Committee for Risk Assessment

RAC

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

8 June 2023

CLH-O-0000007313-80-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **2,3-epoxypropyl isopropyl ether**

EC Number: **223-672-9**

CAS Number: **4016-14-2**

The proposal was submitted by **Sweden** and received by RAC on **31 May 2022.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Sweden has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **4 July 2022**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **2 September 2022**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Wendy Rodriguez**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **8 June 2023** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	2,3-epoxypropyl isopropyl ether	223-672-9	4016-14-2	Repr. 1B	H360F	GHS08 Dgr	H360F			
RAC opinion	TBD	2,3-epoxypropyl isopropyl ether	223-672-9	4016-14-2	Repr. 1B	H360F	GHS08 Dgr	H360F			
Resulting Annex VI entry if agreed by COM	TBD	2,3-epoxypropyl isopropyl ether	223-672-9	4016-14-2	Repr. 1B	H360F	GHS08 Dgr	H360F			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

2,3-epoxypropyl isopropyl ether (IPGE) is manufactured and imported to the EEA, at ⩾ 1 to < 10 T per annum and used industrially (coatings, paints, laboratory chemicals, intermediate in polymer production) as well as professionally (washing and cleaning products).

At room temperature IPGE is a liquid. It has a measured logKow of 0.8 and is considered to be soluble in water. No toxicokinetic studies are available but the registrant has provided an assessment of the ADME properties of IPGE based on its size, structure, physico-chemical properties and toxicological information. According to the registrant's evaluation, the absorption in rats (all exposure routes) was estimated to be 100% and systemic bioavailability was considered to be high. O-dealkylation and aliphatic hydroxylation were identified as the mode of action during Phase-I-metabolism. IPGE and its metabolites (isopropanol and acetone) are expected to be excreted rapidly via kidneys (urine) and potentially lungs (breath) with a minor accumulation potential. The registrant mentioned that due to the presence of an epoxy group in the molecule, a fraction of the substance may possibly bind to proteins and/or DNA. Nevertheless, according to registrant's evaluation, these covalently bounded molecules are likely to be excreted fast due to the intrinsic repair mechanisms of the body. The impairment of reproductive function seen in OECD TG 422 study (see below) is indicative of a wide distribution of this substance throughout the body and was considered as supportive to indicate high systemic bioavailability.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Sexual function and fertility

Four studies were reported in the summary tables in the CLH report:

- One combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test, performed on rats (Anonymous, 2017, purity 99.8%, compliant with OECD TG 422 and GLP), with related dose range finding study (Unnamed, 2016, purity not stated, compliant with OECD TG 422 and GLP)
- Two sub-chronic studies extracted from Hine et al. (1956): one inhalation study, performed on rats and one dermal study, performed on rabbits. In both cases, purity was not stated (only theorical concentration provided) and the studies were not compliant to GLP.

The CLH report only discussed the study from Anonymous (2017). In that study, although all animals mated, none of the females from the mid- (300 mg/kg bw/d) and high dose (600 mg/kg bw/d) groups became pregnant. At the lowest dose of 100 mg/kg bw/d, 4/12 females did not become pregnant either. One other female, although showed one *corpora lutea* and one implantation site, failed to give birth to any offspring and another one showed an abnormally high number of pre-implantation losses. Consequently, the fertility index in the low dose group was 67% compared to 100% in the control group. In that group, a statistically significant decrease in number of corpora lutea (-28%) and implantation sites (-31%) were also described. In addition, the majority of females from mid- and high dose groups as well as one female from

the low dose group had the "appearance of increased corpora lutea" and were in metestrus and diestrus, suggesting a disturbance of the reproductive cycle. It appears that this expression refers to the number of corpora lutea, although the counting was not available for non-pregnant rats. The CLH report mentioned some signs of toxicity but estimated that it does not correspond to marked general toxicity. Therefore, and as there was no mechanistic evidence to indicate that the adverse effects on fertility seen in rats are irrelevant for humans, the dossier submitter (DS) concluded that a classification as Repr. 1B, H360F is warranted. No SCL was proposed, as the ED10 based on linear interpolation (in 100 mg/kg bw/day group 33% animals affected and in the control group 0% animals affected) was estimated to be 30 mg/kg bw/day, which is within the medium potency group (4 mg/kg bw/day < ED10 value < 400 mg/kg bw/day).

