CLH report

Proposal for Harmonised Classification and Labelling

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

Chemical name: *O*-isopropyl ethylthiocarbamate

EC Number: 205-517-7

CAS Number: 141-98-0

Index Number: -

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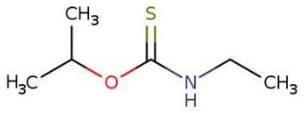
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

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

Name(s) in the IUPAC nomenclature or other international chemical name(s)	*O*-isopropyl ethylthiocarbamate N-ethyl(propan-2-yloxy)carbothioamide
Other names (usual name, trade name, abbreviation)	Danafloat 262 Hostaflot X-23 Thionocarbamate IPETC
ISO common name (if available and appropriate)	Not applicable
EC number (if available and appropriate)	205-517-7
EC name (if available and appropriate)	*O*-isopropyl ethylthiocarbamate
CAS number (if available)	141-98-0
Other identity code (if available)	Not applicable
Molecular formula	C6H13NOS
Structural formula	
SMILES notation (if available)	CCNC(=S)OC(C)C
Molecular weight or molecular weight range	147.24g
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable
Degree of purity (%) (if relevant for the entry in Annex VI)	Not applicable

1.2 Composition of the substance

Table 2: Constituents (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)
O-isopropyl ethylthiocarbamate	Mono-constituent substance	None	Acute Tox. 4, H302 Skin Irrit. 2, H315 Repr. 2, H361 Aquatic Chronic 3, H412

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

No impurities relevant for classification.

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

No additives relevant for classification.

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 for *O*-isopropyl ethylthiocarbamate 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	*O*-isopropyl ethylthiocarbamate	205-517-7	141-98-0	Repr. 1B Aquatic Chronic 2	H360D H411	GHS08 GHS09 Dgr	H360D H411			
Resulting Annex VI entry if agreed by RAC and COM	TBD	*O*-isopropyl ethylthiocarbamate	205-517-7	141-98-0	Repr. 1B Aquatic Chronic 2	H360D H411	GHS08 GHS09 Dgr	H360D H411			

Table 6: 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
Endocrine disruption for HH	Hazard class not assessed in this dossier.	No
Hazardous to the aquatic environment	Harmonised classification proposed.	Yes
Endocrine disruption for ENV	Hazard class not assessed in this dossier.	No
PBT/vPvB	Hazard class not assessed in this dossier.	No
PMT/vPvM	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

There is no harmonised classification and labelling for *O*-isopropyl ethylthiocarbamate, and it was not previously discussed by the Technical Committee for Classification and Labelling under Directive 67/548/EEC.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level.

In accordance with Article 36(1) of CLP, justification for action is not required for substances which fulfil the classification criteria for carcinogenicity, germ cell mutagenicity or reproductive toxicity. The dossier submitter proposes classification as a category 1B reproductive toxicant and therefore no justification for this hazard class is required.

Justification that action is needed at Community level is required.

In accordance with Article 36(3) of CLP, justification for action is required for hazard classes other than those referred to in Article 36(1). The REACH registrant has self-classified *O*-isopropyl ethylthiocarbamate as a reproductive toxicant category 2 and aquatic chronic 3. The dossier submitter considers that the data presented in this dossier supports classification as a category 1B reproductive toxicant. In addition, the dossier submitter considers that the available data on aquatic environment supports classification as Aquatic Chronic 2.

There are five other notifications to ECHA's Classification and Labelling inventory and 4/5 have not classified for reproductive toxicant but for other hazards, 2/5 have classified as aquatic chronic 2, 2/5 have classified as aquatic chronic 3 and 1/5 have notified as 'Not classified' for any human health or environmental hazard. Thus, harmonised classification for the hazard classes reproductive toxicant and aquatic environment are proposed due to the disagreement by the dossier submitter with the current self-classifications.

5 IDENTIFIED USES

O-isopropyl ethylthiocarbamate is a liquid substance used in industrial settings and/or in formulation and repacking settings in the production of the following products: polymers, extraction agents, pH regulators and water treatment. During formulation, reported uses include batch processing in synthesis or formulation, transfer of chemicals, closed batch processing in synthesis or formulation, closed, continuous processes with occasional controlled exposure, mixing in open batch processes and laboratory work. The substance has industrial uses (e.g. floatation agent, flocculant, reactive processing aid, pH regulators, precipitants and neutralisation agents) in mining and in the manufacture of chemicals and metals.

6 DATA SOURCES

Data for *O*-isopropyl ethylthiocarbamate are taken from:

- Publicly disseminated REACH registration dossier (ECHA dissemination site, 2024).
- Unpublished study reports provided by the registrants for the reproductive toxicity and aquatic toxicity endpoints.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g., measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid	ECHA dissemination site, 2024	Yellow/red liquid
Melting/freezing point	-20 °C	ECHA dissemination site, 2024	Measured at 101,3 kPa
Boiling point	75 °C	ECHA dissemination site, 2024	Measured at 101,3 kPa
Relative density	0.993	ECHA dissemination site, 2024	Measured at 20 °C
Vapour pressure	950 Pa	ECHA dissemination site, 2024	Measured at 20 °C
Surface tension	54.9 mN/m	ECHA dissemination site, 2024	Measured at 20 °C
Water solubility	2.65 g/L	ECHA dissemination site, 2024	Measured at 25°C, pH7
Partition coefficient n-octanol/water (KOW)	Log Kow = 2.3	ECHA dissemination site, 2024	Measured at 30 °C
Partition coefficient n-octanol/air (K_{OA})	Not applicable		
Flash point	182.2 °C	ECHA dissemination site, 2024	Measured at 1013
Flammability	Not applicable	ECHA dissemination site, 2024	
Explosive properties	Not explosive	ECHA dissemination site, 2024	According to EU method A.14
Self-ignition temperature	355 ± 5 ºC	ECHA dissemination site, 2024	Measured at 1004 mbar
Oxidising properties	Non oxidising	ECHA dissemination site, 2024	According to EU method A.21
Granulometry	Not applicable		
Stability in organic solvents and identity of relevant degradation products	Not applicable		
Dissociation constant	8.67 at 20.6 ºC	ECHA dissemination site, 2024	Measured at 20.6 °C
Viscosity	2.19 mPa · s at 20 ºC	ECHA dissemination site, 2024	Measured at 20 °C

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Not evaluated as part of this dossier.

8.2 Flammable gases (including chemically unstable gases)

Not evaluated as part of this dossier.

8.3 Oxidising gases

Not evaluated as part of this dossier.

8.4 Gases under pressure

Not evaluated as part of this dossier.

8.5 Flammable liquids

Not evaluated as part of this dossier.

8.6 Flammable solids

Not evaluated as part of this dossier.

8.7 Self-reactive substances

Not evaluated as part of this dossier.

8.8 Pyrophoric liquids

Not evaluated as part of this dossier.

8.9 Pyrophoric solids

Not evaluated as part of dossier.

8.10 Self-heating substances

Not evaluated as part of this dossier.

8.11 Substances which in contact with water emit flammable gases

Not evaluated as part of this dossier.

8.12 Oxidising liquids

Not evaluated as part of this dossier.

8.13 Oxidising solids

Not evaluated as part of this dossier.

8.14 Organic peroxides

Not evaluated as part of this dossier.

8.15 Corrosive to metals

Not evaluated as part of this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Expert statement based on ECHA *Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7c: Endpoint specific guidance*, V3.0 June 2017. The toxicokinetic profile was determined by examining the physical-chemical properties of the *O*-isopropyl ethylthiocarbamate in combination with results of toxicity studies. The registrant presented a case based on the test substance's physiochemical properties: - log P of 2.3 - a low molecular weight (147g/mol) - Water soluble;2.65 g/L - Vapour pressure of 950 Pa at 20°C - Liquid -The registrants reported that the test substance showed systemic toxic effects in several oral toxicity tests and was a skin irritant in an OECD 439 study.	<u>Oral absorption</u> The registrants stated, "*an oral absorption rate of 100% is assumed"* for the test substance. <u>Dermal absorption</u> The registrants stated, "*a dermal absorption rate of 100% is assumed"* for the test substance. <u>Respiratory absorption</u> The registrant stated, "*respiratory exposure is possible"* and "*as worst case, 100 % inhalation absorption is assumed."* <u>Distribution and accumulation</u> The registrant stated that the test substance "*is expected to be widely distributed in the body via blood circulation"* and "*no accumulation in fatty tissue or stratum corneum is expected."* <u>Excretion</u> The registrant stated that the test substance "*favours urinary excretion"* and "*will be filtered out of the blood by the kidneys as conjugated metabolites from phase II metabolism."*	There were no physical measurements performed to determine actual values for absorption, distribution or excretion. Reliability: 3 not reliable.	ECHA dissemination site, 2024.

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

The registrant reported there was no test study data available for the adsorption, distribution, metabolism or excretion (ADME) parameters of *O*-isopropyl ethylthiocarbamate. The registrant prepared an expert statement based on the ECHA *Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7c: Endpoint specific guidance*, (V3.0 June 2017) to approximate the ADME properties of the test substance, and this was made available in the registration dossier. The test substance is a water soluble (solubility; 2.65g/L) liquid with a "*low"* molecular weight of 147 g/mol, a log P value of 2.3 and a vapour pressure of 950 Pa at 20°C.

"*An oral absorption rate of 100% is assumed"* for the test substance based on the following assumptions:

- it is likely to follow an absorption route by passive diffusion which is favoured by substances with a moderate log P value (range between -1 and +4).
- On the basis of a low molecular weight coupled with the test substance being soluble in water, it is assumed that the test substance will be absorbed via the aqueous pores or being carried through the epithelial barrier.
- Several oral toxicity studies support systemic toxic effects including mortality.

"*A dermal absorption rate of 100% is assumed*" for the test substance based on the following assumptions:

- With a log P value > 0 and low molecular weight, the test substance may "*...be absorbed by the stratum corneum*".
- As the test substance is "*sufficiently soluble in water*," it may penetrate deeper, viable layers of the epidermis.
- The test substance is considered to be a skin irritant so it must interact with elements sub-dermally.

