CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Chemical name:

2,3-epoxypropyl isopropyl ether

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

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

Index Number: **-**

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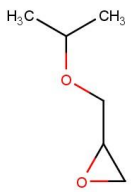
Version number: 2 **Date: 2022-05-31**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Names in the IUPAC nomenclature or other international chemical names	2,3-epoxypropyl isopropyl ether 2-(isopropoxymethyl)oxirane 2-[(propan-2-yloxy)methyl]oxirane Glycidyl Isopropyl Ether Isopropylglycidether
Other names (usual name, trade name, abbreviation)	IPGE
ISO common name	*n.a.*
EC number	223-672-9
EC name	
CAS number	4016-14-2
Other identity code	*n.a.*
Molecular formula	C6H12O2
Structural formula	
SMILES notation	
Molecular weight or molecular weight range	116.16 g/mol
Information on optical activity and typical ratio of (stereo) isomers	*n.a.*
Description of the manufacturing process and identity of the source (for UVCB substances only)	*n.a.*
Degree of purity (%) (if relevant for the entry in Annex VI)	*n.a.*

1.2 Composition of the substance

Table 2: Constituent (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3 (CLP)**	**Current self-classification and labelling (CLP)**

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)
2,3-epoxypropyl isopropyl ether EC 223-672-9	-	None	Flam. Liq. 3 Acute Tox. 4 (oral) Skin Irrit. 2 Eye Irrit. 2 Acute Tox. 3 (inhalation) Repr. 2 Aquatic Chronic 3 Skin Sens. 1 Acute Tox. 4 (inhalation) STOT SE 3 (nervous system)

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
-				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
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2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: **Proposed harmonised classification and labelling according to the CLP criteria**

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	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 submitter's proposal	TBD	2,3-epoxypropyl isopropyl ether	223-672-9	4016-14-2	Repr. 1B	H360F	GHS08 Dgr	H360F			

Table 5: Reason for not proposing harmonised classification and status under consultation

Hazard class	Reason for no classification	Within the scope of consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity	hazard class not assessed in this dossier	No
Reproductive toxicity	Harmonised classification proposed	Yes
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

No previous harmonised classification and labelling.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level. 2,3-epoxypropyl isopropyl ether (IPGE) is considered to fulfil the criteria for classification as toxic to reproduction (Repr. 1B, H360F). Therefore, a harmonised classification is justified according to Article 36(1)(d) of the CLP Regulation.

5 IDENTIFIED USES

The substance is used industrially in coatings, paints, laboratory chemicals, and as an intermediate in polymer production. The substance is also used by professionals in washing and cleaning products.

6 DATA SOURCES

The registration dossier in ECHA dissemination site is the main source of information (Registration Dossier - ECHA (europa.eu)). The full study report of Test guideline study according to OECD 422 was also available to the dossier submitter.

7 PHYSICOCHEMICAL PROPERTIES

Table 6: Summary of physicochemical properties.

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid	Registration dossier, ECHA's dissemination site, 2021.	Sensorial observation
Melting/freezing point	-54.7°C	Registration dossier, ECHA's dissemination site, 2021.	Estimated (QSAR)
Boiling point	137°C	Registration dossier, ECHA's dissemination site, 2021.	Estimated (Peer reviewed handbook)
Relative density	0.92	Registration dossier, ECHA's dissemination site, 2021.	Estimated (QSAR)
Vapour pressure	13 hPa	Registration dossier, ECHA's dissemination site, 2021.	Estimated (Peer reviewed handbook)
Surface tension	-		
Water solubility	19 g/L	Registration dossier, ECHA's dissemination site, 2021.	Estimated (QSAR)
Partition coefficient n-octanol/water	0.8	Registration dossier, ECHA's dissemination site, 2021.	Measured
Flash point	33°C	Registration dossier,	From peer reviewed database

Property	Value	Reference	Comment (e.g. measured or estimated)
		ECHA's dissemination site, 2021.	
Flammability	-		
Explosive properties	-		
Self-ignition temperature	290°C	Registration dossier, ECHA's dissemination site, 2021.	Measured
Oxidising properties	-		
Granulometry	-		
Stability in organic solvents and identity of relevant degradation products	-		
Dissociation constant	-		
Viscosity	-		

