Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane

EC Number: -
CAS Number: -

CLH-O-0000007002-89-01/F

Adopted

10 June 2021

10 June 2021

CLH-O-0000007002-89-01/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: **Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane**

EC Number: **-**

CAS Number: **-**

The proposal was submitted by **Norway** and received by RAC on **20 March 2020.**

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

PROCESS FOR ADOPTION OF THE OPINION

Norway 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 May 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **3 July 2020**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Ralf Stahlmann**
(Adviser: Theresa Martin)

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 **10 June 2021** 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	Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane	-	-	Muta. 2 Repr. 1B	H341 H360F	GHS08 Dgr	H341 H360F			
RAC opinion	TBD	Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane	-	-	Muta. 2 Repr. 1B	H341 H360F	GHS08 Dgr	H341 H360F			
Resulting Annex VI entry if agreed by COM	TBD	Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane	-	-	Muta. 2 Repr. 1B	H341 H360F	GHS08 Dgr	H341 H360F			

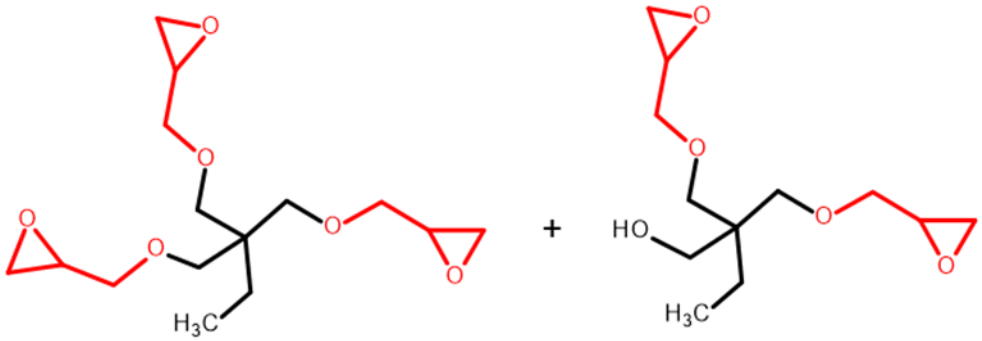
GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The reaction mass of 1-(2,3-epoxypropoxy-2,2-bis[(2,3-epoxypropoxy)methyl] butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane from hereinafter will be referred as "reaction mass".

This multiconstituent substance is used in inks and toners, in printing and recorded media reproduction as well as in adhesives and sealants.

Both constituents are bi- or tri-ethers of 1,1,1-trimethylolpropane (TMP). In the structural formulas the glycidyl moiety is highlighted in red.



The registrant stated that the substance of toxicological interest is TMP. This implies that the constituents are hydrolysed under physiological conditions resulting in the formation of TMP. There are no data available supporting this hypothesis and no information on where and to what extent hydrolysis takes place. In the registration dossier, toxicokinetic data for trimethylolpropane phosphate (TMPP) are reported. However, the relevance of TMPP kinetic data remains unclear. As glycidol ($C_3H_6O_2$) might be a relevant active metabolite of the reaction mass and it has a harmonised classification as Muta. 2 (H341), Carc. 1B (H350) and Repr. 1B (H360F), further investigation on metabolites and hydrolysis products of these TMP ethers (reaction mass) would be desirable.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) listed three *in vitro* studies and one *in vivo* study for evaluation of germ cell mutagenicity.

In vitro

The Ames Test showed clearly positive results in the presence and absence of metabolic activation (rat liver S9 mix) in the strains TA 100 and TA1535 and in presence of metabolic activation in *E. coli* WP2 *uvr*A.

One Chromosome Aberration Assay showed statistically significantly increased numbers of structural aberrations in treatment groups with or without S9 mix. These effects were dose-

dependent. Number of polyploid cells and cells with endoreduplicated chromosomes were not affected.

In the mammalian cell gene mutation assay a clearly positive and dose-dependent response was observed in a concentration range which was still acceptable for the test but that already caused clear cytotoxicity.

In vivo

The comet assay in rats confirmed the positive results *in vitro*. Positive results were observed in the liver of animals exposed to mid and high doses and in duodenum in the animals exposed to high doses. This points to the possibility of the test material to induce DNA strand breaks after oral administration by gavage.

In conclusion, the DS suggested to classify the reaction mass of these trimethylolpropane ethers as Muta. 2.

Comments received during consultation

Two MSCAs commented and supported the proposed classification as Muta. 2 based on positive results obtained in the Comet Assay and supported by positive results from *in vitro* mutagenicity assays.