"*Respiratory exposure is possible"* and *"as worst case, 100% inhalation absorption is assumed"* for the test substance based on the following assumptions:

- the test substance has a "*moderate volatility*," and it is likely available for inhalation as a vapour.
- the test substance's moderate water solubility allows it to dissolve in the mucus of the respiratory tract and inhalation as a vapour allows the possibility of the test substance penetrating all the way into the alveolar region.
- the log P value would indicate the possibility for direct absorption of the test substance across the respiratory tract epithelium by passive diffusion and the water solubility allows for passive transfer via aqueous pores or through the epithelial barrier by the bulk passage of water.

As a result of the test substance's water solubility and low molecular weight, the test substance "*is expected to be widely distributed in the body via blood circulation*." As the log P value of the test substance was <3, *"no accumulation in fatty tissue or stratum corneum is expected".*

On the basis of the test substance's water solubility and low molecular weight, the test substance may favour "*urinary excretion*" and may "*...be filtered out of the blood by the kidneys as conjugated metabolites from phase II metabolism."*

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Not evaluated as part of this dossier.

10.2 Acute toxicity - dermal route

Not evaluated as part of this dossier.

10.3 Acute toxicity - inhalation route

Not evaluated as part of this dossier.

10.4 Skin corrosion/irritation

Not evaluated as part of this dossier.

10.5 Serious eye damage/eye irritation

Not evaluated as part of this dossier.

10.6 Respiratory sensitisation

Not evaluated as part of this dossier.

10.7 Skin sensitisation

Not evaluated as part of this dossier.

10.8 Germ cell mutagenicity

Not evaluated as part of this dossier.

10.9 Carcinogenicity

Not evaluated as part of this dossier.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 9: 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
OECD 422; Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test. GLP Compliant. Rat, CD® / Crl: CD(SD), male and female, 10/sex/group. Deviations from OECD 422: -10 females instead of 12-13. -No information on oestrous cycle monitoring. -Females were treated until lactation day (LD) 3. -Testing lasted for 59 days rather than 63. -There were no thyroid hormone assessments carried out. -There was no historical control data reported.	IPETC or Danafloat™262 (tradename of *O*-isopropyl ethylthiocarbamate). Purity: 95.7% Oral gavage, once daily. 0, 31, 103 and 309 mg/kg bw/day. Vehicle: Corn oil. Males were treated once daily, treatment commenced two weeks pre-mating and lasted for at least 28 days. Females were treated once daily, treatment commenced two weeks pre-mating and lasted until at least LD 3. Reliability: 2, reliable with restrictions.	**Top dose: 309 mg/kg bw/day:** **-Female:** 1/10 died on test day 3. All other animals survived to scheduled sacrifice. **-Clinical signs:** **-Both sexes:** ↑ in salivation in males in pre-mating, mating and post-mating period and in females in gestation period. **Females**: piloerection during pre-mating period. - **Note**: there was no data available for females at 309 mg/kg bw/day for mean body weight, mean body weight gain or food consumption during the lactation period due to complete litter loss. - **Males bw**: ↓ in mean body weight on day 8 (8.7%), 15 (9.4%), 22 (8.3%), 29 (8.9%), 36 (10.7%) and 43 (11.9%) and a ↓ mean body weight gain throughout the testing period (27.41% from day 1-43). There was also a 12% ↓ in mean terminal body weight. -- **Females, bw:** ↓ in mean body weight during pre-mating period (12.2%) and gestation period (33%). ↓ in mean body weight gain during pre-mating period (139%) and gestation period (78%). There was a ↓ (18%) in mean terminal body weight. - **Males, food consumption:** 15% ↓ on pre-mating days 1-8 and an 8% ↑ in food consumption on pre-mating days [1-15]. - **Females, food consumption:** 28% ↓ during pre-mating days [1-8]. There were no effects observed during pre-mating days [8-15], during	Anonymous, 2012a

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		the gestation period or the lactation periods. - **Both sexes, water consumption:** ↑ in 10/10 males during pre-mating, mating, and post-mating periods. In females ↑ in water consumption in 4/9 females during the pre-mating and mating periods and 5/9 females in the gestation period. 1/9 females ↓ water consumption during the pre-mating period. - **Histopathology: Males:** interstitial lymphocytic infiltrate and mononuclear cell infiltration of the epididymis was observed in 3/5 and 5/5 males, respectively. **<u>Mid dose: 103 mg/kg bw/day</u>:** - **Both sexes**; ↓ in motility from mating to gestation period and prone position during pre-mating period. - **Males, bw:** no effects of concern. **-Females, bw:** ↓ in mean body weight during pre-mating period (5.8%) and gestation period (8.8%). ↓ in mean body weight gain during pre-mating period (71%) and gestation period (33%). There were no bw effects observed during the lactation period. - **Females, food consumption:** 28% ↓ in food consumption during pre-mating days [1-8]. There were no effects observed during pre-mating days [8-15], nor was there any effect during the gestation or the lactation periods. **<u>Low dose: 31 mg/kg bw/day</u>:** - **Females, bw:** no effects of concern. - **Females, food consumption:** 8% ↓ in food consumption during pre-mating days [1-8]. There were no effects observed during pre-mating days [8-15], during the gestation period or the lactation periods. **Effects on sexual function and fertility parameters:** - **Males:** at ≥ 31mg/kg bw/day an ↑ in the relative epididymides weights and right relative gonad weight. There was a 7-12% ↑ in the left relative epididymides' weights (with statistical significance at 309 mg/kg/bw/day) and a 7-20% ↑ in the right absolute epididymides' weights (with statistical significance at ≥31 mg/kg/bw/). There was a 7-19% ↑ in the right relative gonad (with statistical significance at ≥ 103 mg/kg/bw/day). - study author reported that "s*permatogenesis was not affected in the high dose group."* - mean pre-coital time was ↑ by 76% and 172%	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		at 103 and 309 mg/kg bw/day, respectively. **- Females:** No information available for the oestrous cycle. - There were no effects observed on the dams' ability to get pregnant, fertility index, mean corpora lutea, pre-implantation loss, total and mean implantation sites. - There were no abortions observed, and no information reported for resorptions. For information on development related parameters, please refer to Table 13: Summary table of animal studies on adverse effects on development. For information on non-reproductive system related repeat dose parameters, please refer to Table 25: Summary table of animal studies on STOT RE.	

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

In an OECD 422 Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test, 10 CD® / Crl: CD(SD) rats per sex per dose were administered 0, 31, 103 and 309 mg/kg bw/day of *O*-isopropyl ethylthiocarbamate by oral gavage. Males were treated once daily, treatment commenced 2 weeks pre-mating and continued for at least 28 days. Females were treated once daily, treatment commenced 2 weeks pre-mating and continued until at least lactation day (LD) 3.

There were clinical signs of prone position in 1 female at 309 mg/kg bw/day on test days 1 and 2 and this dam was found dead on test day 3. Gastric lesions were observed during necropsy of this animal, the study authors reported this was a test substance related death, but no further information was provided. The dossier submitter (DS) considers the biological significance unclear in this case and considers if accidental gavage error had occurred. There is no data to support this death was test substance related. All other animals survived to scheduled sacrifice. In the *Anonymous, 2016* dose-range finding study for the main OECD 414 prenatal development toxicity (PNDT) study (*Anonymous, 2017a*), it is noted that there were no deaths in animals treated at either 300 or 500 mg/kg bw/day.

There was a reduction in motility observed in both male and females, at ≥ 103 mg/kg bw/day, during the pre-mating period, at 309 mg/kg bw/day during mating and in females at 309 mg/kg bw/day during gestation. Prone position was observed in both sexes at 309 mg/kg bw/day during pre-mating. At 309 mg/kg bw/day, salivation (graded slight to extreme) was observed in males during pre-mating and mating/post-mating period and in 6/9 females during gestation. In females, at 309 mg/kg bw/day, piloerection was observed during premating.

At 309 mg/kg bw/day, there was a statistically significant decrease in male mean body weight and mean body weight gain throughout the testing period i.e., from day 8 to day 43. The decrease in mean body weight was, 8.7%, 9.4%, 8.3%, 8.9% and 10.7% on days 8, 15, 22, 29 and 36 respectively. On day 43, the mean body weight (434g) in the highest treatment group was 12% lower compared to 493g in the control group. There was a 25% - 57% decrease in mean body weight gain throughout the testing period. During the last observation period (days 1 - 43), the mean body weight gain was 55g at 309mg/kg bw/day, 28% lower compared to 76g in the control group. There was also a statistically significant decrease (12%) observed in mean terminal body

weight in males at 309 mg/kg bw/day, the mean terminal body weight was 474, 471, 449 and 417g at 0, 31, 103 and 309 mg/kg bw/day, respectively.

In females at ≥ 103 mg/kg bw/day, there was a statistically significant decrease in mean body weight and mean body weight gain during the pre-mating and gestation periods and in terminal body weight.

There was a statistically significant decrease in mean body weight at ≥ 103 mg/kg bw/day on pre-mating day 8 (5.8% and 8.3% at 103 and at 309 mg/kg respectively) and at 309 mg/kg bw/day on pre-mating day 15 (12%). There was a statistically significant decrease in mean body weight gain at ≥ 103 mg/kg bw/day on pre-mating days 1 - 8 (71% and 117% at 103 and at 309 mg/kg, respectively). On pre-mating days 1 - 15, there was a negative statistically significant decrease in mean body weight gain (-139%) observed at 309 mg/kg bw/day, the mean body weight gain was 9.95, 8.44, 3.06 and -3.89g at 0, 31, 103 and 309 mg/kg bw/day, respectively.

During the gestation period there was a statistically significant decrease in mean body weight on gestation days (GD) 7 at 309 mg/kg bw/day (9.5%) and at ≥ 103 mg/kg bw/day on GD 14 (8.8% and 16% decrease at 103 and 309 mg/kg bw/day, respectively) and on GD 20 (26% and 33% decrease at 103 and at 309 mg/kg bw/day, respectively). On GD 20, the mean body weight was 396, 382, 291 and 264g at 0, 31, 103 and 309 mg/kg bw/day, respectively. There was a statistically significant decrease in body weight gain at 309 mg/kg bw/day on GD 0-7 (35%) and at ≥103 mg/kg bw/day on GD 0-14 (33% and 49% decrease at 103 and at 309 mg/kg, respectively) and on GD 0 - 20 (68% and 78% decrease at 103 and at 309 mg/kg, respectively). On GD 0 - 20 the mean body weight gain was 59, 54, 19 and 13g at 0, 31, 103 and 309 mg/kg bw/day, respectively.