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this CLH proposal.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 7: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
An assessment of the basic toxicokinetic behaviour of IPGE was performed by the registrant, by considering the chemical structure, the available physico-chemical- and toxicological data.	Absorption in rats (all exposure routes) were estimated to 100%. Systemic bioavailability was considered very high. O-dealkylation and Aliphatic hydroxylation were identified as the mode of action during Phase-I-metabolism. IPGE and its estimated metabolites are small and soluble in water. A very fast excretion of the compounds via the kidneys, urine and potentially lungs can be expected. IPGE has a minor potential for bioaccumulation and will be excreted rapidly.	The assessment of the toxicokinetic behaviour of IPGE was performed by the registrant, considering the chemical structure, the available physico-chemical and toxicological data. No toxicokinetic study is available.	Registration dossier, ECHA's dissemination site, 2021.

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification

No toxicokinetic study is available. The registrant has assessed the toxicokinetic behaviour of IPGE based on structure, physico-chemical properties, and toxicological information on the substance. According to the assessment the absorption and systemic bioavailability is high. IPGE and its metabolites are expected to be excreted rapidly. There is a minor potential for bioaccumulation.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Not evaluated in this CLH proposal.

10.2 Acute toxicity - dermal route

Not evaluated in this CLH proposal.

10.3 Acute toxicity - inhalation route

Not evaluated in this CLH proposal.

10.4 Skin corrosion/irritation

Not evaluated in this CLH proposal.

10.5 Serious eye damage/eye irritation

Not evaluated in this CLH proposal.

10.6 Respiratory sensitisation

Not evaluated in this CLH proposal.

10.7 Skin sensitisation

Not evaluated in this CLH proposal.

10.8 Germ cell mutagenicity

Not evaluated in this CLH proposal.

10.9 Carcinogenicity

Not evaluated in this CLH proposal.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 8: Summary table of animal studies on adverse effects on sexual function and fertility

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. Wistar rats 12 males and 12 females per group. Reliability according to registrant: 1	Rats were dosed daily with IPGE dissolved in arachis oil (purity flagged as confidential) by gavage at 0, 100, 300, 600 mg/kg bw/day. Females were dosed 14 days prior to pairing, during pairing and pregnancy, and 4 days afterwards. Males were dosed daily from Day 1 and were terminated on Day 43 or 44. At Day 5 post-partum, all surviving females and surviving offspring were killed.	All animals mated within the first four days of pairing, however, no females treated with 300 or 600 mg/kg bw/day became pregnant. The pregnancy rate at 100 mg/kg bw/day was also reduced (4 of 12 females were not pregnant and one female showed one corpora lutea and one implantation site but failed to give birth to any offspring). The majority of females treated with 300 and 600 mg/kg bw/day and one female treated with 100 mg/kg bw/day had increased corpora lutea and were in metestrus or diestrus, indicating a disturbance of the reproductive cycle. No marked general toxicity in terms of body weight and clinical condition was noted in parental animals. See below, and in Annex I, section 3.10.1.1 for more details.	Study report, 2017, Registration dossier, ECHA's dissemination site, 2021.

Table 9: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
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Table 10: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Dose range finding study, 14 days to the	Rats were given IPGE dissolved in arachis oil	Wistar rats, 3 males and 3 females per dose group.	No clinical effects were observed. Animals in the high dose group demonstrated sporadic increased salivation on	Unnamed 2016. Robust study summary in Registration dossier, ECHA's

