger" is not given in the required coded form with "Dgr". This is required according to Annex VI Part 3 Table 3 (List of harmonized classification and labeling of dangerous substances) as well as Table 5 of the CLH dossier.

Dossier Submitter's Response

Thank you for carefully reading the document.
Regarding your comment 1: We understand that the sentence might be misleading. In all studies reported in the proposal the test substance was glycerol formal.

Comment 2: We agree that the substances reported in some studies as stabilisers should be considered as additives not as impurities.

Comment 3: We agree that the classification results in the labelling GHS08, Dgr, H360Df and the coded form for "Danger" should be "Dgr".

RAC's response

Thank you for the clarification. The information has been considered in the RAC opinion. The correct labeling has been mentioned in the table on page 2 of the RAC opinion. The puritiy of glycerol formal and the stabilisers has been mentioned in the description of the studies as far as the information was available.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
31.03.2022	Germany		MemberState	3

Comment received

Adverse effects on sexual function and fertility
Reliable generation studies explicitly addressing the endpoint "adverse effects on sexual function and fertility" are not available. Thus, the assessment is based on studies on repeated dose toxicity.

According to the CLH report, the oral 90-d study in rats from 1973 is the only study, which deserves a reliability score of 2 and thus is designated the key study. The dose spacing is larger than usual (0, 12, 121, 1218 mg/kg bw/d: factor 10), and the dose-dependent decrease or increase of parameters mentioned in the CLH report imply a very flat dose-response relationship. Marked toxicity on the male gonads (testes, seminal vesicles, epididymis) is found at the highest dose slightly above the limit dose, also in the very small recovery group (two males only). It is stated in table 10 that "Dose-dependent lower relative organ weights (in percent of body weight) are reported for uterus, seminal vesicles, testes and epididymis". With respect to the testes, a lower relative organ weight is limited to the highest dose (0.87/0.89/0.89/0.52) and as to the epididymis (0.30/0.29/0.27/0.18) and seminal vesicles (0.15/0.12/0.12/0.095), a pronounced effect is also limited to the highest dose. Unfortunately, there is no information on the statistical significance. Thus, the relevance of the small reductions in the seminal vesicles and epididymis at the medium and low dose is somewhat difficult to assess. On page 16, a "dose-dependent increase of adverse effects on testes" is mentioned. This could be claimed with respect to the histopathological effects (0/10, 1/10, 2/10, 10/10), because

at the medium dose two sensitive animals (2/10) were affected, but also in the recovery group one of two animals showed a testes effect. In the low-dose group, a slight inhibition of spermiogenesis was detected in only one animal. Regrettably, as mentioned in the CLH report, no information on the severity of the effects is provided (e.g., severity scores) and no analysis of sperm parameters (number, quality etc.) was performed. There is also an effect on the relative uterus weight, but this is not supported by dose-related histopathological changes (0/10, 2/10, 3/10, 1/10).

With respect to general toxicity, the relative body weight gain (in % of control) in males showed a graduated dose-response relationship down to the lowest dose (100 % /80.87 %/
68.31 %/57.36 %), indicating a very flat dose-response relationship. Thus, a NOAEL for general toxicity was not detected. The reduced bw gain corresponds to a reduced feed consumption and relative feed efficiency. The highest dose was obviously too high, because lethality of nearly 20 % was observed in males and females. This should be considered as marked systemic toxicity and in the guidance (p. 400) it is stated: "Adverse effects on fertility and reproductive performance seen only at dose levels causing marked systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma) are not relevant for classification purposes". No further clinical signs, changes in organ weights, haematological or histopathological effects were detected beyond those on the male gonads, which should not induce fatalities, especially not in females. Thus, there is no plausible explanation for the spontaneous lethality. Below the high dose, the effects at the medium dose seem to be limited to low incidences of histopathological effects in testes and small reductions of the relative weight of epididymis and seminal vesicles of unclear significance and relevance. Unfortunately, a dose of 300 mg/kg bw was not applied, the large dose spacing, the absent information on severity and sperm parameters (number, quality etc.) in addition to the missing statistical analysis hamper a sound evaluation of effects and some uncertainties surround the reliability of the study.