The study author noted that the observed increase in post-implantation losses in 7/10 and 9/9 females at 103 mg/kg bw/day and 309 mg/kg bw/day, respectively, accounted for the decrease in body weight gain observed at ≥ 103 mg/kg bw/day.

During the lactation period, due to complete litter loss at 309 mg/kg bw/day, there was no body weight data available for females at this dose. There was no effect on mean body weight or mean body weight gain at ≤ 103 mg/kg bw/day.

Table 10: Female mean body weight (g) data measured during the gestation period in the Combined Repeated dose toxicity Study with Reproduction/Developmental toxicity screening test of IPETC (Danafloat™ 262) in Rats by Oral Gavage Administration. (*Anonymous 2012a*).

Dose (mg/kg bw/day)	0	31	103	309
Gestation Period	**Mean body weight (g)**			
GD 0	248.34±12.92	248.26 ±9.96	244.68 ±15.41	233.93 ±16.76
GD 7	279.39±10.99	279.70 ±10.50	267.34 ±15.22	**252.88 ±17.00****
GD 14	317.37±10.70	315.94 ±12.24	**289.94 ±17.76****	**266.87 ±14.96****
GD 20	395.48±19.47	382.08 ±22.26	**291.27 ±30.42****	**263.72 ±17.08****

****p < 0.01**

There was a statistically significant decrease (9.8% and 18% decrease at 103 and at 309 mg/kg, respectively) observed in female mean terminal body weight (297, 292, 268 and 244g at 0, 31, 103 and 309 mg/kg bw/day, respectively).

To further assess if the effect on body weight observed at ≥ 103 mg/kg bw/day was due to maternal toxicity or an intrauterine effect, the dossier submitter attempted to calculate the corrected mean maternal body weight changes in accordance with Annex I, 3.7.2.4.4 of CLP. However, it was not possible to calculate the corrected

maternal body weights at 309 mg/kg bw/day, as there was complete litter loss and therefore there was no gravid uterine weight or pup weight data available at this dose. Similarly, at 103 mg/kg bw/day, complete litter loss was observed in 7/10 dams and there was limited data (5 pup in 3 dams) available to calculate the corrected maternal body weight. The DS concluded that the data was insufficient to carry out an accurate comparison of the corrected maternal weight and thus was unable to conclude if the effects were related to maternal or intrauterine toxicity.

In males, at 309 mg/kg bw/day, there were statistically significant differences noted in food consumption during the pre-mating period. There was a statistically significant decrease (15%) in consumption on day 1 - 8 (60g, at 309 mg/kg bw/day compared to 71g in the control group) and a statistically significant increase (8%) in consumption on day 1 - 15 (63g at 309 mg/kg bw/day compared to 58g in the control group).

In females at ≥ 31 mg/kg bw/day, there was a statistically significant decrease in food consumption during the pre-mating period days 1 - 8. The mean food consumption was 71, 65 (8% reduction), 60 (15% reduction) and 51g (28% reduction) at 0, 31, 103 and 309 mg/kg bw/day, respectively. There were no effects observed in pre-mating days 8 - 15, during the gestation period for control or treated females or during the lactation periods for females at ≤ 103 mg/kg bw/day. There was no data collected for females at 309 mg/kg bw/day during the lactation period.

At 309 mg/kg bw/day, an increase in water consumption was observed in both sexes. 10/10 males had increased consumption during pre-mating, mating and post-mating periods. 4/9 females had increased consumption during the pre-mating and mating periods and 5/9 females had increased consumption during the gestation period. At the same concentration decreased water consumption was observed in 1/9 females during the pre-mating period. There were no abnormalities observed in control animals or treated animals at ≤ 103 mg/kg bw/day.

In males, there was an increase in the left and right relative epididymides weight, with statistical significance achieved in the right epididymis at ≥ 31mg/kg bw/day and in the left epididymis at 309 mg/kg bw/day. The left relative epididymides weights were 1.52, 1.62 (7% increase), 1.65 (8% increase) and 1.70 (12% increase) g/kg bw and the right relative epididymides weights were 1.43, 1.53 (7% increase), 1.60 (12% increase) and 1.71 (20% increase) g/kg bw at 0, 31, 103 and 309 mg/kg bw/day, respectively. The mean left and right relative epididymides weights of treated males were within the background data of the test laboratory (8 studies from 2012 - 2013, n = 80; left relative epididymis weight mean: 1.56 g/kg bw, range: 1.12 - 2.18 g/kg bw and right relative epididymis weight mean: 1.58 g/kg bw, range: 0.91 - 2.23 g/kg bw). At 309 mg/kg bw/day, interstitial lymphocytic infiltrate and mononuclear cell infiltration of the epididymis was observed in 3/5 and 5/5 males respectively compared to 2/5 and 3/5 in the control males. The DS noted that these histopathological findings at the 309 mg/kg bw/day were quite close to the background histopathological findings in the control males. It is also noted that there were no other significant histopathological findings, and the DS considers the biological significance of these effects to be indetermined.

In males, an increase in the right relative gonad weight was observed, with statistical significance at ≥ 103 mg/kg bw/day. The right relative gonad weight was 4.07, 4.37 (7% increase), 4.62 (14% increase) and 4.85 (19% increase) g/kg bw at 0, 31, 103 and 309 mg/kg bw/day, respectively. The right relative gonad weights of treated males were within the background data of the test laboratory (8 studies from 2012 - 2013, n = 80; mean: 3.92 g/kg bw, range: 1.31 - 5.07g/kg bw). There were no effects observed in female relative or absolute gonad weights. There were no histopathological findings reported in the male or female gonads.

Table 11: Reproductive organ weight data measured data measured during Combined Repeated dose toxicity Study with Reproduction/Developmental toxicity screening test of IPETC (Danafloat™ 262) in Rats by Oral Administration. (*Anonymous 2012a*).

Organ weights	Dose (mg/kg bw/day)							
	Males				Females			
	0	31	103	309	0	31	103	309
Absolute Epididymides (g) Left	0.721± 0.062	0.762± 0.046	0.733± 0.096	0.709± 0.032	-	-	-	-
Relative Epididymides (g/kg bw) Left	1.519± 0.134	1.618± 0.121	1.646± 0.293	**1.704± 0.140****	-	-	-	-
Absolute Epididymides (g) Right	0.677± 0.054	0.719± 0.049	0.716± 0.073	0.708± 0.056	-	-	-	-
Relative Epididymides (g/kg bw) Right	1.427± 0.118	**1.527± 0.090***	**1.602± 0.213***	**1.708± 0.207****	-	-	-	-
Absolute gonad Left (g)	2.133±0.369	2.064±0.124	2.084±0.106	1.988±0.191	0.071±0.021	0.070±0.013	0.061±0.010	0.053±0.016
Relative Gonad Left (g/kg bw)	4.539±1.095	4.386±0.344	4.661±0.393	4.779 ±0.522	0.237±0.067	0.239±0.053	0.228±0.049	0.220±0.071
Absolute gonad Right (g)	1.924±0.093	2.055±0.141	2.066±0.104	2.018±0.206	0.074±0.017	0.086±0.020	0.063±0.016	0.053±0.015
Relative Gonad Right (g/kg bw)	4.066±0.326	4.368±0.377	4.619±0.391*	4.854±0.561**	0.246±0.057	0.293±0.079	0.236±0.074	0.214±0.052

*** p < 0.05; **p < 0.01.**

There was no data on oestrous cycle reported. The study author reported that, *"spermatogenesis was not affected in the high dose group*," there was no raw data available in the study for the sperm parameters, so the DS could not assess this parameter.

There was an increase in pre-coital time observed at ≥ 103 mg/kg bw/day (76% and 172% at 103 and 309 mg/kg bw/day, respectively). The pre-coital time was 2.5, 2.7, 4.4 and 6.0 days at 0, 31,103 and 309 mg/kg bw/day, respectively. The pre-coital time range for the individual dams were 1 - 5 days, 1 - 4 days, 1 - 15 days and 1 - 20 days at 0, 31,103 and 309 mg/kg bw/day, respectively. At 103 mg/kg bw/day, 1/10 dams had a pre-coital time of 15 days and at 309 mg/kg bw/day, 2/10 dams had a pre-coital time of 15 and 20 days.

There was no effect on the number of pregnant females, or the fertility index observed for control or treated females.

There was no treatment-related effect on the mean corpora lutea, pre-implantation loss, though there was a small reduction noted in both total implantation sites and mean implantation sites. There were no abortions observed and there was no information reported for resorptions.

The most notable effect was on foetal development. This is elaborated in more detail in section 10.10.4 Adverse effects on development and summarised briefly here. There was 100% post-implantation loss at 309 mg/kg bw/day, compared to 3.7% in control dams and there were no mean live foetuses in this group compared to 14.7 in the control group (similar findings were observed in a dose range finding study (*Anonymous, 2016*) for the main OECD 414 PNDT study).

Table 12: Summary of reproductive parameters from the Combined Repeated dose toxicity Study with Reproduction/Developmental toxicity screening test of IPETC (Danafloat™ 262) in Rats by Oral Administration. (*Anonymous 2012a*).

Reproductive parameters				
Dose (mg/kg bw/day)	**0**	**31**	**103**	**309**
Number of pregnant dams	9	10	10	9
Pre-coital time	2.5	2.7	4.4	6.0
Fertility index (%)	90	100	100	100
Mean duration of gestation (days)	22.7	23.1	23.3	-
Mean corpora lutea	15.8	17.5	14.2	13.2
Pre-implantation loss (%)	3.5	7.4	4.0	5.1
Total implantation sites	137	160	137	113
Mean implantation sites	15.2	16.0	13.7	12.6

****= p<0.01**; -= No data for litters at 309 mg/kg bw/day

10.10.3 Comparison with the CLP criteria

In accordance with Annex I to the CLP Regulation, substances may be classified as category 1A reproductive toxicants if they are known "human reproductive toxicants". There is no epidemiological or human data available to demonstrate reproductive toxicity in humans of *O*-isopropyl ethylthiocarbamate; therefore, classification at category 1A is not warranted.