Assessment and comparison with the classification criteria

Three in vitro studies and one study in rats are available to assess the mutagenicity / genotoxicity of the reaction mass.

In vitro

Table: *Summary of mutagenicity/genotoxicity tests in vitro (modified from table 9, CLH-report)*

Method, guideline	Test substance	Study information	Results	Reference
Bacterial gene mutation test Ames test OECD TG 471 GLP: yes	Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane	Strains: *Salmonella typhimurium* TA 1535, TA 1537, TA 98, TA 100, *E. coli* WP2 *uvr*A Metabolic activation system: rat S9 liver (S9-mix), induced with Aroclor 1254 Initial toxicity-mutation assay (n=2): 1.5, 5.0, 15.0, 50.0, 150.0, 500.0, 1500.0 µg/plate with or without metabolic activation Confirmation assay (n=3): 50, 150, 500 and 5000 µg/plate with and	Positive strains: TA100 and TA 1535 (+/- S9-mix), WP2 *uvr*A in presence of S9-mix Revertants maximum increased in initial assay (+ S9-mix): TA100: 11-fold; TA1535: 68.6-fold; WP2 *uvr*A: 4.3-fold Revertants maximum increased in confirmatory assay (+ S9-mix): TA100: 12-fold; TA1535: 93.9-fold; WP2*uvr*A: 4.2-fold Neither precipitate nor toxicity was observed	Anonymous, 2014a

Method, guideline	Test substance	Study information	Results	Reference
		without metabolic activation Positive controls: yes Vehicle: DMSO		
Chromosome aberration assay in mammalian cells OECD TG 473 GLP: yes	Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane	Chinese hamster ovary (CHO-K1) cells Metabolic activation system: rat S9 liver (S9-mix), induced with Aroclor 1254 Preliminary toxicity assay: 0.302 to 3020 µg/mL (10 mM) **Assay 1:** 4h treatment and 16h recovery (+/- S9-mix), concentrations: 15 to 150 µg/mL without S9-mix, 50 to 350 µg/mL with S9-mix; **Assay 2:** 20h treatment (-S9-mix), concentrations: 5 to 50 µg/mL Concentrations for Assay 1 and Assay 2 were selected on basis of cytotoxicity assay (no details provided) Positive controls: yes Vehicle: DMSO	Statistically significantly and dose-dependent increased number in structural aberrations in treatment groups with and without S9-mix Structural aberrant cells in 4h treatment group (-S9-mix) (Mean %): 1, 4, 34, 48, 21 (vehicle control, 15 µg/mL, 30 µg/mL, 50 µg/mL, positive control) Structural aberrant cells in 4h treatment group (+S9-mix) (Mean %): 1.5, 2, 16, 18, 26 (vehicle control, 50 µg/mL, 100 µg/mL, 275 µg/mL, positive control) Structural aberrant cells in 20h treatment group (-S9-mix) (Mean %): 0, 14, 20, 43, 21 (vehicle control, 5 µg/mL, 10 µg/mL, 25 µg/mL, positive control)	Anonymous, 2014b
Gene mutation study in mammalian cells OECD TG 476 GLP: yes	Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-	Chinese hamster ovary (CHO) cells (CHO-K1-BH4 cells) Target gene: HPRT locus Metabolic activation system: rat S9 liver	Average relative survival: - 25.72% at concentration of 350 µg/mL with S9-mix - 15.88% at concentration of 40 µg/mL without S9-mix	Anonymous, 2014c

Method, guideline	Test substance	Study information	Results	Reference
	epoxypropoxy)methyl)-2-hydroxymethyl butane	(S9-mix), induced with Aroclor 1254 Test concentrations based on preliminary toxicity assay (no details provided) Assay 1: treatment (duration confidential) with S9-mix: 50, **100**, **200**, **300**, **350**, 400, 450 and 500 µg/mL Assay 2: treatment (duration confidential) without S9-mix: **5**, **10**, **20**, 25, **30**, 35, **40** and 50 µg/mL Concentrations marked in bold were evaluated Vehicle: DMSO No visible precipitate was seen at the beginning or end of treatment	Significant increase in mutant frequency at highest acceptable dose levels with and without S9-mix, as compared to vehicle controls ($p < 0.05$) Increases were dose-dependent	

The bacterial gene mutation test (Ames Test) revealed a positive response in the strains TA100 and TA1535 with and without metabolic activation and in the strain *E. coli* WP2 *uvr*A with metabolic activation. The positive mutagenic responses in the initial toxicity-mutation test with metabolic activation ranged from 4.3-fold to 68.6-fold maximum increases for the strains TA100, TA1535 and WP2 *uvr*A. The same strains tested positive in the mutagenicity assay where the responses ranged from 4.2-fold to 93.9-fold maximum increases in the presence of S9-activation.