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
OECD TG 422 study (Study report, 2017). GLP compliant. Reliability according to registrant: 1	(purity not stated) via gavage daily at 0, 75, 250 and 500 mg/kg bw.		Day 7 post dosing. Animals in the high dose group showed a reduction in body weight gain between Day 1 and 4. A slight reduction was also seen in mid-dose males.	dissemination site, 2021.
Sub-chronic toxicity study via inhalation. Not GLP. Reliability according to registrant: 2	Ten male Long-Evans rats were exposed (whole body) to IPGE at doses of 400 ppm (vapour), 7 hours daily, 5 days per week for 10 weeks.		In two rats, mottling of the liver was observed. One of the latter showed confluent pneumonia on microscopic examination, but all other sections examined were within normal limits. Slight eye irritation and laboured breathing were observed; the body weight gain of the exposed animals was less than that of the controls. Mild emphysema was found in the lungs of 4/10 rats (40%).	Summarised in Registration dossier, ECHA's dissemination site, 2021. Original reference: Hine, C. H., J. K. Kodoma, J. S. Wellington, M. K. Dunlap, H. H. Anderson: "The toxicology of glycidol and some glycidyl ethers", Arch. Ind. Health 14, 250 (1956).
Sub-chronic toxicity study via dermal exposure. Not GLP. Reliability according to registrant: 4	Daily applications of 0.2 ml IPGE (ca. 90 mg/kg) to the skin of 6 male rabbits (California Albino or New Zealand White rabbit), 5 times weekly on a total of 7 days until the degree of eschar formation at the site made further applications undesirable, or the animals showed signs of systemic	No information available on purity of test substance, vehicle. Lack of control animals. Area of exposure: back. Percent coverage: 1 cm in diameter. The fur was shaved from the backs of rabbits at least 20 hours before the tests started. Test substance was removed at the end of one hour of exposure by wiping with laboratory tissues followed by tissues moistened with acetone.	Application of IPGE to the skin of rabbits caused reductions in body weight gain and skin erythema.	Summarised in Registration dossier, ECHA's dissemination site, 2021. Original reference: Hine, C. H., J. K. Kodoma, J. S. Wellington, M. K. Dunlap, H. H. Anderson: "The toxicology of glycidol and some glycidyl ethers", Arch. Ind. Health 14, 250 (1956).

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
	toxicity.			

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) of IPGE in rat (Study report, 2017)

In an OECD TG 422 guideline study, IPGE was administered daily by gavage to 3 dose groups each of 12 male and 12 female Wistar Han strain rats, at dose levels of 100, 300 and 600 mg/kg bw/day. A control group of 12 males and 12 females was dosed with vehicle alone (Arachis oil BP). 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.

Fertility, parturition, and sexual function

All animals mated within the first four days of pairing (i.e. at their first estrus opportunity), however, no females treated with 300 or 600 mg/kg bw/day became pregnant. The pregnancy rate at 100 mg/kg bw/day was also lower, with four females not pregnant and one female showing one corpora lutea and one implantation site but failing to give birth to any offspring.

The mating index did not differ between controls and treated animals (100%) (Table 11). However, 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 that mated. The incidence of non-pregnant females increased with increasing dose and the fertility index was 100%, 67%, 0 and 0 for controls, low-, mid- and high dose groups, respectively.

Gestation lengths for controls and females in 100 mg/kg bw/day groups were between 22.5 and 23.5 days. The distribution of gestation lengths for the females treated with 100 mg/kg bw/day was similar to control.

The majority of females treated with 300 and 600 mg/kg bw/day and in one female treated with 100 mg/kg bw/day had the appearance of increased corpora lutea and was in metestrus and diestrus, suggesting a disturbance of the reproductive cycle.

The mean number of corpora lutea (-28%) and implantation sites (-31%) were statistically significantly lower in females treated with 100 mg/kg bw/day compared to controls. The mean pre-implantation loss in these females was higher compared to controls (not significant), but this was due to one female with a particularly high number, as the remaining females were similar to controls.

Table 11: Fertility parameters, OECD TG 422 study, 2017.

Dose levels (mg/kg/day)	**0**	**100**	**300**	**600**
No. of pairs examined	12	12	11*	12
No. of pairs with successful mating	12	12	11	12
Mating index (%) = (No. of pairs with successful mating/ No. of pairs examined) X 100	100	100	100	100
No. of pregnant females	12	8	0	0
Fertility index (%) = (No. of pregnant animals/ No. of pairs with successful mating) x 100	100.0	67.0	0	0
Total litter loss in utero	0	1 of 8 (12.5%)	-	-

*One female treated with 300 mg/kg bw/day was killed in extremis on Day 4. Histopathological examination revealed infection of both kidneys, which was considered not to be treatment related but likely to have caused the poor condition of the animal (which included hunched posture, pilo-erection, decreased respiratory rate, lethargic).

Reproductive organ weights and histopathology

Males treated with 600 mg/kg bw/day showed statistically significant reduction in absolute (-9%) and relative (-7%) testes weight compared to controls. However, the majority of individual values for testes weights were within the historical control range. At termination, one male treated with 600 mg/kg bw/day had a small and flaccid right testis and another male of this treatment group had a small and flaccid left testis and epididymis.