In accordance with Annex I to the CLP Regulation, substances may be classified as category 1B reproductive toxicants if presumed to be a human reproductive toxicant. The classification of a substance as category 1B reproductive toxicant *'…is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate'*. The DS does not consider the animal data provided in the OECD 422 study with *O*-isopropyl ethylthiocarbamate sufficient to demonstrate clear evidence of an adverse effect on sexual function and fertility and therefore, classification into category 1B is not proposed.

In accordance with Annex I to CLP Regulation, a substance may be classified as category 2 if it is a suspected human reproductive toxicant. The classification of a substance as category 2 reproductive toxicant is warranted *"…where there is some evidence from humans or experimental animals…of an adverse effect on sexual function and fertility, or on development…if deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification".* The DS notes that the OECD 422 study with *O*-isopropyl ethylthiocarbamate provides some evidence of other toxicity in P0 animals; decreases in paternal body weights and food consumption at 309 mg/kg bw/day, a decrease in maternal body weights and food consumption at ≥ 103 mg/kg bw/day, clinical effects in both sexes at ≥ 103 mg/kg bw/day. The increased mean pre-coital time and decreased mean corpora lutea and implantation sites at ≥ 103 mg/kg bw/day and effects on reproductive organ weights are not considered sufficient to demonstrate adverse effects on sexual function and fertility. This is further supported by the lack of adverse effects observed in the number of pregnant females, fertility index and pre-implantation loss. The DS does not consider the test substance a suspected human reproductive toxicant affecting sexual function and fertility, and therefore, classification in category 2 is not proposed.

10.10.4 Adverse effects on development

Table 13: 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
OECD 414; Prenatal developmental toxicity. Dose range study to registrant's key study. Rat Wistar Crl:WI (Han), female, 8 control animals and 4/treatment group. On GD 8, due to increased weight loss and clinical signs at 500 mg/kg bw/day, **the dosing regimen for the dams in this testing group was decreased to 300 mg/kg bw/day from GD 8 - 19.** GLP Compliant.	IPETC (tradename of *O*-isopropyl ethylthiocarbamate). Purity: 95.7% Oral gavage, once daily. 0, 300 and 500 mg/kg bw/day. Vehicle: corn oil. Females received treatment, daily from GD5 - GD19 Reliability: 1, reliable without restrictions.	-No mortality reported at any dose level. **500 mg/kg bw/day (up to GD8 only):** -**Females bw:** All females had ↑ weight loss on GD 6 or GD 7. On GD 6, 2/4 dams ↑ body weight loss (8.5% and 9.2%). On GD 7, 2/4 dams ↑ body weight loss (3.8% and 5.7%). **≥300 mg/kg bw/day (post GD8 combined highest dose groups):** - **Females at ≥ 300 mg/kg:** signs of weight loss (7/8) piloerection (8/8), disturbance of bedding (8/8), dehydration (1/8) and salivation (2/8). - **Females at ≥ 300 mg/kg bw/day:** ↓ mean body weight (29% on GD 20) and ↓ mean body weight gain (85% on GD 0 - 20) during the gestation period. There was a 10% ↓ in adjusted maternal weight - **Females at ≥ 300 mg/kg bw/day**: 24% ↓ in food consumption from GD 0 - 20. - **Females at ≥ 300 mg/kg bw/day**: 99% ↓ in uterus weight. - **Females at ≥ 300 mg/kg bw/day:** 100% post-implantation loss due to an ↑ in mean early resorptions (100%). -At **≥ 300 mg/kg bw/day**: There were no live foetuses, unable to compare total litter weight, mean foetal weight and sex ratio.	Anonymous, 2016

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
OECD 414; Prenatal developmental toxicity. Rat Wistar Crl: WI (Han), female, 24/control, and 3 mg/kg bw/day and 25/10 and 30 mg/kg bw/day. Deviations from OECD 414: -No thyroid parameters i.e., weight, hormone and/or histopathology data reported - No anogenital distance reported GLP Compliant.	IPETC (tradename of *O*-isopropyl ethylthiocarbamate). Purity: 95.7% Oral gavage, once daily. 0, 3, 10 and 30 mg/kg bw/day. Vehicle: corn oil. Females received treatment, daily from GD5 - GD19 Reliability: 1, reliable without restrictions.	**<u>Maternal Effects:</u>** -**Mortality:** No mortality observed. -**Clinical signs:** Alopecia was observed on various areas of the body at 0, 3, 10 and 30 mg/kg bw/day, respectively. There were no other clinical signs reported. - **Mean body weight**: at 3 mg/kg bw/day there was a 3.5%-4.6% ↑ in bw from GD 0-14. At 30 mg/kg bw/day there was a 4%-4.4% ↑ in bw from GD 0 - 8. No effect noted at 10 mg/kg bw/day. -There were no effects observed in mean body weight gain, terminal body weight on GD 20 or in adjusted maternal body weight. -**Reproductive parameters:** **-At 30 mg/kg bw/day:** slight ↑ in early resorptions (1.05% vs 0.76% in controls). -**At ≥ 10 mg/kg bw /day**: slight ↑ in post-implantation loss (7.1 – 8.2% vs 5.7% in controls). - No effect observed on number of pregnancies, late resorptions, number of implantations, pre-implantation loss or corpora lutea. **<u>Foetal Effects:</u>** - **At 10 mg/kg bw/day:** statistically significant ↑ in males born. - **At 30 mg/kg bw/day:** statistically significant ↓ in mean foetal weight. - **Malformations:** **≥ 3 mg/kg bw/day**: ↑ in incidences of rudimentary seventh right cervical rib with statistical significance at 30 mg/kg bw/day. - **≥ 10 mg/kg bw/day:** ↑ in incidence of misshapen humeri of the forelimb with statistical significance at 30 mg/kg bw/day. - - **At 30 mg/kg bw/day**; ↑ in incidences of rudimentary seventh bilateral cervical rib and short bilateral scapula. - **Variations:** - **≥ 3 mg/kg bw/day:** ↑ in incidences of incomplete ossification of the skull and bone (hyoid body, interparietal, bilateral parietal and supraoccipital), bent scapula (bilateral and right), ribs (fourteenth full right and wavy) and unossified forelimb (metacarpal). - **≥ 10 mg/kg bw/day:** ↑ in incidences of incomplete ossification of the skull (bilateral frontal and right zygomatic arch) and bent (bilateral) scapula.	Anonymous, 2017a

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		-**At 30 mg/kg bw/day**: ↑ in incidences of bent scapula and spine (bilateral and right), incomplete ossification of scapula (bilateral), incomplete ossification of sternebrae (1st, 2nd, 3rd, and 4th), unossified sternebrae (4th), misaligned sternebrae (3rd), and incomplete ossification of the forelimb (humeri). - **Craniofacial findings**: -A**t 10 mg/kg bw/day:** statistically significant ↑ in small pituitary gland. -**At 30 mg/kg bw/day:** ↑ in dilated third ventricle.	
OECD 422; Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test. GLP Compliant. Rat, CD® / Crl: CD(SD), male and female, 10/sex/group. Deviation from OECD 422: -10 females instead of 12-13. -No information on oestrous cycle monitoring. -Females were treated until lactation day (LD) 3. -Testing lasted for 59 days rather than 63. -There were no thyroid hormone assessments carried out. -There was no historical control data reported.	IPETC or Danafloat™262 (tradename of *O*-isopropyl ethylthiocarbamate). Purity: 95.7% Oral gavage, once daily. 0, 31, 103 and 309 mg/kg bw/day. Vehicle: Corn oil. Males were treated once daily, treatment commenced two weeks pre-mating and lasted for at least 28 days. Females were treated once daily, treatment commenced two weeks pre-mating and lasted until at least LD 3. Reliability: 2, reliable with restrictions.	For information on general toxicity and sexual function and fertility related parameters, please refer to Table 9: Summary table of animal studies on adverse effects on sexual function and fertility. **Developmental effects:** -**At 309 mg/kg bw/day:** there were no surviving pups so there is no data available for live birth index, viability index, number of runts or malformed pups. -**At ≥ 31 mg/kg bw/day:** statistically significant ↑ in post-implantation loss and statistically significant ↓ in % birth index. -**At ≥ 103 mg/kg bw/day:** statistically significant ↓ in the gestation index(by 3-fold and complete litter loss at 103 and 309 mg/kg bw/day, respectively), in total number of pups born, number of live pups and number of dams with live pups. -**At 103 mg/kg bw/day:** biologically significant ↓ in viability index. For information on non-reproductive system related repeat dose parameters, please refer to Table 25: Summary table of animal studies on STOT RE.	Anonymous, 2012a

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

Study #01: OECD TG 414 dose range finding study (*Anonymous, 2016*).

In a dose range finding study for the main prenatal development toxicity study, female, Wistar Crl:WI (Hans) rats were paired 2:1 with males. On GD 5, eight female rats were treated via oral gavage with control (corn oil) and four female rats per dose group were treated with test substance (300 or 500 mg/kg bw/day) daily until GD 19. Male rats were not treated.

Observations including body weight, food consumption and clinical signs were made during the testing period and on GD 20, sperm positive females were sacrificed and examined macroscopically for any structural abnormalities or pathological changes that may have affected pregnancy. The uterine contents of pregnant and non-pregnant females were examined.

On GD 6 and 7, females at 500 mg/kg bw/day had increased weight loss. Two dams lost 21g (8.5%) and 22g (9.2%) in body weight respectively between day 1 and 2 (GD 5 and GD 6) of dosing. The remaining two dams lost 9g (3.75%) and 15g (5.69%), respectively between day 1 and 3 (GD 5 and GD 7) of dosing. These dams also had significant clinical signs. As a result of these findings, the dosing concentration for these 4 dams was reduced to 300 mg/kg bw/day for the remainder of the study (i.e., from GD 8 - 19).

There was no mortality observed in any treatment group. Dams in the test substance treatment groups showed signs of weight loss (7/8) piloerection (8/8), disturbance of bedding (8/8), dehydration (1/8) and salivation (2/8).