In the chromosome aberration assay, statistically significant and dose-dependent increases in structural aberrations in the treatment groups with and without metabolic activation were observed. The maximum mean number of structural aberrant cells reached 48%, 18% and 43% for the groups 4h treatment (-S9-mix), 4h treatment (+S9-mix), 20h treatment (+S9-mix), respectively.

A positive and dose-dependent response was also recorded in the gene mutation assay with mammalian cells (CHO). A significant increase ($p < 0.05$) in mutant frequency as compared to controls was observed at the highest acceptable dose levels with and without metabolic activation. The average relative survival was 25.72% at a concentration of 350 µg/mL with S9-mix and 15.88% at a concentration of 40 µg/mL without S9-mix.

Study in rats

One Mammalian Alkaline Comet Assay is available to evaluate the genotoxicity of the reaction mass. The assay was conducted according to OECD TG 489 with minor deviations (interval between first and second dosing was ca. 24 to 25h instead of 21h; during electrophoresis the buffer temperature at the end of electrophoresis was 11.2°C, which is outside the protocol range of 2 to 10°C). These deviations were not considered to impact the study validity.

Six male Sprague Dawley rats were exposed orally by gavage to the test substance at doses of 0, 500, 1000 and 2000 mg/kg bw/d. The dose of 2000 mg/kg bw/d is the highest dose for this assay recommended in the guideline. This dose is estimated to be the maximum tolerated dose. The two doses were given by gavage on two consecutive days (second dose was administered 24 to 25h after the first dose). Polyethylene glycol 400 was used as vehicle. Animals were killed 3 to 4 hours after the last dose at day 2. Liver, glandular stomach and duodenum were investigated in this study. Three slides/wells per organ/animal were prepared for analysis and 50 randomly selected, non-overlapping cells per slide were scored. In total, 150 cells per animal per organ were evaluated.

No mortality at any tested dose level or positive control (ethyl methanesulfonate, EMS, 200 mg/kg bw) was observed. Appreciable reductions in mean group body weights in the highest dose group were observed during the course of the study. No histopathologically visible cytotoxicity was recorded in any organ.

The comet assay revealed genotoxic effects in the liver. A dose-responsive and statistically significant increase in % tail DNA in the liver samples was observed in the mid and high dose group (0.58%, 2.75% and 7.55% for vehicle control, 1000 and 2000 mg/kg bw/d). The increase in the 2000 mg/kg bw/d group was outside the historical control data and 95% confidence range (HCD on ECHA dissemination website). For the duodenal samples, a dose responsive, statistically significant increase in % tail DNA was recorded for the high dose group only (20.62% in high dose group compared to 6.95% in vehicle control). No increases in % tail DNA was observed in the stomach samples. The % tail DNA for positive and vehicle control were within the expected ranges for all three tested organs.

Conclusion

The experimental data provide evidence that the reaction mass induce mutagenicity in common *in vitro* assays. Three different types of *in vitro* assays revealed positive results and induction of gene mutations and chromosome mutations can be assumed. The results of the comet assay in rats show that the reaction mass is able to induce DNA strand breaks in liver and duodenum. These supporting data strengthen the evidence for a possible induction of chromosome mutations.

It remains unclear whether the substance could reach the germ cells. The results of an OECD TG 422 study in rats showed detrimental effects on male fertility after exposure to the reaction mass. Although the data provide some indication that the substance reaches male germ cells, the mechanism underlying the effects on fertility remains unclear. Therefore, the data do not unequivocally show that the reaction mass cause damage in the germ cells.

Based on these findings RAC supports the DS proposal to classify the reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane for **germ cell mutagenicity Cat. 2, H341**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Effects on sexual function and fertility

The DS listed two relevant studies to evaluate effects on sexual function and fertility.

One combined repeated dose toxicity study with reproduction / developmental toxicity screening test in rats revealed a clear effect on fertility at the highest dose of 300 mg/kg bw/d. None of the females of this high dose group became pregnant, whereas no effects were observed at the lower dose groups (30 and 100 mg/kg bw/d). Histopathological investigations of reproductive organs did not show adverse effects. No effects on functional observations and sensory reactivity assessment, gestation length and mating performance were seen.