Detailed qualitative examination of the testes was undertaken, taking into account the tubular stages of the spermatogenic cycle. The examination was conducted to identify treatment-related effects such as missing germ cell layers or types, retained spermatids, multinucleated or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell-or stage-specificity of testicular findings was noted. There were no test item related microscopic findings in the testes, including following the qualitative examination of the stages of spermatogenesis in the testes (no test item related abnormalities in the integrity of the various cell types present within the different stages of the sperm cycle).

Females treated with 600 mg/kg bw/day showed a statistically significant reduction in uterus and cervix weights, both absolute (-19%) and relative to terminal body weight (-13%) compared to controls. The majority of the individual values were within historical control ranges and there were no histopathological changes detected. One female treated with 300 mg/kg bw/day had a fluid filled uterus at necropsy.

Organ weights - males

Males treated with 600 mg/kg bw/day showed statistically significant increases in kidney (+21%) and liver (+28%) weights, both absolute and relative to terminal body weight. The majority of individual values for kidney and liver weights were outside of the historical control ranges but there were no associated histopathological findings. Males treated with 300 mg/kg bw/day showed a statistically significant reduction in thyroid weight, both absolute (-30%) and relative to terminal body weight (-

29%). However, all the individual values were within the historical control range and there were no associated histopathological findings. No such effect was seen in males at 600 mg/kg bw/day.

Organ weights - females

Females treated with 100 mg/kg bw/day showed a statistically significant reduction in spleen weight both absolute (-24%) and relative to terminal body weight (-19%). All the individual values for relative weights and all but one absolute weight was within historical control ranges and there were no associated histopathological findings.

Females treated with 300 and 600 mg/kg bw/day showed statistically significant reductions in absolute (-23% and -26%, respectively) and relative liver weights (-17% and -18%) and in absolute (-31% and -28%) and relative spleen weights (-26% and -20%). In addition, statistically significant increases in absolute (+64% and +37%) and relative thymus weight (+79% and +54%) were shown. Since the females treated at 300 and 600 mg/kg bw/day were not pregnant they were all in a different physiological state than the other females in the study, thus comparisons between the groups should be made with caution.

Pathological findings

At termination, nine males and one female treated with 600 mg/kg bw/day had raised white patches on the non-glandular region of the stomach.

Two control males, two control females, two males and one female treated with 300 mg/kg bw/day and two females treated with 600 mg/kg bw/day had reddened lungs at necropsy. One female treated with 600 mg/kg bw/day had a fibrous mass (approximately 5mm x 5mm) on the liver.

General toxicity

Both males and females treated with 600 mg/kg bw/day showed incidences of increased salivation between Days 18 and 25. No such effects were seen in animals of either sex treated with 300 or 100 mg/kg bw/day.

Females treated with 300 and 600 mg/kg bw/day were all non-pregnant, and their body weight gain during the first week post coitum was comparable to control females. However, the body weight gain for these females during the remaining treatment period was reduced with the majority of females showing actual body weight losses. Body weight gain of females treated with 100 mg/kg bw/day was reduced (not statistically significantly) during the final two weeks of gestation and cumulative body weight gain between Days 0 and 20 of gestation was lower in these females (-10%) compared to control animals. A statistically significant reduction in body weight gain was also evident in low dose females during lactation (-50%). No adverse effects were detected on food consumption for treated females during maturation. Food consumption for 100 mg/kg bw/day females was comparable to controls throughout gestation, however, it was statistically significantly reduced during lactation. This lower food consumption was thus consistent with the lower body weight gain compared to control during this phase of the study.

Males treated with 600 mg/kg bw/day showed a statistically significant 10% reduction in body weight gain during the first week of treatment. Although recovery was seen thereafter, a slight reduction in body weight gain was seen during the final week of treatment. A 10% reduction in overall body weight gain was seen in these males (not significant). No adverse effects were detected in male food consumption.

Haematological findings: The effects detected on a few of the hematological parameters measured for males treated with 300 and 600 mg/kg bw/day or both sexes at 100 mg/kg bw/day were considered to be of no toxicological significance as the individual values were within historical control ranges combined with lack of dose-response.