The mean body weight and body weight gain was lower in the treated dams throughout the treatment period. On GD 20, the non-adjusted mean body weight (terminal body weight) was 235g in the treated dams, 29% lower compared to 332g in the control group. During the gestation period (GD 0 - 20), there was an 85% decrease observed in the non-adjusted mean body weight gain (15.5g) in the treated dams compared to the control group (108.5g). The adjusted mean maternal weight of the treated dams was slightly lower (10% decrease), it was 235g compared to 262g in controls.

Table 14: Female mean body weight (g) data measured during the gestation period in the dose range finding study for prenatal development toxicity study after repeated oral gavage administration in Wistar rats with IPETC. (*Anonymous 2016*).

Dose (mg/kg bw/day)	**0**	**≥300**
Gestation Period	**Mean body weight (g)**	
GD 0	223.67± 8.29	220.17± 6.91
GD5	239.33± 7.37	238.83±7.41
GD 8	248.33±10.09	225.33±6.80
GD11	260.33±8.87	232.83±6.37
GD 14	269.17±12.09	237.50±7.97
GD17	295.83±12.67	238.83±13.80
GD 20	332.17±12.89	235.67±6.12

Mean food consumption was also lower in the treated dams compared to the control dams throughout most of the treatment period, the mean food consumption from GD 0 - 20 was 24% lower in the treated dams (332g) compared in the control dams (435g).

Biologically significant observations were noted during examinations of the reproductive parameters in the treated dams. The mean uterus weight was biologically significantly lower in the treated females, 0.97g (1.4% of the control value) compared to 70.5g in the control dams. There was 100% post-implantation loss compared to 5.42% in control dams, there were no mean live foetuses in treated dams compared to 13 in the control dams, and the mean number of early resorptions was 10.50 (100 % implantation loss) in the treatment group compared to 0.5 in the control group. The mean number of corpora lutea and implantations sites were slightly decreased in treated dams (11.00 and 10.50 respectively) compared to the control dams (14.50 and 13.67

respectively). Due to complete implantation loss in the treated dams, it was not possible to make a comparison for the following parameters mean number of late resorptions and number of dead foetuses. There was no difference observed in the mean pre-implantation loss (5.8% in control and 6.8% in treated dams).

Table 15: Maternal reproduction parameters examined during the dose range finding study for prenatal development toxicity study after repeated oral administration in Wistar rats with IPETC. (*Anonymous 2016*).

Reproductive Parameter		
Dose (mg/kg bw/day)	**0** **N=8**	**≥300** **N=8**
Uterus Weight (g)	70.53±9.88	0.97±0.32
Mean number of corpora lutea	14.50±1.05	11.00±3.69
Mean no. of early resorptions per litter	0.50±0.55	10.50±3.89
Mean % of late resorptions per litter	0.17±0.41	Not applicable (100% early resorptions)
Mean number of implantation sites	13.67±1.51	10.50±3.89
Mean % pre-implantation loss	5.84±6.92	6.75±9.72
Mean % post-implantation loss	5.42±7.18	100±0.00

N= total number of animals examined.

There were no foetuses in the treated dams' group, and thus there was no data available for comparison of the sex ratio, mean foetuses' weight, number of foetuses, mean total litter weight and external examinations.

There were no external abnormalities reported for the control foetuses.

Table 16: Foetal parameters examined during the dose range finding study for Prenatal Development Toxicity Study after repeated oral administration in Wistar rats with IPETC. (*Anonymous 2016*).

Reproductive Parameter		
Dose (mg/kg bw/day)	**0** **N=8**	**≥300** **N=8**
Number of live foetuses	13.00±2.19	Not applicable (100% post-implantation loss)
Number of dead foetuses	0.00±0.00	Not applicable (100% post-implantation loss)
Total litter weight (g)	46.20±7.13	Not applicable (100% post-implantation loss)
Mean foetal weight (g)	3.57±0.20	Not applicable (100% post-implantation loss)
Sex ratio (M:F)	0.84±0.31	Not applicable (100% post-implantation loss)

N= total number of animals examined.

The authors of the dose range finding study concluded that based on the findings in the present study and increased post-implantation loss at 31 mg/kg bw/day in the OECD 422 study (*Anonymous, 2012a*), the dosing schedule for the main OECD 414 study (*Anonymous, 2017a*) was set at 3, 10 and 30 mg/kg bw/day.

Study #02: OECD TG 414 main study (*Anonymous, 2017a*).

In an OECD 414 prenatal developmental toxicity study, 24 Wistar Crl:WI (Han) female rats per dose group were administered 0, 3, 10 and 30 mg/kg bw/day of *O*-isopropyl ethylthiocarbamate via oral gavage from GD 5 - 19. There were no deaths observed. Alopecia was observed on various areas of the body; hindlimb, forelimb, abdomen, and dorsal back in 1/24, 2/24, 1/25 and 3/25 females at 0, 3, 10 and 30 mg/kg bw/day, respectively. There were no other clinical signs reported.

During the gestation period, there was a statistically significant but small increase in mean body weight at 3 mg/kg bw/day and 30 mg/kg bw/day. At 3 mg/kg bw/day, there was a statistically significant 3.5% - 4.6% increase from GD 0 - 14 and at 30 mg/kg bw/day there was a statistically significant 4% - 4.4% increase from GD 0 - 8. There was no difference in mean body weight observed at 10 mg/kg bw/day throughout the gestation period. The mean body weights were all within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), n = 416, mean: 324.18g, range: 245 - 384g). The study author reported that the increase in mean body weight was not dose-dependent and was not considered test substance related. The DS agrees with the original study author, the increase in mean body weight was not test substance related. There were no effects on mean body weight gain observed.

The study author calculated the adjusted maternal weight (271, 278, 274 and 279g at 0, 3,10 and 300 mg/kg bw/day, respectively), there were no treatment effects observed. The adjusted maternal weights were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), n = 416, mean: 266, range: 222 - 316g).

There were no effects on terminal body weight (335, 349, 337 and 339g at 0, 3,10 and 300 mg/kg bw/day, respectively) observed on GD 20.

Table 17: Maternal Mean body weight measured during the Prenatal Development Toxicity Study after repeated oral gavage administration in Wistar Rats with IPETC. (*Anonymous 2017a*).

Dose (mg/kg bw/day)	0	3	10	30
Gestation Period	**Mean body weight (g)**			
GD 0	225.90±9.44	**233.88±11.76***	232.29 ±11.59	**235.05±10.99***
GD 5	243.95 ±10.34	**253.04±12.64***	249.46 ±9.77	**254.24±11.26****
GD 8	246.90 ±14.84	**258.17±10.04****	253.92 ±11.29	**257.81±10.72****
GD 11	260.67 ±12.70	**271.96±12.74****	265.75±10.90	269.29±12.75
GD 14	271.24 ±15.23	**282.88±14.36***	275.04±12.10	279.95 ±13.14
GD 17	297.57 ±17.79	309.42±14.88	300.29±15.95	302.05 ±15.01
GD 20	335.14±23.94	348.75±17.26	336.75±20.63	338.81 ±18.01

*** p < 0.05; **p < 0.01**. N= 21, 24, 24 and 21 at 0, 3, 10 and 30 mg/kg bw/day, respectively.

There were no effects observed on food consumption.

There was no effect on the gravid uterine weight, the mean uterine weights were 64, 71, 63 and 60g at 0, 3, 10 and 30 mg/kg bw/day, respectively. The mean uterine weight was also within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), n = 416, mean: 58.4g, range: 0.5 - 109.5g). Other organ data was not reported.

At 30 mg/kg bw/day, there was a slight increase in the mean percentage of early resorptions (0.76%, 0.46%, 0.67% and 1.05% at 0, 3, 10 and 30 mg/kg bw/day, respectively). However, there was no statistical significance noted and all values were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), n = 416, mean: 0.65%, range: 0% - 8%).

There was a slight increase in post-implantation loss at ≥ 10 mg/kg bw/day, the mean post-implantation loss per litter was 5.7%, 3.5%, 7.1% and 8.2% at 0, 3, 10 and 30 mg/kg bw/day, respectively. There was no statistical significance noted and the value was within the historical control (HCD) range of the test laboratory (Rat Wistar, (2011 – 2015), n= 416, mean: 6.96%, range: 0% - 100%). The DS queries the validity of this historical control data range as there was 100% post-implantation loss in the absence of treatment. The mean value of the HCD indicates the 100% value is an outlier, or there is some problem with the animal test facility controls and is not representative of the whole HCD (if the HCD was normally distributed between 7 – 100% then a mean value of approximately 50% would be expected and the measurement of post-implantation loss in this instance would be meaningless). Comparing the historical control mean value (6.96%) to the concurrent control and treated dams, the DS concludes there is little evidence of a substance mediated effect at the doses tested. However, the DS acknowledges that this mean value for the HCD could be skewed high if it incorporated the high and unlikely value of 100%.

The DS notes that both findings (early resorptions and post-implantation loss), were not significantly increased compared to the control values and are within the general historical control range of the test laboratory.

There were no effects observed on the number of pregnancies, mean percentage of late resorptions, number of implantation sites, pre-implantation loss or corpora lutea.

Table 18: Maternal reproduction parameters examined during the Prenatal Development Toxicity Study after repeated oral administration in Wistar Rats with IPETC. (*Anonymous 2017a*).