Developmental Toxicity

One combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test, performed on rats, was reported under developmental toxicity section of the CLH report (Anonymous, 2017, purity 99.8%, compliant with OECD TG 422 and GLP). Pups were born only in the low dose group. Compared to controls, the pups from that group appeared normal, without particular clinical signs or mortality increase, although a lower litter size was mentioned (-27%, without statistical significance). Offspring body weights at birth, PND 1 and 4 as well as offspring body weight gain between PND1-4 exceeded the control litters. Neither the type, incidence nor distribution of necropsy findings indicated any obvious effect on the offspring as a consequence of parental treatment. Nevertheless, it should be noted that both females and offspring were killed at Day 5 post-partum, and not on Day 13 as indicated in the test guideline. The DS concluded that a classification for developmental toxicity was not justified.

Adverse effect on or via lactation

The DS stated that the data available on IPGE was not sufficient to assess effects on or via lactation, and therefore comparison with CLP criteria is inapplicable.

Comments received during consultation

Two MSCAs supported the classification of IPGE as Repr. 1B, H360F. One MSCA indicated that the data available does not allow an adequate conclusion on development (offspring produced only in 7/12 females from the low dose group) or on effects on/via lactation.

Assessment and comparison with the classification criteria

Sexual function and fertility

Table 1*: Summary of relevant information*

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results*	Reference
Combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test, OECD TG 422, GLP compliant. **Deviation:** Females and offspring killed at PND 5,	IPGE dissolved in arachis oil (purity 99.8%), daily by gavage at 0, 100, 300, 600 mg/kg bw/day.	**General toxicity:** Increased salivation (9 m and 12 f) between day 18-25 at 600 mg/kg bw/day. **Body weight gain**: **M**: **First week of treatment**: 10.7g (600 mg/kg bw/day), 18.0g in control; **F: Gestation (not stat significant):** GD7-14: 25.4g (control), 0.1g (300 mg/kg bw/day) and -2.7g (600 mg/kg bw/day); GD14-20: 56.4g (control), -1.2g (300 mg/kg bw/day)	Anonymous, 2017