The relevance of the other studies is questioned by various and marked deficiencies, which led to reliability scores of 3 (not reliable) and 4 (not assignable). However, gonadal toxicity in males is partly described also at doses between the medium and high dose of the key study.

In another subchronic study (study report, no date) 0, 292.3, 584.6 and 1461.6 mg/kg bw/d of the substance were administered subcutaneously to rats. Beside the application route, this study was considered to be of good quality. Relative weights of testes and epididymis were markedly reduced only in the high-dose group. However, testis changes occurred dose-dependently with increasing incidence (disturbances of spermiogenesis with interstitial oedema in five of ten animals in the medium-dose group, atrophy of the seminiferous tubules combined with an interstitial oedema in all animals of the high-dose group as well as changes in seminal vesicles and epididymis). Effects on testes were also seen in the recovery group.

A subchronic study in beagles (study report, no date) with intramuscular application of 0, 29.23, 292.3 (30 % solution) and 292.3 (50 % solution) mg/kg bw/d of the test substance found similar effects on the testes in both high-dose groups (partly atrophy of the seminiferous tubules, minimal depression of spermiogenesis, changes of epididymis and content of the tubules of the epididymis).

The testes effects in the key study and supporting studies generally would support a classification as reproductive toxicant Category 2 (H360f). However, in light of nearly 20 % lethality at 1218 mg/kg bw/d (a dose above the limit dose of 1000 mg/kg bw/d) and

further shortcomings of the key study, the deficiencies of the other studies and missing reliable generation studies, the data seems to be borderline. Thus, alternatively "no classification" may also be considered.

Adverse effects on development

For this endpoint, two key studies according to OECD TG 414 are available with a reliability of 2 assigned by the DS. Additionally, four developmental toxicity studies as well as a frog embryo teratogenesis assay (FETAX) and QSAR predictions are available as supporting information.

In the oral key study (similar to OECD TD 414, study report from 1981), pregnant rats were gavaged with 0, 75, 150, 300 or 600 mg/kg bw/d from GD 6 – 17. Maternal toxicity was not observed. In the highest dose group, the total number of resorptions and the number of resorptions/number of implants ratio per female was significantly increased. The total number of live foetuses was decreased and the number of dead foetuses increased. The number of live foetuses/pregnant female was significantly decreased in the highest dose group. The average foetal weight per litter was dose-dependently decreased at ≥ 150 mg/kg bw/d. External malformations were increased in the two highest dose groups (anal atresia, tail malformations and anasarca). Visceral malformations were observed in the highest dose group (mainly cardiovascular defects: primarily defects of the ventricular septum, retrooesophageal aortic arch malformations). Additionally, several skeletal variations were observed with increased incidences in higher doses as well as a dose-dependent delay in foetal ossification (considered as variations), primarily of the skull bones.

In another PNDT study by Aliverti et al. (1980), several experiments were carried out. In the first experiment according to OECD TG 414, the test substance was administered intramuscularly at doses of 0, 300, 600, 1200 mg/kg bw/day (ten pregnant rats/dose). Maternal toxicity was not observed. Postimplantation loss was increased dose-dependently from 4.4 % (control) to 63.7 % (high dose). Mean foetus weight was dose-dependently decreased in all dose groups (-25 % in the high-dose group as compared to the control). The number of females with malformed foetuses increased dose-dependently as did the incidence of visceral malformations (particularly in the cardiovascular system, i.e. ventricular septal defect, sometimes accompanied by cardiomegaly, atrial hypertrophy, and right and retrooesophageal aortic arch malformation). In experiment 4 within this study, intramuscular application of the substance was compared to oral and subcutaneous application of 600 and 1200 (only oral) mg/kg bw/d. Similar effects were observed; postimplantation loss rates and visceral malformation rates were even higher after oral exposure.

A FETAX and two QSAR predictions for individual constituents of the reaction mass support developmental toxicity of the substance.

Overall, the adverse effects on development (increased resorptions, decrease in foetal body weight accompanied by a delay in foetal ossification, teratogenic effects, especially malformations of the cardiovascular system) shown in a reliable study according to OECD TG 414 and supported by other studies with varying reliability, justify a classification as Repro 1B (H360D) as proposed by the DS.

Dossier Submitter's Response

Thank you for your careful reading and analysis of the data. We will address your comments separately regarding sexual function/fertility and development.