Reproductive Parameter					
Dose (mg/kg bw/day)	**0**	**3**	**10**	**30**	**HCD**
Number of pregnant females (%)	21	24	24	21	Not reported
Mean % of early resorptions per litter	0.76±1.41	0.46±0.78	0.67±1.05	1.05±1.20	Mean=0.65 Range= 0-8
Mean % of late resorptions per litter	0.00±0.00	0.00±0.00	0.04±0.20	0.00±0.00	Mean=0.02 Range= 0-1
Mean number of implantation sites	12.14±2.90	13.13±1.57	11.79±2.47	12.38±1.86	Mean=11.11 Range= 1-17
Mean % pre-implantation loss	12.96±17.54	5.17±5.01	11.83±15.79	7.45±9.61	Mean=14.82% Range= 0-85.71%
Mean % post-implantation loss	5.68±9.66	3.47±5.95	7.14±13.39	8.23±8.68	Unreliable
Mean number of corpora lutea	14.00±2.93	13.88±1.83	13.33±1.37	13.38±1.47	Mean= 12.98 Range=1-20

N= 21, 24, 24 and 21 at 0, 3, 10 and 30 mg/kg bw/day, respectively. HCD; Rat Wistar, Study Date Range: 2011 – 2015, Number of animals in historical control group=416

There was a statistically significant decrease (8.6%) in mean foetal weight at 30 mg/kg bw/day. The mean foetal weights were 3.7, 3.7, 3. 7 and 3.4g at 0, 3, 10 and 30 mg/kg bw/day, respectively and all values were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), n = 416, mean: 3.67g, range: 2.85 - 5.69g). The DS notes that the decrease in mean foetal weight was < 10% in comparison to the control value, and this decrease is probably of little to no biological significance.

There was an apparent statistically significant increase observed in the number of males born at 10 mg/kg bw/day. The number of males were 5.5, 7.0, 5.5 and 5.4 at 0, 3, 10 and 30 mg/kg bw/day, respectively. The number of males born at 10 mg/kg bw/day was within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), n= 416, mean: 5.24%, range: 0 - 12%). The relevance is of little concern here as there is no apparent dose response. There were no effects observed on the number of females born (5.9, 5.7, 5.5 and 5.9 at 0, 3, 10 and 30 mg/kg bw/day, respectively). There was no statistically significant difference noted in the male to female ratio for the control and treatment groups (1.1, 1.6, 1.1 and 1.1 at 0, 3, 10 and 30 mg/kg bw/day, respectively).

There was a significant increase on male litter weight at 10 mg/kg bw/day, the male litter weight was 20.8, 26.2, 20.8 and 18.6g at 0, 3, 10 and 30 mg/kg bw/day, respectively. The male litter weights in the control and treatment groups were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), n = 416, mean: 19.52g, range: 0 - 58.30g). There were no effects observed on female litter weight or in total litter weight. The DS does not consider the increase in males born at 10 mg/kg bw/day biologically relevant

and the increase in male litter weight at the same dose was likely related to the increase in the number of males born.

There was no effect observed for litter size, mean number of total foetuses, or the number of live and dead foetuses per litter.

Table 19: Foetal parameters examined during the Prenatal Development Toxicity Study after repeated oral administration in Wistar Rats with IPETC. (*Anonymous 2017a*).

Foetal Parameter					
Dose (mg/kg bw/day)	**0**	**3**	**10**	**30**	**HCD**
Mean number of foetuses	11.38±2.84	12.67±1.66	11.08±2.80	11.29±1.55	Not reported
Live foetuses per litter	11.38±2.84	12.67±1.66	11.08±2.80	11.29±1.55	Mean=10.43 Range= 0-17
Dead foetuses per litter	0.00±0.00	0.00±0.00	0.00±0.00	0.05±0.00	Mean=0.01 Range= 0-1
No. of male foetuses	5.52±2.36	**7.00±1.14***	5.54±2.21	5.38±1.32	Mean=5.24 Range= 0-12
No. of female foetuses	5.86±2.06	5.67±1.86	5.54±1.91	5.90±1.92	Mean=5.22 Range= 0-12
Sex ratio	1.12±0.70	1.63±1.40	1.13±0.66	1.13±0.90	Mean=1.30 Range= 0-11
Mean foetal weight (g)	3.70±0.20	3.66±0.21	3.67±0.16	**3.38±0.28*****	Mean=3.67 g Range= 2.85-5.69 g
Total litter weight (g)	41.92±10.35	46.33±6.62	40.67±10.34	37.99±5.08	Mean=37.92 g Range= 0-85.30g
Male litter weight (g)	20.80±8.97	**26.23±5.67***	20.80±8.20	18.64±3.84	Mean=19.52 g Range= 0-58.30 g
Female litter weight (g)	21.12±7.41	20.10±6.75	19.86±6.96	19.35±6.19	Mean=18.40 g Range= 0-44.20 g

p<0.05; **p<0.01;p<0.001;** N= 21, 24, 24 and 21 at 0, 3, 10 and 30 mg/kg bw/day, respectively. HCD; Rat Wistar, Study Date Range: 2011 – 2015, Number of animals in historical control group=416

Teratogenicity:

There was an increase in the foetal incidence, litter incidence and number of affected litters with incidence of rudimentary seventh right and bilateral cervical rib (grey zone anomaly). The foetal incidence data for both parameters are outlined in Table 20. The litter incidence of rudimentary seventh right cervical rib was 0%, 18%, 10% and 25% and the number of affected litters was 0, 4, 2 and 5 at 0, 3, 10 and 30 mg/kg bw/day, respectively. Statistical significance was achieved at 30 mg/kg bw/day for number of affected litters. The litter incidence and the number of affected litters of rudimentary seventh right cervical rib at 3 and 30 mg/kg bw/day were outside the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 1.45%, litter incidence range: 0.0% - 14.3%, number of affected litters range: 0 - 2). The study author considered these incidences at 30 mg/kg bw/day '*adverse effects of treatment'* and, the DS considers the biological relevance of this finding indicative of a substance related effect even in the absence of a clear dose response. The incidences in the low dose group of 3 mg/kg bw/day are considered similar to normal background levels.
The litter incidence of rudimentary seventh bilateral cervical rib was 0%, 0%, 0% and 15% and the number of affected litters was 0, 0, 0 and 3 at 0, 3, 10 and 30 mg/kg bw/day, respectively. The number of affected litters at 30 mg/kg bw/day was outside the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 1.02%, litter incidence range: 0.0% - 18.2%, number of affected litters range: 0 - 2). The DS, considers these incidences biologically relevant.

There was an increase in the foetal and litter incidence of misshapen humeri (malformation), of the forelimb and there was a statistical increase in the number of affected litters with incidence at 30 mg/kg bw/day. The foetal incidence data is outlined in Table 20. The litter incidence was 0%, 0%, 5% and 25% and the number of affected litters was 0, 0, 1 and 5 at 0, 3, 10 and 30 mg/kg bw/day, respectively. There was no historical control data for this parameter reported. The study author considered these incidences at 30 mg/kg bw/day as '*adverse effects of treatment',* the DS considers that this increase in incidences may be indicative of a treatment related effect.

There was an increase in the foetal incidence, litter incidence and the number of affected litters with incidence of short bilateral scapula (variation), at 30 mg/kg bw/day. The foetal incidence data is outlined in Table 20. The litter incidence was 0%, 0%, 0% and 10% and the number of affected litters was 0, 0, 0 and 2 at 0, 3, 10 and 30 mg/kg bw/day, respectively. There was no statistical difference reported and the parameters were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 0.57%, litter incidence range: 0.0%-12.5%, the number of affected litters range: 0 - 2). The biological relevance of this finding is somewhat unclear but in general bent or shortened long bones in the rat are considered to be variations rather than malformations. Since the rat skeletal system undergoes further development and ossification postnatally these effects are typically characterised as being transient in nature with no long-term adverse effects on function or survival.

Table 20: Foetal skeletal anomalies or malformations observed during the Prenatal Development Toxicity Study after repeated oral administration in Wistar Rats with IPETC. (*Anonymous 2017a*).

Anomaly		Dose (mg/kg bw/day)				
		0	**3**	**10**	**30**	**HCD Litter incidence**
Scapula (B) short (variation)	Foetal incidence	0	0	0	2	Mean=0.57
	Litter incidence (%)	0.00	0.00	0.00	10.00	% Range=0-12.50%
	No of Litters with at least 1 Incidence	0	0	0	2	Range= 0-3
Cervical rib (7th) (B) rudimentary (grey zone anomaly)	Foetal incidence	0	0	0	4	% Mean=1.02%
	Litter incidence (%)	0.00	0.00	0.00	15.00	% Range=0-18.18%
	No of Litters with at least 1 Incidence	0	0	0	3	Range= 0-2
Cervical rib (7th) (R) rudimentary (grey zone anomaly)	Foetal incidence	0	4	2	6	% Mean=1.45%
	Litter incidence (%)	0.00	18.18	10.00	25.00	% Range=0-14.29%
	No of Litters with at least 1 Incidence	0	4	2	**5***	Range= 0-2
Forelimb humeri - misshapen (malformation)	Foetal incidence	0	0	1	9	No data
	Litter incidence (%)	0.00	0.00	5.00	25.00	
	No of Litters with at least 1 Incidence	0	0	1	**5***	

***p<0.05;** N= 20, 22, 20 and 20 at 0, 3, 10 and 30 mg/kg bw/day, respectively. HCD; Rat Wistar, Study Date Range: 2011 – 2015, Number of animals in historical control group=416. (B)= bilateral, (L)=left and (R)= right.

There was an increase in the foetal incidence, litter incidence and the number of affected litters in skull and bone variations; incomplete ossification in the frontal bilateral skull, hyoid body, interparietal bone in the skull, parietal bone in the bilateral skull, supraoccipital bone in the skull, and zygomatic arch in the right skull.

The foetal incidence data of incomplete ossification in the frontal bone bilateral skull is outlined in Table 21. The litter incidence of incomplete ossification in the frontal bone bilateral skull was 0%, 0%, 20% and 35% and the number of affected litters was 0, 0, 4 and 7 at 0, 3, 10 and 30 mg/kg bw/day, respectively, with statistical significance achieved at 30 mg/kg bw/day for the number of affected litters. Both parameters were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 12%, litter incidence range: 0.0% - 47.4%, number of affected litters range: 0 - 9).

The foetal incidence data of incomplete ossification of the hyoid body is outlined in Table 21. The litter incidence of incomplete ossification of the hyoid body was 5%, 9%, 5% and 25% and the number of affected litters was 1, 2, 1 and 5 at 0, 3, 10 and 30 mg/kg bw/day, respectively. There was no statistical significance achieved however, both parameters at 30mg/kg bw/day were outside the historical control range of the test

laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 2%, litter incidence range: 0% - 20%, number of affected litters range: 0 - 2).