An additional study was performed to further investigate the effects on fertility observed in the combined repeated dose toxicity study. Males and females were treated with the reaction mass at doses of 300 mg/kg bw/d. Treated males were paired with control females and treated females were paired with control males. There were no treatment-related effects on mating performance. The evidence of mating appeared similar in both groups. All control females mated with treated males failed to achieve pregnancy whereas two out of 12 treated females, which were mated with control males, failed to achieve pregnancy. Absolute and relative left epididymal weights were statistically significantly lower in treated males than in control. Mean homogenisation resistant spermatid count from the cauda epididymis was statistically significantly lower than the control counts. No obvious effect of treatment was evident on mean homogenisation resistant spermatid count from the testis, sperm concentration or motility or on sperm morphology.

A subchronic 90-day study also revealed no effects on testes histopathology, oestrus cycle status and thyroid hormone level at 300 mg/kg bw/d.

The DS concluded that there is clear evidence from experimental studies showing effects on male fertility in absence of systemic toxicity. Due to the severity of the effects, classification in category 1B for fertility is proposed.

Effects on development

The combined repeated dose toxicity study with reproduction/developmental toxicity screening test in rats did not indicate any adverse effect on development of pups up to PND4 up to 100 mg/kg bw/d. No offspring were born in the highest dose group of 300 mg/kg bw/d as none of the females in this dose group became pregnant.

One additional prenatal developmental toxicity study in rats recorded neither effects on maternal toxicity nor on development after exposure to doses up to 180 mg/kg bw/d.

The DS concluded that based on these studies, no conclusions on possible developmental effects can be drawn as only doses without any toxic effects were investigated. Due to limited data, developmental toxicity cannot be assessed.

Effects on or via lactation

There are no human or experimental data available which investigate effects on or via lactation. The DS concluded that in the absence of any data, effects on or via lactation cannot be assessed.

Taken together, the DS proposed to classify the reaction mass of 1-(2,3-epoxypropoxy-2,2-bis[(2,3-epoxypropoxy)methyl] butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane as Repr. 1B, H360F.

Comments received during consultation

Three MSCAs commented and supported classification as Repr. 1B, H360F.

Assessment and comparison with the classification criteria

Effects on sexual function and fertility

Combined repeated dose toxicity study

In the combined repeated dose toxicity study (Anonymous, 2015a) with reproduction/developmental screening test, conducted according to OECD TG 422 and GLP, male and female Wistar rats (12 animals/sex/dose) were exposed via gavage to the reaction mass at doses of 0, 30, 100 and 300 mg/kg bw/d. The exposure period had a duration of up to 56 days, daily during two-week pre-mating phase, mating and for females during gestation and early lactation. Surviving adult males were terminated on day 43 or 44, females and offspring were terminated on day five post-partum and all non-pregnant females of the highest dose group were terminated on or after day 25 post coitum. Animals were paired on a one male:one female per cage basis.

All males and the majority of the females of the high dose group showed increased post-dosing salivation. Functional performance revealed no abnormal observations. Body weight gain in males of either dose group was unaffected by treatment. There was no effect on food consumption in males and females of the low and mid dose. Males of the high dose group showed a lower food consumption compared to control during the first week. Afterwards food consumption was similar to control and unaffected by treatment.

Mating performance was not affected by treatment. However, a clear effect on fertility was observed at 300 mg/kg bw/d, as none of the females achieved pregnancy. No effects on gestation length was observed. Histopathological investigations of reproductive organs did not reveal any treatment related effect.

No adverse effects on corpora lutea count, pre-implantation loss, numbers of implantations, post-implantation loss, litter size at birth / day 1 and subsequent survival to day 4 were recorded at 30 or 100 mg/kg bw/d. Furthermore, no adverse effect on offspring body weight and litter weights at day 1 and body weight gain to day 4 post-partum was observed for these dose groups.

Oral reproduction study

To further investigate the observed fertility effects at a dosage of 300 mg/kg bw/d an additional oral reproduction study (Anonymous, 2015b) was performed. Male and female Wistar rats (12 animals/sex/dose) were exposed via gavage to the reaction mass at doses of 0 and 300 mg/kg bw/d. The exposure period was 38 consecutive days for males and at least four weeks (including a two-week pre- mating phase, mating and then to gestation day (GD) 13) for females. On day 15 animals were paired on a one male:one female per cage basis. Males were terminated on day 39 and females were terminated on GD 14/ day 14 post coitum. To separately assess possible effects on fertility on each sex, treated males were paired with control females and control males were paired with treated females.