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results*	Reference
and not on PND 13 Haematological and blood chemistry performed on 5 animals/sex/dose Wistar rats: 12/sex/dose group. Reliability according to registrant: 1		and 1.8g (600 mg/kg bw/day); **Lactation**: 6.4g (100 mg/kg bw/day), 12.7g in control. **Pathological findings at 600 mg/kg bw/day**: Non-gland. stomach white patches: 9/12 (M) and 1/12 (F) and hyperplasia 11/12 (M) and 5/12 (F); Fibrous mass on the liver: 1/12 (F); Reddened lungs: 2/12 (F); **at 300 mg/kg bw/day**: Reddened lungs: 1/11 (F) and 2/12 (M) and 4/24 controls (2M and 2F). **Organ weight**: M** (300, 600 mg/kg bw/day)**:** Decrease testis absolute (-, -9%) and relative (-, -6.6%) weight; Increase kidney absolute (-, 21%) and relative (-, 19%) weight – both outside of HCD ranges; Increase liver absolute (-, 28%) and relative (-, 25%) weight – relative outside of HCD range; Decrease of thyroid weight absolute (-30%, -) and relative (-29%, -). **F** (100, 300 and 600 mg/kg bw/day): Decrease uterus & cervix absolute (-, -19%) and relative (-, -13%) weight***; Spleen absolute (-24%, -31%, -28%) and relative (-19%, -26%, -20%) weight decrease, liver absolute (-, -23%, -26%) and relative (-, -17%, -18%) weight decrease - absolute weight at high dose outside of HCD ranges, thymus absolute (-, 64%, 37%) and relative (-, 79%, 54%) weight increase – relative weight at mid dose outside of HCD ranges. **Haematological effects **: M** (300 and 600 mg/kg bw/day, respectively): WBC: -30%, -17%; Lymp: -32%, -19%. **F** (300 and 600 mg/kg bw/day, respectively): Haematocrit 11%, 11%; Haemoglobin: 13%, 10%; Erythrocytes counts: 14%, 13%; Neutrophils: -67%, -62%; Platelet count: -31%, -24%. **Clinical biochemistry**: M** (100, 300, 600 mg/kg bw/day): A/G ratio: 12%, 9%, 9%; ALAT: -, -, 18%; Bile acid: -, -, 176%. **F** (100, 300 and 600 mg/kg bw/day): A/G ratio: 9%, 8%, 12%, Bile acid: -, 166%, 239% - outside of HCD ranges; Phosphorus: -, 68%, 72%; Bilirubin: -, -, 38%; Creatinine: -, -, -12%; Urea: -, -, -20%. **Fertility:** All animals mated within the first four days of pairing. **300 or 600 mg/kg bw/day:** No females became pregnant. Corpora lutea apparent increase: 8/12 and 7/12 (respectively) **100 mg/kg bw/day:** Pregnancy rate reduced: 4/12 not pregnant, 1/12 total litter loss (despite one corpora lutea and one implantation site). One additional female despite having pups, showed a high level of pre-implantation loss. Corpora lutea apparent increase: 1/12 (in oestrus). The mean number of corpora lutea (-28%) and	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results*	Reference
		implantation sites (-31%) were statistically significantly lower.	
A 14 days dose range finding study, GLP compliant. Wistar rats: 3/sex/group. Reliability according to registrant: 1	IPGE dissolved in arachis oil (purity not stated), daily during 14 days via gavage at 0, 75, 250 and 500 mg/kg bw/day.	**General toxicity:** At 500 mg/kg bw: Sporadic salivation on day 7 (both sex). **Body weight:** 250 and 500 mg/kg bw: Body weight gain reduction at the beginning of the exposure, but the animals recovered. Fertility parameters were not investigated.	Unnamed, 2016
Sub-chronic toxicity study via inhalation (whole body). Non-GLP. 10 male Long-Evans rats Reliability according to registrant: 2	IPGE at doses of 400 ppm (vapour), 7 h/d, 5 d/w for 10 weeks (purity not stated).	Slight eye irritation and laboured breathing were observed; body weight gain lowered in exposed animals ($p<0.01$). No mortality. At necropsy: Mild emphysema (lungs): 4/10 rats. Mottling of the liver: 2 rats, one with confluent pneumonia (microscopic examination). All other sections examined were within normal limits.	Hine *et al.*, 1956
Sub-chronic toxicity study via dermal exposure. Non-GLP. 6 male rabbits (California Albino or NZ White) Reliability according to registrant: 4	Undiluted compound 0.2 ml, 7h/d, 5 times/w, 1cm in the back, until further application were undesirable, (purity not stated).	Application to the rabbits skin caused reductions in body weight gain and skin erythema and was discontinued in some animals after the 5th exposure due to eschar formation. Experiment was stopped after the 7th application following the death of 3/6 animals.	Hine *et al.*, 1956

*Most relevant and statistically significant (except if mentioned otherwise) effects mentioned. Hematological and clinical biochemistry variation: mentioned if changes ≥10% and significant.

** If not mentioned, values are inside the historical control data (HCD) range (Anonymous, 2017)

***It is unclear if normal range provided for uterus weight in full study comprise cervix weight.

In Anonymous (2017), 12 rats of each sex were exposed by gavage to IPGE (99.8% of purity) at 0, 100, 300 or 600 mg/kg bw/day. This study was considered compliant to OECD TG 422 and GLP. The doses were fixed based on a dose-range finding study (described below). Males were dosed daily from Day 1 and were terminated after 43 or 44 days. Females were dosed 2 weeks prior to pairing, during pairing and pregnancy and 4 days afterwards. At Day 5 post-partum all surviving females and offspring were terminated. One female from mid dose group was killed on Day 4 due to its poor condition, which was considered caused by pyelonephritis of both kidneys. No unexpected deaths associated to the treatment were observed. Only slight clinical observations (as salivation) were seen in the animals of the highest dose group but were considered of limited toxicological relevance.