The foetal incidence data of incomplete ossification of the interparietal bone in the skull is outlined in Table 21. The litter incidence of incomplete ossification of the interparietal bone in the skull was 55%, 55%, 75% and 85% and the number of affected litters was 11, 12, 15 and 17 at 0, 3, 10 and 30 mg/kg bw/day, respectively. Statical significance was not achieved, and both parameters were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 65%, litter incidence range: 10% - 91%, number of affected litters range: 0 - 20).

The foetal incidence data of incomplete ossification of the parietal bone in the bilateral skull is outlined in Table 21. The litter incidence of incomplete ossification of the parietal bone in the bilateral skull was 25%, 36%, 65% and 60% and the number of affected litters was 5, 8, 13 and 12 at 0, 3, 10 and 30 mg/kg bw/day, respectively. Statical significance was not achieved, and both parameters were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 49%, litter incidence range: 5% - 87.50%, number of affected litters range: 1-15).

The foetal incidence data of incomplete ossification of the supraoccipital bone in the skull is outlined in Table 21. The litter incidence of incomplete ossification of the supraoccipital bone in the skull was 35%, 59%, 55% and 80% and the number of affected litters was 7, 13, 11 and 16 at 0, 3, 10 and 30 mg/kg bw/day, respectively. Statical significance was achieved for the number of affected litters at 30 mg/kg bw/day. The test laboratory HCD for this parameter in 416 Wistar rat foetuses per litter during a time range of 2011 – 2015, was reported as a mean litter incidence of 39%, a litter incidence range of 14% - 100% and number of affected litters range of 1 - 23. The DS, has concerns related to the reliability of this HCD and there was no HCD raw data available to confirm the data's reliability.

The foetal incidence data of incomplete ossification of the zygomatic arch in the right skull is outlined in Table 21. The litter incidence of incomplete ossification of the zygomatic arch in the right skull was 5%, 0%, 5% and 35% and the number of affected litters was 1, 0, 1 and 7 at 0, 3, 10 and 30 mg/kg bw/day, respectively. At 30 mg/kg bw/day, statistical significance was achieved for the number of affected litters and both parameters were outside the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 1.4%, litter incidence range: 0% -13%, number of affected litters range: 0 - 1).

The DS considers most of these effects as variations and indicative of an adverse substance-related effect.

There was an increase in foetal incidence, litter incidence and the number of affected litters in scapula variations; bent bilateral and right scapula and spine, bent bilateral and right scapula and incomplete ossification of the bilateral scapula (outlined in table 21). There was no statistical significance achieved for any of these variations. The litter incidences of bent bilateral and right scapula and spine and incomplete ossification of the bilateral scapula was relatively low (5-15%), there was no historical data for these variations.

The foetal incidence data of both scapula parameters are outlined in Table 21. The litter incidence of bent bilateral scapula was 0%, 0%, 5% and 20% and the number of affected litters was 0, 0, 1 and 4 at 0, 3, 10 and 30 mg/kg bw/day, respectively. The litter incidence of bent right scapula was 5%, 4.6%, 10% and 25% and the number of affected litters was 1, 1, 2 and 5 at 0, 3, 10 and 30 mg/kg bw/day, respectively. The litter incidence and number of affected litters for the right scapula at ≥ 10 mg/kg bw/day and for the bilateral scapula at 30 mg/kg bw/day were outside the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 1.08%, litter incidence range: 0% - 5.3%, number of affected litters range: 0 - 1). These findings are indicative of treatment related effects.

At 30mg/kg bw/day, there was an increase in foetal incidence, litter incidence and the number of affected litters in sternebrae variations; incomplete ossification of the first, second, third and fourth sternebrae, unossified fourth sternebrae and misaligned third sternebrae (outlined in table 21). None of these incidences were observed in the concurrent control or other treatment groups. There was a low litter incidence (10 - 15%) and there was no statistical significance achieved. When comparing the findings to the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416), only the litter incidence (10%) and the number of affected litters (2) of misaligned third sternebrae were outside the historical control range of the test laboratory (litter incidence mean: 0.21%, litter incidence range: 0% - 4.6%, number of affected litters range: 0 - 1).

There was an increase in foetal incidence, litter incidence and the number of affected litters with rib anomalies such as, full right fourteenth rib and wavy ribs. The foetal incidence of full right fourteenth rib is outlined in Table 21. The litter incidence of full right fourteenth rib was 0%, 4.6%, 10% and 15% and the number of affected litters was 0, 1, 2 and 3 at 0, 3, 10 and 30 mg/kg bw/day, respectively. The litter incidence and number of affected litters were both within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 4.8%, litter incidence range: 0% - 18%, number of affected litters range: 0 - 4). Although statistical significance was not achieved and the findings are within the historical control range, the DS considers that the increase in incidence with increasing concentration, albeit minor indicative of a dose-related effect.

The foetal incidence of wavy rib is outlined in Table 21. The litter incidence of wavy ribs was 45%, 32%, 60% and 80% and the number of affected litters was 9, 7, 12 and 16 at 0, 3, 10 and 30 mg/kg bw/day, respectively. At 30 mg/kg bw/day, statistical significance was achieved for the number of affected litters. At the same dose, litter incidence of wavy ribs was outside the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 35%, litter incidence range: 0% - 73%, number of affected litters range: 0 - 16). This finding is indicative of a treatment effect at 30 mg/kg bw/day.

There was an increase in the foetal incidence, litter incidence and the number of affected litters in forelimb variations such as incomplete ossification of the humeri and unossified metacarpals. The foetal incidence of both parameters is outlined in Table 21.

At 30 mg/kg bw/day the litter incidence of incomplete ossification of the humeri was 10% and the number of affected litters was 4, compared to 0% and 0, respectively in the control and other treatment groups.

The litter incidence of unossified metacarpals was 10%, 36%, 20% and 60% and the number of affected litters was 2, 8, 4 and 12 at 0, 3, 10 and 30 mg/kg bw/day, respectively. At 30 mg/kg bw/day, statistical significance was achieved for the number of affected litters. Both parameters were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 14%, litter incidence range: 0% - 63%, number of affected litters range: 0 - 15). The DS considers the statistical increase of the number of affected litters indicative of a treatment effect at 30 mg/kg bw/day.

Table 21: Foetal skeletal variations observed during the Prenatal Development Toxicity Study after repeated oral administration in Wistar Rats with IPETC. (*Anonymous 2017a*).

Variations		Dose (mg/kg bw/day)				
		0	**3**	**10**	**30**	**HCD** **Litter incidence**
Skull frontal (B) Incomplete ossification	Foetal incidence Litter incidence (%) Litters with at least 1 Incidence	0 0.00 0	0 0.00 0	5 20.00 4	9 35.00 **7****	% Mean=11.96 % Range=0-47.37% Range= 0-9
Hyoid body Incomplete ossification	Foetal incidence Litter incidence (%) Litters with at least 1 Incidence	1 5.00 1	2 9.09 2	1 5.00 1	7 25.00 5	% Mean=2.13 % Range=0-20% Range= 0-2
Skull interparietal Incomplete ossification	Foetal incidence Litter incidence (%) Litters with at least 1 Incidence	28 55.00 11	24 54.55 12	43 75.00 15	62 85.00 17	% Mean=64.65 % Range=10-90.91% Range= 0-20
Skull parietal (B) incomplete ossification	Foetal incidence Litter incidence (%) Litters with at least 1 Incidence	14 25.00 5	13 36.36 8	27 65.00 **13***	31 60.00 12	% Mean=49.31 % Range=5-87.50% Range= 1-15
Skull supraoccipital incomplete ossification	Foetal incidence Litter incidence (%) Litters with at least 1 Incidence	12 35.00 7	23 59.09 13	19 55.00 11	34 80.00 **16****	Unreliable
Skull zygomatic arch (R) incomplete ossification	Foetal incidence Litter incidence (%) Litters with at least 1 Incidence	1 5.00 1	0 0.00 0	1 5.00 1	9 35.00 **7***	% Mean=1.42 % Range=0-12.50% Range= 0-1
Scapula (and spine) (B) bent	Foetal incidence Litter incidence (%) Litters with at least 1 Incidence	0 0.00 0	1 4.55 1	1 5.00 1	2 10.00 2	no data
Scapula (and spine) (R) bent	Foetal incidence Litter incidence (%)	0 0.00	0 0.00	0 0.00	5 15.00	no data

Variations		Dose (mg/kg bw/day)				
		0	**3**	**10**	**30**	**HCD Litter incidence**
	Litters with at least 1 Incidence	0	0	0	3	
Scapula (B) bent	Foetal incidence	0	0	1	4	% Mean=1.08
	Litter incidence (%)	0.00	0.00	5.00	20.00	% Range=0-5.26%
	Litters with at least 1 Incidence	0	0	1	4	Range= 0-1
Scapula (R) bent	Foetal incidence	1	1	2	6	% Mean=1.08
	Litter incidence (%)	5.00	4.55	10.00	25.00	% Range=0-5.26%
	Litters with at least 1 Incidence	1	1	2	5	Range= 0-1
Scapula (B) incomplete ossification	Foetal incidence	0	0	0	2	no data
	Litter incidence (%)	0.00	0.00	0.00	10.00	
	Litters with at least 1 Incidence	0	0	0	2	
Sternebrae (1st) incomplete ossification	Foetal incidence	0	0	0	2	% Mean=6.90
	Litter incidence (%)	0.00	0.00	0.00	10.00	% Range=0-87.50%
	Litters with at least 1 Incidence	0	0	0	2	Range= 0-7
Sternebrae (2nd) incomplete ossification	Foetal incidence	0	0	0	4	% Mean=19.06
	Litter incidence (%)	0.00	0.00	0.00	15.00	% Range=0-65.22%
	Litters with at least 1 Incidence	0	0	0	3	Range= 0-15
Sternebrae (3rd) incomplete ossification	Foetal incidence	0	0	0	4	% Mean=5.38
	Litter incidence (%)	0.00	0.00	0.00	15.00	% Range=0-40.00%
	Litters with at least 1 Incidence	0	0	0	3	Range= 0-3
Sternebrae (4th) incomplete ossification	Foetal incidence	0	0	0	3	% Mean=10.53
	Litter incidence (%)	0.00	0.00	0.00	10.00	% Range=0-58.33%
	Litters with at least 1 Incidence	0	0	0	2	Range= 0-14
Sternebrae (4th) unossified	Foetal incidence	0	0	0	2	% Mean=1.33
	Litter incidence (%)	0.00	0.00	0.00	10.00	% Range=0-11.11%

