Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

α,α'-propylenedinitrilodi-*o*-cresol

EC Number: 202-374-2
CAS Number: 94-91-7

CLH-O-0000007246-73-01/F

Adopted

16 March 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON α,α'-PROPYLENEDINITRILODI-*O*-CRESOL

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: α,α'-propylenedinitrilodi-*o*-cresol
EC number: 202-374-2
CAS number: 94-91-7
Dossier submitter: The Netherlands

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2022	United Kingdom	<confidential>	Company-Manufacturer	1
Comment received				
Classification as a germ cell mutagen is not warranted and this conclusion is supported by the results of the available in vivo study which was negative.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Thank you for your comment. RAC noted.				

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2022	Germany		MemberState	2
Comment received				
The German CA supports the conclusion of the CLH dossier submitter on insufficiency of available data to propose a classification for mutagenicity (p. 5 and p. 15).				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Thank you for your comment. RAC noted.				

Date	Country	Organisation	Type of Organisation	Comment number
10.06.2022	France		MemberState	3
Comment received				
FR agrees α,α'-propylenedinitrilodi-o-cresol do not meet the classification criteria for germ cell mutagenicity.				

Dossier Submitter's Response
Thank you for agreeing with us.
RAC's response
Thank you for your comment. RAC noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2022	United Kingdom	<confidential>	Company-Manufacturer	4
Comment received				
Classification as suspected human reproductive toxicant (Cat. 1B, H360 FD) and applying the generic concentration limit of 0.3% ("group 2", medium potency) is supported based on the available data showing adverse effects on sexual function, fertility and development at 250 mg/kg bw/day. The NOAEL for these effects was at 75 mg/kg bw/day and therefore effects below 4 mg/kg bw/d are not likely which warrants the application of the generic concentration limit of 0.3% ("group 2", medium potency).				
Dossier Submitter's Response				
Thank you for agreeing to the classification proposal for reproductive toxicity and the generic concentration limit.				
RAC's response				
Thank you for your comment. RAC noted.				

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2022	Germany		MemberState	5
Comment received				
Effects on sexual function and fertility supporting Repr. 1B, H360F (p. 16-21): Reproducible reduction of gestation index was demonstrated in two GLP-compliant studies with α,α'-propylenedinitrilodi-*o*-cresol, tested under the limit concentration (-22.2 % and -20.8 % vs Ctrl.). While in the first study the cause of the complete litter loss was not clear, in the follow up study with a single dose of 250 mg/kg bw/d of α,α'-propylenedinitrilodi-*o*-cresol, 16 % of females (4/25) failed to deliver live-born pups, 3 of them dying during parturition and were unable to deliver. Uncertainty remains as to whether poor fetal conditions could also have an influence on birth complications. However, this is argued against by the fact that one dam survived with a complete litter loss. One more female died on GD10 with no apparent signs of general toxicity. One more female experienced dystocia, but delivered live/healthy pups. No apparent signs of neither avert nor general toxicity were observed for the females treated with 250 mg/kg bw/d of the test substance (n=35 in both studies combined) that could explain the profound effects on pregnancy outcome. Overall, observed effects on sexual function and fertility support the proposed by the CLH dossier submitter classification of α,α'-propylenedinitrilodi-*o*-cresol as Repr. 1B (H360F – May damage fertility). Effects on development supporting Repr. 1B, H360D, (p. 21-26): In the GLP-compliant study according to OECD TG 422, exposure to 250 mg/kg bw/d of α,α'-propylenedinitrilodi-*o*-cresol led to death of developing organisms, as evident from				

the increased number of dead pups (15 vs. 1 in Ctrl.) and the number of affected litters (4 vs 1 in Ctrl). At the same dose group, the mean number of live pups at the first litter check was reduced by 41.8% vs untreated controls (11.0, 10.2, 12.4, 6.4 at 0, 25, 75, 250 mg/kg bw/d accordingly). In the follow up study with a single dose of 250 mg/kg bw/d of α,α'-propylenedinitrilodi-*o*-cresol, adverse litter effects included increased number of stillborn pups (34 vs. 5 in Ctrl) and reduced viability index on PND 0-4 to 88 % ($p<0.01$). These effects were further supported by slight (up to 9 %) reduction in pups mean body weight and presence of runts. These effects occurred in the absence of overt maternal toxicity, as evident by the unaffected body weight of dams during gestation or lactation phases of the study. The death of 3 dams in treated group was caused by the abnormal parturition and therefore not considered as a sign of overt maternal toxicity. Overall, the observed effects on development justify the proposed by the CLH submitter classification of α,α'-propylenedinitrilodi-*o*-cresol as Repr. 1B (H360D – May damage the unborn child).
Dossier Submitter's Response
Thank you for your comprehensive comment and agreeing to the classification proposal for adverse effects on sexual function, fertility, and adverse effects on development.
RAC's response
Thank you for your comment. RAC noted.

Date	Country	Organisation	Type of Organisation	Comment number
10.06.2022	France		MemberState	6
Comment received				
FR agrees with the classification proposal Repr. 1B, H360FD and the GCL of 0.3% for fertility and development.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Thank you for your comment. RAC noted.				