The body weight gain (BWG) of females from the mid and high dose groups was comparable to control during the first week post coitum but was reduced without statistical significance during the remaining treatment period. Since all females from these dose groups were not pregnant, comparisons with the control group should be made with caution. BWG of females treated with 100 mg/kg bw/day was reduced (not statistically significantly) during the final two weeks of gestation and their cumulative BWG between days 0 and 20 of gestation was also lower (-10%, not statistically significant). A statistically significant reduction in BWG was also evident in these females during lactation (-50%), which was consistent with a significantly reduced (-28%) food consumption observed during the same period. Males treated with 600 mg/kg bw/day showed a

statistically significant reduction of BWG during the first week of treatment (Table 1), but recovering was evident and the reduction of the overall BWG (10%) was not significant. No changes of BWG were seen in males from other exposure groups and no statistically significant changes were reported in male food consumption.

Hematological and blood chemistry effects were evaluated in 5 animals/sex/dose. None of the changes reported on males (all dose groups) and in females (low dose group) were considered of toxicological significance. Further it was noted that none of the females in high and mid dose groups were not in the same physiological state (not pregnant) than control and low dose group females and therefore, that comparison should be done with caution. In addition, in both sexes, different variations observed were not significant, or significant without dose dependency and they were within the historical control ranges (Table 1). The main blood chemistry change observed was a statistically significant increase of bile acid in males from the high dose group (176%) and in females from the two highest doses (166% and 239%, respectively). In females, the level was outside the historical control ranges.

Some statistically significant changes in organ weights (Table 1) were described in both sexes. Overall, no dose-dependency was observed, the values stayed within the historical control data (HCD) and/or observations were inconsistent between males and females. No associated histological findings were identified to these weight variations, which were therefore considered of no toxicological significance. Findings in non-glandular stomach (discolored patches, hyperplasia) could be associated to local irritancy properties (substance self-classified as Skin irrit. 2 and Eye irrit. 2) rather than a marked systemic effect. One female treated with 300 mg/kg bw/day had a fluid filled uterus at necropsy. Females from high dose group showed a statistically significant reduction in uterus and cervix weights (absolute: -19% and relative: -13%) compared to controls, but without supportive histopathological findings, and knowing that these females were not pregnant, the toxicological relevance of these findings alone appear uncertain. Two males from the high dose group had a small and flaccid testis (with additional small epididymis in one male). Males from this group showed also statistically significant reduction in testes weight, but the values were within the historical control range. Detailed qualitative examination of the testes was undertaken, but no related microscopic findings were identified.

Although all the animals mated in the first estrus opportunity and the mating index did not differ between controls and treated animals (100%), exposure to IPGE had a clear impact on the pregnancy outcomes since no pregnancy was induced in any of the mid- and high dose females, resulting in a strong and dose-dependent decrease of the fertility index.

Table 2: *Summary of relevant information*

Dose levels (mg/kg/day)	**0**	**100**	**300**	**600**
No. of pairs with successful mating	12	12	11*	12
No. of pregnant females	12	8	0	0
Fertility index (%) = (N° pregnant/ N° successful mating) x 100	100.0	67.0	0	0
Total litter loss in utero	0	1/8 (12.5%)	-	-
Apparant increase of Corpora lutea	0/12	1/12	8/12	7/12
Vagina: cycle step (n° animals examined: 5 in LD and 12 at other concentrations)	Mucificat.: 10 Diestrus: 1 Anestrus: 1	Estrus: 3 (2 NP) Diestrus: 1 (NP) Metestrus: 1 (NP)	Estrus: 2 Diestrus: 5 Metestrus: 5	Estrus: 1 Diestrus: 6 Metestrus: 5
N° of Corpora Lutea****	12.3±1.9	8.9±3.2***	Not provided	Not provided
Number of implantation site	12.0±1.5	8.3±3.9**	Not provided	Not provided
Pre-implantation loss (%)	1.7±4.0	8.2±21.6	-	-
Post-implantation loss (%)	12.2±19.7	6.1±8.6	-	-

NP= not pregnant. * One female killed due to poor condition at Day 4, not examined. ** Statistically significant ($p<0.05$). *** Statistically significant ($p<0.001$). **** Counted only in for pregnant females.