Females treated with 300 and 600 mg/kg bw/day demonstrated statistically significantly higher hemoglobin (+13% and +10%, respectively), erythrocyte count (+14% and +13%, respectively) and hematocrit (+11%), lower neutrophils (-67% and -62%, respectively) and platelet count (-31% and -24%, respectively) compared with controls. All individual values for these parameters were within the historical control range, except for one female treated with 300 mg/kg bw/day for platelet count. Assessment of hematology parameters for females at 300 and 600 mg/kg bw/day has to be treated with caution since these females were non-pregnant at the time of blood sampling and therefore in a different physiological state in comparison to the other females on the study, and to females contributing to the historical control data.

Clinical biochemistry findings: There were no toxicologically significant effects detected in the blood chemical parameters measured for males treated with 300 mg/kg bw/day or both sexes at 100 mg/kg bw/day. Males treated with 600 mg/kg bw/day demonstrated significantly higher alanine aminotransferase (+18%) compared to controls. Females treated with 300 and 600 mg/kg bw/day demonstrated higher bile acids (+166% and +239%, respectively), inorganic phosphorus (+68% and +72%, respectively), and albumin/globulin ratio (+8% and +12%, respectively) (statistically significant) compared to controls. For inorganic phosphorus and albumin/globulin ratio, all individual values were within the historical control ranges, whereas for bile acids the majority of individual values were outside of the historical control range. In addition, higher bilirubin (+38%) and lower creatinine (-12%) and urea levels (-20%) were statistically significantly different in females treated with 600 mg/kg bw/day compared to controls, but all individual values were within the historical control ranges.

See Annex I, section 3.10.1.1 for more information on the study.

Conclusion

A clear effect on fertility was evident in mid- and high dose animals (300 and 600 mg/kg bw/day) in the Study report, 2017. Among the females treated at these dose levels, which all mated, no pregnancies were achieved. The incidence of animals without induced pregnancy increased with increasing dose starting from the lowest dose (100 mg/kg bw/day). No marked general toxicity in terms of body weight and clinical condition was noted in females. Males in the highest dose group had a slightly reduced (not significant) overall body weight gain.

10.10.3 Comparison with the CLP criteria

The criteria for classification in Repr. 1B for adverse effects on sexual function and fertility are considered fulfilled since: A clear effect on fertility was evident in mid- and high dose animals in the Study report from 2017. Of the females treated at these dose levels, which all mated, no pregnancies were achieved. In addition, the incidence of animals without induced pregnancy increased with increasing dose, as only 7 or 12 females (58%) in the lowest dose groups produced offspring. No marked general toxicity in terms of body weight and clinical condition was noted in parental animals.

The available data provide clear evidence of an adverse effect on sexual function and fertility and there is no mechanistic evidence to indicate that the observed effects are not relevant for humans. Classification in Repr. 1B, H360F is therefore warranted.

Classification in Repr. 1A is not appropriate as it should be based on human data and no human data are available.

Classification in Repr. 2 is not appropriate as the evidence for adverse effects on sexual function and fertility from existing experimental data on IPGE is considered as clear evidence and not some evidence.

10.10.4 Adverse effects on development

Table 12: Summary table of animal studies on adverse effects on development

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. Wistar rats 12 males and 12 females per group. Females and offspring were killed on Day 5 post-partum and not on Day 13 post-partum, as indicated in the Test guideline. Reliability according to registrant: 1	Rats were dosed daily with IPGE dissolved in arachis oil (purity flagged as confidential) by gavage at 0, 100, 300, 600 mg/kg bw/day. Females were dosed 14 days prior to pairing, during pairing and pregnancy, and 4 days afterwards. Males were dosed daily from Day 1 and were terminated on Day 43 or 44. At Day 5 post-partum, all surviving females and surviving offspring were killed.	No offspring was produced in the mid- and high dose groups. No adverse effect of maternal treatment on offspring development was observed at 100 mg/kg bw/day. Live birth index and offspring viability in litters from females treated with 100 mg/kg bw/day was comparable to controls. See below and in Annex I, section 3.10.1.1 for more details.	Study 2017, Registration dossier, ECHA's dissemination site, 2021.

Table 11: Summary table of human data on adverse effects on development

Type of data/report	**Test substance,**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
-				

Table 12: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
-				

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

Study report from 2017 (OECD TG 422)

All the females treated with 300 and 600 mg/kg bw/day were non-pregnant.