Adverse effects on sexual function and fertility:
As outlined by the submitter of the comment, the reliable 90-day study (similar to OECD TG 408) from 1973 does not report information on the severity of effects (toxicity to testes, seminal vesicles and epididymis). However, the histopathological changes are described in detail.
Lethality in the highest dose group was observed in 4/24 animals (16,7%, 2 males and 2 females). If effects on male gonads would only have been observed in the highest dose group, the high mortality would indeed justify "no classification" for this endpoint. However, the same effects were also observed in 2/10 animals of the middle dose group and in 1/2 animals in the middle dose recovery group. In the low dose group slight inhibition of spermiogenesis was observed in 1/10 animals.
Taken together with the results obtained in several studies with limited reliability (reliability 3 or 4) where gonadal toxicity was also shown in male rats and Beagle dogs, we consider a classification of glycerol formal as a substance to be suspected of showing adverse effects on sexual function and fertility in humans (Repro 2, H360f) appropriate.

Adverse effects on development:
Thank you for agreeing on our proposal to classify the substance as Repro 1B (H360D).

RAC's response

Thank you for the analysis and the clarifications. The arguments have been considered in the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
17.02.2022	Czech Republic	Dischem s.r.o.	Company-Importer	4

Comment received

We do not have any toxicological and ecotoxicological studies to improve the following proposed future entry in Annex VI of CLP Regulation by the dossier submitter.

Dossier Submitter's Response

Thank you for checking and your feed-back.

RAC's response

Thank you for the search for studies.

Date	Country	Organisation	Type of Organisation	Comment number
08.04.2022	France		MemberState	5

Comment received

10.10.1 Adverse effects on sexual function and fertility.
"No studies explicitly addressing the endpoint "adverse effects on sexual function and fertility" are available in the registration dossier." It should have been mentioned that two studies investing adverse effects on sexual function and fertility (1982b and 1982c) have been identified. These two studies are however of low reliability due to the low administered dose, and therefore do not allow an appropriate assessment of the endpoint.

10.10.3 Comparison with the CLP criteria (sexual function and fertility)
Despite the highlighted uncertainties linked to the available dataset, the proposal for classification of glycerol formal for effects on sexual function and fertility in category 2 is agreed. Indeed, effects on testis and epididymis were consistently observed in several species. The changes include inhibition of spermiogenesis and atrophy and as it is

mentioned page 21, humans are much more sensitive to impairments of sperm production or sperm quality compared to rats.

10.10.6 Comparison with the CLP criteria (development)
It is agreed that a classification in Category 1B for developmental toxicity is justified. Indeed, evidence of death of the developing organism, structural abnormality (clearly teratogenic) and altered growth (decreased fetal weight) is well substantiated in the absence of maternal toxicity.

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation
The study (1982b, reported as study 2 in Annex 1) should be mentioned. No effect on survival and pup weights were observed up to PND 21. However the reliability of the study is limited due to the low administered dose (no impact on the classification proposal).

Dossier Submitter's Response

Thank you for comments and for agreeing with our classification proposals.

We agree that the two study reports from 1982 (1982b and 1982c) are the only studies explicitly addressing the endpoint sexual function and fertility. Despite the low administered dose, these studies were therefore included in the Annex and described there in as much detail as possible. We are sorry if the introducing sentence above Table 10 ("No studies explicitly addressing the endpoint "adverse effects on sexual function and fertility" are available in the registration dossier.") caused misunderstandings. We should have added the information that these two studies are available but not included in the registration dossier.

In the study from 1982 (1982b) female rats were orally exposed to doses of 0, 1, 5 or 25 mg/kg bw/d before and during gestation and up to PND 20. No adverse effects were observed at any dose and at any time point. As the study design does not allow to differentiate the effects caused by pre- and postnatal exposure no conclusion on effects via lactation can be derived from this study. We therefore refrain from reporting this study in section 10.10.7 where adverse effects on or via lactation are discussed. As mentioned in the comment, this would have no influence on the classification proposal.

RAC's response

Thank you for the analysis and the clarifications. The arguments have been taken into account in the RAC-opinion. The oral reproduction study in female rats (1982b) has been mentioned in the chapter "Adverse effects on or via lactation" for completeness.