In the low dose group, 4/12 females did not get pregnant and 1/12 female did not have any offspring although had one implantation site and one corpora lutea (total litter loss). This female with no litter was excluded from calculation of mean and standard deviation. In addition, another female (1/12) had a smaller litter and presented a particularly high number of pre-implantation loss (57%, calculated as corpora lutea minus implantation - normal range of this strain at this age is of 0% to 39%). The non-significant increase of pre-implantation loss group mean (Table 2) was considered to be a consequence of this 6th rat as no other females of that group were affected. A statistically significant implantation site decrease (8.3 per exposed dam versus 12.0 in control animals) was also described in animals from that group who gave birth to pups (7/12), but the mean was still within HCD range for this strain (7-19). Litter response (including pre and post implantation losses) assessment was not possible at mid- and high dose (non-pregnant females).

A dose-dependent increase of animals in metestrus or diestrus was visible in all exposed groups (40%, 83% and 92% in low, mid and high dose group respectively, Table 2). This finding strongly suggests a cycle disturbance that could be responsible for the lack of pregnancy. Nevertheless, in these groups there are still indications of cyclical activity and some animals succeeded to reach the estrus phase. Therefore, other mechanisms participating to the strong decrease of fertility cannot be excluded. After histological examination, most of the females from mid and high dose group were described as having an apparent increase of corpora lutea (Table 2). This finding was also reported in one non-pregnant female from the low dose group. However, limited details were available (counting reported for pregnant animals only, no statistical significance provided) and no dose dependance was observed (Table 2). Furthermore, a statistically significant decrease of corpora lutea was detected in animals who gave birth to pups although it must be noted that the corpora lutea number group mean (8.9) was just below the lower value of the HCD range (9-19).

A dose-range finding study was available in ECHA dissemination site (Unnamed, 2016, details not made available to RAC). In that study, IPGE (purity not provided) was administrated in rats at dose levels of 75, 250 and 500 mg/kg bw/day during 14 consecutive days. The main effects were seen in animals exposed to 500 mg/kg bw/day of IPGE (salivation, transient body weight gain reduction). No macroscopic abnormalities were detected at necropsy. As fertility parameters were not available, this dose range finding study has very limited value. The DS also summarized in Table 10 of the CLH report two repeated dose toxicity studies from the registration dossier. Both were extracted from Hine *et al.* (1956) publication, that compiled several studies (acute and repeated exposure) performed with glycidol and glycidyl ethers. None of them investigated fertility parameters. Both of these studies from Hine *et al.* (1956) appear of low relevance for the current classification proposal.

Conclusion on sexual function and fertility

Anonymous (2017) is the only relevant study for the classification proposal. Altogether, general toxicity after IPGE exposure does not correspond to marked systemic effects, especially at the lowest doses. In addition, the variations described in females from mid and high dose group should be taken with caution, as the females were not pregnant and therefore were in a different physiological state compared to animals from control groups or HCD. All the animals succeeded to mate, but none succeeded to become pregnant in mid and high dose group. In low dose group, 40% of the females did not get pregnant either. In addition to this severe decrease of fertility, the dose-dependent increase of animals in metestrus or diestrus strongly suggest a cycle disturbance in females. Altogether, these findings provide clear evidence of a dose-dependent adverse effect on fertility after IPGE exposure, apparent from the lowest dose, without marked

systemic effects. Based on these results and as no mechanistic evidence raising doubt on human relevance of these observations were provided, **a classification as Repr. 1B (H360F) is warranted**. RAC supports the approach of the DS not to propose a SCL, as the ED10 based on linear interpolation is within the medium potency group.

