Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2,3-epoxypropyl isopropyl ether

EC Number: 223-672-9

CAS Number: 4016-14-2

CLH-O-0000007313-80-01/F

Adopted

8 June 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2,3-EPOXYPROPYL ISOPROPYL ETHER

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.

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Substance name: 2,3-epoxypropyl isopropyl ether
EC number: 223-672-9
CAS number: 4016-14-2
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2022	Germany		MemberState	1
Comment received				
As expected from the structure of the substance, its genotoxic potential was confirmed in a number of in vitro studies, including a positive chromosomal aberration test in human lymphocytes (https://echa.europa.eu/de/registration-dossier/-/registered-dossier/23504/7/7/1). Presumed pre-implantation loss in the mated females in the screening reproductive toxicity study provides further in vivo evidence of a highly likely DNA-alkylating mode of action of 2,3-epoxypropyl isopropyl ether (IPGE). Considering high water solubility of the substance, systemic bioavailability is expected as well.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comments.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2022	Germany		MemberState	2
Comment received				
The DE CA supports the proposed classification of IPGE (EC no. 223-672-9) as a reproductive toxicant category 1B - H360F based on the adverse effects on fertility observed in mated females in a reliable OECD TG 422-compliant study. Reduced successful pregnancy rate (7/12 vs. 12/12 in control) was evident at the lowest tested dose (100 mg/kg bw/d), which progressed to complete infertility in mid- and high-dose-group females, where all females were non-pregnant (0/11, 0/12 at 300 and 600 mg/kg bw/d). (We assume "non-pregnancy" means in this context absence of				

implantation sites.) Since mating behaviour was not affected (mating index in all groups: 100 %) and test item- related microscopic findings were absent in the testes of parental males, a pre-implantation loss of conceptus seems to be the most probably explanation of the missing pregnancies in successfully mated females.
Simultaneously, only some evidence of general toxicity was observed in the treated females during the pre-mating, mating and gestation phases of the study: It was limited to periodically increased salivation at 600 mg/kg bw/d and a 10 % lower body weight gain of pregnant treated females in the low dose group (100 mg/kg bw/d) on GD 0 - 20. Slower body weight gain in all non-pregnant treated females starting from GD 7 is rather associated with a lower feed-demand due to a non-pregnant state, rather than being a sign of general toxicity.
An increased haematocrit in non-pregnant females treated with 300 and 600 mg/kg bw/d IPGE was not reproduced in treated males, and therefore it cannot be excluded that it is an incidental finding attributed to differences in physiological status of non-pregnant treated females vs. pregnant controls. The same is true for the comparison of other parameters between control and mid and high-dose females, such as changes in absolute and relative organ weights.
The substance is a known skin and eye irritant (self-classified as Skin Irrit. 2 and Eye Irrit. 2); however, no ulceration in the digestive tract in treated females was observed, with findings limited to raised white patches of epithelium in the non-glandular stomach in males (n = 9) and females (n = 2) at 600 mg/kg bw/d.
Taken as a whole, the observed general toxic effects in parental animals do not disregard the relevance of the reproductive toxic effects observed, i.e. prevention of pregnancies in mated rats starting from 100 mg/kg bw/d IPGE. Hence, classification as reproductive toxicant into category Repro 1B (H360F) based on adverse effects on fertility is warranted.
Despite our support for the dossier submitter's proposal, we would appreciate a short statement on the following open questions:
1) Is the low-dose female that "showed one corpora lutea and one implantation site but failed to give birth to any offspring" identically equal to the female that experienced „a total litter loss in utero" according to table 11 on p.11 of the CLH report? (We are asking this question because if two different animals were affected, classification for developmental toxicity might need to be discussed as well.)

2) It is stated in the CLH dossier: "The majority of females treated with 300 and 600 mg/kg bw/day and one female treated with 100 mg/kg bw/day had [the appearance of] increased corpora lutea and were in metestrus or diestrus, indicating a disturbance of the reproductive cycle." What does „[the appearance of] increased corpora lutea" mean exactly? Does it refer to the number of corpora lutea or to their size? Or to another property?

3) It is stated in the CLH dossier: "For all females, the uterus was examined for signs of implantation and the number of uterine implantations in each horn was recorded. This procedure was enhanced; as necessary, by staining the uteri with a 0.5% ammonium polysulphide solution (Salewski 1964). The corpora lutea were also counted." Do you have any information on the number of corpora lutea counted in females from the mid- and high-dose group? Table 12 in the confidential annex to the CLH report shows data for the control and low-dose group only.

Dossier Submitter's Response

Thank you for your support and your comments. Question 1) It appears to be the same female (that "failed to give birth to any offspring" and "experienced total litter loss in utero"). Question 2) Based on statements in the study report it appears to involve *the*

number of corpora lutea, not the size. However, no detailed data on non-pregnant individual females in low-, mid- and high dose groups are available on this exact number. Question 3) As described in the answer above, no details on number of corpora lutea in non-pregnant low-, mid- and high dose females are provided in the study report. There are, however, histopatological reports available for each female, which state "corpora lutea increased, minimal" for the majority of females in mid- and high dose groups, as well as for 1 female in the low dose group. The one low dose female with increased corpora lutea was not pregnant.
RAC's response
Thank you for your comments. The answer of the DS is supported.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2022	France		MemberState	3
Comment received				
FR agrees with the proposed classification as Repr. 1B – H360F based on a severe dose-related effect on fertility index, occurring at all tested doses, in the OECD 422 study. Some signs of toxicity are observed at the highest tested dose of 600 mg/kg bw/day. However, they cannot explain the lack of pregnant females at this dose. Fertility effects occurring at lower doses are not associated with general toxicity. Indication of increased corporea lutea is mentioned in the CLH report in the majority of females treated with 300 and 600 mg/kg bw/d. Increased number of corporeal lutea can be caused by a hormonal alteration (e.g. decreased PRL release) (Yoshihazu Taketa. Luteal toxicity evaluation in rats. J Toxicol Pathol. 2022 Jan; 35(1): 7–17). In contrast, it is noted in the CLH report that the mean number of corporea lutea is lower in females treated with 100 mg/kg bw/day. Could you please provide more information / interpretation on this parameter for each tested dose? Regarding developmental toxicity, the unique OECD 422 study available does not allow adequate conclusion since offspring were only produced from 7/12 females in the low dose group of 100 mg/kg bw/day. There is no data to adequately assess effects on or via lactation.				
Dossier Submitter's Response				
Thank you for your support and your comments. There are no details on the number of corpora lutea in non-pregnant low-, mid- and high dose females provided in the study report. There are histopatological reports available for each female, which state "corpora lutea increased minimal" for the majority of females in mid- and high dose groups and for 1 female in the low dose group. The one low dose female with "increased" corpora lutea was not pregnant. Study authors conclude it is the number of corpora lutea that is increased. We cannot interpret the data further. Thank you for providing the review article on luteal toxicity.				
RAC's response				
Thank you for your comments and for the review reference. Whereas the increase of CL seem indeed indicate an hormonal alteration as you suggested, the lack of consistency with the statistically significant decrease of CL at the lowest dose tends to decrease the robustness of this finding. Therefore, in that regard, the dose-dependant increase of animals in metoestrus and diestrus were considered as the key finding for indicating cycle disturbance.				