No unscheduled deaths were observed. Clinical observations revealed increased post-dosing salivation for both sexes, with the majority of treated animals being affected. Body weight gain of treated males was statistically significantly reduced during the first two weeks of treatment and was accompanied by lower food consumption. Body weight gain and food consumption of treated females was unaffected.

No treatment-related effects on mating performance could be observed (assessed by pre-coital interval). All treated males and the majority of treated females mated within the first four days of pairing. Evidence of mating was similar in both groups. Two treated females (mated with control males) failed to achieve pregnancy and one treated female failed to mate. This is considered to reflect poor fertility of the control male which was indicated by changes in the male reproductive organ weight and sperm analysis (no detailed data available). All control females mated with treated males failed to achieve pregnancy. Absolute and relative left epididymal weights of treated males were statistically significantly lower than controls. Mean homogenisation resistant sperm count from the cauda epididymis of treated males was statistically significantly lower than control. No decrease was observed for mean homogenisation resistant sperm count from the testis of treated males. No treatment-related effect on sperm concentration, motility and sperm morphology was observed.

Repeated dose oral toxicity study

In the repeated dose toxicity study (OECD TG 408) (Anonymous, 2019), Wistar rats (10/sex/dose, 5/sex/dose for recovery) were exposed to the reaction mass in doses of 0, 30, 90 and 270 mg/kg bw/d by gavage for 90 days followed by a subsequent 28 days recovery period, to assess the reversibility of any effects.

No effects on oestrus cycle status, thyroid hormone level (TSH, T4 and T3) and on testes histopathology (only high dose group and control group investigated).

Conclusion

Experimental data from combined repeated dose toxicity study and oral reproduction study showed a clear effect on male fertility with an absence of relevant signs of systemic toxicity. The data give some evidence for effects on epididymis (statistically significantly lower mean homogenisation resistant spermatid count from the cauda epididymis compared to controls) but not for testis. Also, no histopathological effects were recorded in female reproductive organs. Mechanisms leading to infertility remain unclear. No additional data and no human data are available.

Due to the severity of the effects and the fact that relevance for humans cannot be ruled out, RAC supports the DS proposal to classify the reaction mass of 1-(2,3-epoxypropoxy-2,2-bis[(2,3-epoxypropoxy)methyl] butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane for effects on sexual function and fertility as **Category 1B (Repr. 1B, H360F)**.

Adverse effects on development

Combined repeated dose toxicity study

The combined repeated dose toxicity study with reproduction / developmental screening test (Anonymous, 2015a) revealed no adverse effect of corpora lutea count, pre-implantation loss, numbers of post implantations, post-implantations loss, litter size and subsequent survival of the offspring to day 4 in the low and mid dose group. The study revealed no clinical signs or necropsy findings in offspring.

Prenatal developmental toxicity study

In the prenatal developmental toxicity study (OECD TG 414, GLP) (Anonymous, 2018) 24 mated female Wistar rats per group were exposed via gavage to the reaction mass at doses of 0, 30, 90 or 180 mg/kg bw/d from GD 5 to GD 19. On GD 20 a caesarean section was performed. One half of the foetuses were examined for visceral anomalies and the other half were examined for skeletal anomalies.

In females no maternal toxicity occurred and no effects were recorded on clinical signs (mortality, body weight and body weight changes, uterine weight, number of corpora lutea, implantations, early and late resorptions and pre- and post-implantation losses up to the highest tested dose). Further, no effects on total number of foetuses, litter size and weights were observed. No external, visceral and skeletal malformations were recorded up to 180 mg/kg bw/d (details are not available).

Conclusion

The combined repeated dose toxicity study with reproduction/developmental toxicity screening test in rats did not show any adverse effects of the reaction mass on the offspring up to a dose level of 100 mg/kg bw/d. The developmental toxicity study in rats revealed neither maternal toxicity effects nor developmental effects in the foetuses up to 180 mg/kg bw/d. Based on these two studies no conclusions on possible developmental effects of the reaction mass can be drawn. It is noted that the doses were rather low and did not induce any signs of toxicity in the pregnant rats. RAC supports the DS opinion that developmental toxicity cannot be assessed.

No classification is proposed due to inconclusive data.

Adverse effects on or via lactation

No human or animal data are available to evaluate effects on or via lactation. In the absence of data this endpoint cannot be assessed. **RAC proposes no classification due to inconclusive 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).