Developmental Toxicity

Table 3: *Summary of relevant information*

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results*	Reference
Combined repeated dose toxicity study with the Reproduction/Development Toxicity Screening Test, OECD TG 422, GLP compliant. **Deviation:** Females and offspring killed at PND 5, and not on PND 13 Wistar rats: 12/sex/dose group. Reliability according to registrant: 1	IPGE dissolved in arachis oil (purity 99.8%), daily by gavage at 0, 100, 300, 600 mg/kg bw/day. **Males** dosed from Day 1 to 43 or 44. **Females** dosed from 2 weeks prior pairing to PND 4.	**General toxicity:** See Table 1 **Development: 300 or 600 mg/kg bw/day:** No offspring was produced. **100 mg/kg bw/day:** only 8/12 pregnancy, including one with total litter loss; **Litter effects** compared to control: Size: -27%; Weight (day 1): -20%. Both not significant. **Offspring weight: Day 1**: (m): 6.50 g ±0.58 (5.9 g ±0.44 in controls), (f): 5.97 g ±0.75, not significant (5.46 g ±0.46 in controls). **Day 4**: (m): 9.33 g ±1.21, not significant (8.54 g ±1.15 in controls); (f): 8.45 g ±1.67, not significant (7.90 g ±1.00 in controls). No increased mortality, malformation or finding at necropsy were observed.	Anonymous, 2017

*Most relevant and statistically significant effects mentioned (except if mentioned otherwise). If not mentioned, values are inside the HCD range.

In Anonymous (2017) study, 12 rats of each sex were exposed by gavage to IPGE (99.8% of purity) at 0, 100, 300 or 600 mg/kg bw/day. Females were allowed to nurse their offspring until Day 5, when all surviving females and offspring were terminated. Only slight general toxicity was reported in parental generation (see the fertility part of this opinion). Gestation lengths for controls and females in 100 mg/kg bw/day groups were between 22.5 and 23.5 days (without changes seen in respective distributions). No females from mid and high dose groups achieved pregnancy despite a successful mating, therefore no assessment of litter response was possible. In the low dose group, one female had total litter loss in utero (one corpora lutea and one implantation site). The mean post-implantation losses were within the HCD (0-40%). There was no substantial difference in group mean live birth index, viability index and sex ratio in the low dose group females compared to the control group. Litter size was lower in the low dose group females (-27%, mean of 7.7±3.7 pups compared to mean of 10.6±2.6 pups in control group) but without statistical significance and was still within the HCD range (between 5 and 18 pups per dams). As a consequence of the decreased litter size, the total litter weights at days 1 (-20%) and 4 (-19%) were reduced compared to controls, although no statistical significance was reached. Body weights at birth, at Days 1 and 4 as well as body weight change between Days 1 and 4 were increased in low dose group pups compared to control group, even though only the body weight increase in males at Day 1 was statistically significant. The surface righting of pups from exposed group was similar to controls, and no specific clinical signs were detected. No adverse effect on development was seen in pups during life or at necropsy.

Conclusion on developmental toxicity

Altogether, except for a slight increase of body weight in male pups at Day 1, no significant developmental effect were seen in exposed dams or pups. This change is still within HCD and could be a consequence of a lower litter size. Some uncertainties remain (pups sacrificed at PND 5 instead of PND 13) and no litter was obtained at higher doses, therefore it cannot be excluded that effects could be detected later in life. Nevertheless, based on the reported experimental data, **no classification for developmental toxicity is warranted**.

Adverse effect on or via lactation

RAC agree with the DS that the current data did not allow a proper evaluation of toxicity on or via lactation, especially as the pups were sacrificed at PND 5 post-partum, and not on PND 13 as indicated in the test guideline. No specific statement was made in the toxicokinetic analysis provided by the registrant regarding a potential transfer to milk. Neither were studies of the milk quantity, quality, or composition available., A comparison with the classification criteria is thus not possible and **no classification is warranted** due to **lack of data**.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).