No effects on body weights were detected in treated females during maturation. Body weight gain of females treated with 100 mg/kg bw/day was reduced (not statistically significantly) during the final two weeks of gestation and cumulative body weight gain between Days 0 and 20 of gestation was lower in these females (-10%) compared to control animals. A statistically significant reduction in body weight gain was also evident in low dose females during lactation (-50%). No adverse effects were detected on food consumption for treated females during maturation. Food consumption for 100 mg/kg bw/day females was comparable to controls throughout gestation, however, it was statistically significantly reduced during lactation. This lower food consumption was thus consistent with the lower body weight gain compared to control during this phase of the study.

The clinical signs apparent for offspring in the study were typical for the age observed. Neither the incidence nor distribution of these observations indicated any adverse effect of maternal treatment on offspring development at 100 mg/kg bw/day.

No mortality among offspring was observed. Live birth index and offspring viability in litters from females treated with 100 mg/kg bw/day was comparable to controls.

The litter size was lower for females treated at 100 mg/kg bw/day (-27%). As a consequence, the litter weights on Days 1 (-20%) and 4 (-19%) post-partum were reduced when compared to controls, although no statistical significance was achieved. Offspring body weights at birth and subsequently on Days 1 and 4 post-partum and offspring body weight gain between Days 1 and 4 post-partum exceeded control litters.

Neither the type, incidence nor distribution of necropsy findings for offspring terminated at Day 5 of age indicated any obvious effect of maternal treatment on the offspring at 100 mg/kg bw/day. Both females and offspring were killed at Day 5 post-partum, and not on Day 13 as indicated in the Test guideline.

To conclude, based on the available data from the reproductive and developmental screening study from 2017 (OECD TG 422) there are no indications of effects on the development of the offspring. However, no offspring was produced in the two highest dose groups (300 and 600 mg/kg bw/day) and only 7 of 12 (58%) females in the lowest dose group (100 mg/kg bw/day) gave birth to litters. No marked general toxicity in terms of body weight and clinical condition was noted in parental animals.

See Annex I, section 3.10.1.1 for more information on the study.

10.10.6 Comparison with the CLP criteria

Classification in Repr. 1A is not justified since there is no human data available.

Classification in Repr. 1B is not justified since the evidence for developmental toxicity from existing experimental data on IPGE is not considered to be clear evidence.

Classification in Repr. 2 is not justified since the evidence for developmental toxicity based on existing experimental data on IPGE is not considered as some evidence.

10.10.7 Adverse effects on or via lactation

Table 13: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
-			

Table 14: Summary table of human data on effects on or via lactation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
-				

Table 15: Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
-				

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

The data available on IPGE are not sufficient to assess effects on or via lactation. In the OECD TG 422 study summarised above (Table 12), both females and offspring were killed at Day 5 post-partum, and not on Day 13 as indicated in the test guideline, therefore data are considered insufficient to assess effects on lactation. Furthermore, there are no studies available on the quantity, quality, or composition of the milk.

10.10.9 Comparison with the CLP criteria

Since data on effects on or via lactation are insufficient, comparison with the CLP criteria is inapplicable.

According to CLP Annex I classification of substances for effects on or via lactation can be assigned on the:

(a) human evidence indicating a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk: and/or

(c) absorption, metabolism, distribution, and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

Classification of IPGE for adverse effects on sexual function and fertility is warranted: Repr. 1B H360F. A specific concentration limit for adverse effects on sexual function and fertility is not considered justified since the calculated ED10 value is within the medium potency group (4 mg/kg bw/day < ED10 value < 400 mg/kg bw/day). The ED10 was estimated based on interpolation between 100 mg/kg bw/day (33% of mated animals failed to induce pregnancy) and the control (0% of the animals affected). This resulted in an ED10 of 30 mg/kg bw/day by interpolation. Application of modifying factors was not considered relevant in this case.

10.11 Specific target organ toxicity-single exposure

Not evaluated in this CLH proposal.

10.12 Specific target organ toxicity-repeated exposure

Not evaluated in this CLH proposal.

10.13 Aspiration hazard

Not evaluated in this CLH proposal.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this CLH proposal.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this CLH proposal.

13 ADDITIONAL LABELLING

Not relevant.

14 REFERENCES

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15 ANNEXES

ANNEX I to the CLH report.