Variations		Dose (mg/kg bw/day)				
		0	**3**	**10**	**30**	**HCD Litter incidence**
	Litters with at least 1 Incidence	0	0	0	2	Range= 0-2
Sternebrae (3rd) misaligned	Foetal incidence	0	0	0	2	% Mean=0.21
	Litter incidence (%)	0.00	0.00	0.00	10.00	% Range=0-4.55%
	Litters with at least 1 Incidence	0	0	0	2	Range= 0-1
Rib (14th) (R) Full	Foetal incidence	0	1	2	3	% Mean=4.80
	Litter incidence (%)	0.00	4.55	10.00	15.00	% Range=0-18.18%
	Litters with at least 1 Incidence	0	1	2	3	Range= 0-4
Ribs wavy	Foetal incidence	18	13	23	62	% Mean=34.86
	Litter incidence (%)	45.00	31.82	60.00	80.00	% Range=0-72.73%
	Litters with at least 1 Incidence	9	7	12	**16***	Range= 0-16
Forelimb humeri incomplete ossification	Foetal incidence	0	0	0	7	No data
	Litter incidence (%)	0.00	0.00	0.00	10.00	
	Litters with at least 1 Incidence	0	0	0	4	
Forelimb metacarpal(s) unossified	Foetal incidence	2	14	7	21	% Mean=13.80
	Litter incidence (%)	10.00	36.36	20.00	60.00	% Range=0-62.50%
	Litters with at least 1 Incidence	2	8	4	**12***	Range= 0-15

p<0.05; **p<0.01;p<0.001;** N= 20, 22, 20 and 20 at 0, 3, 10 and 30 mg/kg bw/day, respectively. HCD; Rat Wistar, Study Date Range: 2011 – 2015, Number of litters in historical control group=392. (B)= bilateral, (L)=left and (R)= right.

There was an increase in foetal incidence, litter incidence and the number of affected litters of dilated third ventricle at 30 mg/kg bw/day. The foetal incidence are outlined in Table 22. The litter incidence was 9.5%, 8.3%, 8.3% and 23.8% and the number of affected litters was 2, 2, 2 and 5 at 0, 3, 10 and 30 mg/kg bw/day, respectively. Both parameters were within the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 24%, litter incidence range: 0% - 86%, number of affected litters range: 0 - 18).

There was an increase in foetal incidence, litter incidence and a statistically significant increase in the number of affected litters of small pituitary gland at 10 mg/kg bw/day. The foetal incidence are outlined in Table 22. The litter incidence was 0%, 8.3%, 33.3% and 4.8% and the number of affected litters was 0, 2, 8 and 1 at 0, 3, 10 and 30 mg/kg bw/day, respectively. Both parameters were outside the historical control range of the test laboratory (Rat Wistar, (2011 – 2015), number of foetuses/litters examined = 416, litter incidence mean: 1%,

litter incidence range: 0% - 13%, number of affected litters range: 0 - 3). The biological significance of this finding is uncertain.

Table 22: Foetal craniofacial findings observed during the Prenatal Development Toxicity Study after repeated oral administration in Wistar Rats with IPETC. (*Anonymous 2017a*).

Craniofacial findings		Dose (mg/kg bw/day)				
		0	**3**	**10**	**30**	**HCD Litter incidence**
Ventricle (3rd) dilated	Foetal incidence	2	2	4	6	% Mean=28.80 % Range=0-85.71% Range= 0-18
	Litter incidence (%)	9.52	8.33	8.33	23.81	
	Litters with at least 1 Incidence	2	2	2	5	
Pituitary gland small	Foetal incidence	0	2	8	1	% Mean=0.96 % Range=0-13.04% Range= 0-3
	Litter incidence (%)	0.00	8.33	33.33	4.76	
	Litters with at least 1 Incidence	0	2	**8****	1	

p<0.05; **p<0.01;p<0.001;** N= 21, 24, 24 and 21 at 0, 3, 10 and 30 mg/kg bw/day, respectively. HCD; Rat Wistar, Study Date Range: 2011 – 2015, Number of litters in historical control group=392. (B)= bilateral, (L)=left and (R)= right.

Study #03: OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (*Anonymous, 2012a*).

In the OECD 422 Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test, 10 CD® / Crl: CD(SD) rats per sex per dose were administered 0, 31, 103 and 309 mg/kg bw/day of *O*-isopropyl ethylthiocarbamate. Males were treated once daily, treatment commenced 2 weeks pre-mating and continued for at least 28 days. Females were treated once daily, treatment commenced 2 weeks pre-mating and continued until at least LD 3.

For other general toxicity effects and observations relevant for classification for sexual function and fertility seen in this study, please see section: 10.10.1 Adverse effects on sexual function and fertility.

At ≥ 31 mg/kg bw/day, there was a statistically significant increase in post implantation loss and a statistically significant decrease in the birth indices and both parameters were outside the background data of the test laboratory. The post-implantation loss was 3.7%, 28%, 97% and 100% at 0, 31,103 and 309 mg/kg bw/day, respectively and the test laboratory background data for post-implantation loss from 8 studies from 2012 - 2013 (n = 80) had a mean of 8%, within a range of 3.6 - 12.7%.

There was a statistically significant decrease in the gestation index at ≥ 103mg/kg bw/day, the gestation index was 100%, 90%, 30% and 0% at 0, 31, 103 and 309 mg/kg bw/day. The gestation indices at ≥ 103 mg/kg bw/day were outside the background data of the test laboratory (8 studies from 2012 - 2013, n = 80; mean: 98.6%, range: 89 - 100%). There was no data for mean duration of gestation for females at 309 mg/kg bw/day, due to complete litter loss at this dose. There was no effect observed at ≤ 103 mg/kg bw/day.

The birth indices were 99%, 75%, 3% and 0% at 0, 31,103 and 309 mg/kg bw/day, respectively, and the test laboratory background data for birth indices from 8 studies from 2012 – 2013 (n = 80), had a mean of 93%, within a range of 87 - 97%.

At ≥ 103 mg/kg bw/day, there was a statistically significant decrease in the total number of pups born (133, 122, 5 and 0 at 0, 31,103 and 309 mg/kg bw/day, respectively) and the number of dams with live pups (9, 9, 3 and 0 at 0, 31,103 and 309 mg/kg bw/day, respectively).

There were no pups at 309 mg/kg bw/day, thus there was no data available for the following parameters: live birth, viability index, number of runts and number of malformed pups at this concentration and the number of stillborn pups and the sex ratio of male: female pups on post-natal day 1 were both reported as 0.

There was a biologically significant decrease in viability index observed at 103 mg/kg bw/day, the viability index was 98%, 98% and 67% at 0, 31 and 103 mg/kg bw/day, respectively.

There were no effects observed in the number of stillborn pups, live birth index, number of runts, number of malformed pups and the sex ratio of male: female pups on post-natal day 1 at ≤ 103 mg/kg bw/day.

Table 23: Summary of developmental parameters from the Combined Repeated dose toxicity Study with Reproduction/Developmental toxicity screening test of IPETC (Danafloat™ 262) in Rats by Oral Administration. (*Anonymous 2012a*).

Developmental parameters				
Dose (mg/kg bw/day)	**0**	**31**	**103**	**309**
Total number of pups born	133	122	5**	0**
Post-implantation loss (%)	3.7	**27.6****	**97.0****	**100.0****
Gestation index (%)	100	90	**30****	**0****
Number of dams with live pups	9	9	**3****	**0****
Birth index (%)	99.4	**75.4****	**3.0****	**0****
Number of stillborn	1	5	0	0
Number of live pups	132	117	**5****	**0****
Live birth index (%)	99.4	97.8	100	-
Viability index (%)	98.0	98.4	66.7	-
Number of runts	0	0	0	-
Number of malformed pups	0	0	0	-
Sex ratio M:F on PND 1	69/63	61/56	3/2	0/0

****= p<0.01; -**= No data for litters at 309 mg/kg bw/day

As there was complete litter loss at 309 mg/kg bw/day, there was no data available for pup body weights during the post-natal development period. There were no effects observed for pup mean body weight on PND 1 and 4 at ≤ 103 mg/kg bw/day.

Table 24: Pup mean body weights in both sexes on PND 1 and 4 observed in the Combined Repeated dose toxicity Study with Reproduction/Developmental toxicity screening test of IPETC (Danafloat™ 262) in Rats by Oral Administration. (*Anonymous 2012a*).

Dose (mg/kg bw/day)	0	31	103	309
Post-natal development period Sex	Mean body weight (g)			
PND 1				
M	6.31±0.78	5.9±0.42	7.03±0.45	--
F	6.06±0.72	5.67±0.38	6.40±-	--
PND 4				--
M	9.08±1.40	9.03±0.75	7.60±-	
F	9.03±1.20	8.90±0.68	8.90±-	--

--= No data for 309 mg/kg bw/day, - = no Std.Dev for M/F pups at 103 mg/kg bw/day.

10.10.6 Comparison with the CLP criteria

In accordance with Annex I to the CLP Regulation, substances may be classified as category 1A reproductive toxicants if they are known "human reproductive toxicants". There is no epidemiological or human data available to demonstrate reproductive toxicity in humans for *O*-isopropyl ethylthiocarbamate; therefore, classification into category 1A is not warranted.

In accordance with Annex I to the CLP Regulation, substances may be classified as category 1B reproductive toxicants if presumed to be a human reproductive toxicant. The classification of a substance as category 1B reproductive toxicant *'…is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate'*.

In the available dose-ranging study to OECD 414 Prenatal development toxicity with *O*-isopropyl ethylthiocarbamate, there was a biologically significant decrease in uterine weight, a biologically significant increase in mean percentage of early resorptions and a radical increase in post-implantation loss at ≥ 300 mg/kg bw/day leading to total litter loss in all animals at ≥ 300 mg/kg bw/day and thus there were no pups available in the treatment groups available for examinations.

In the OECD 414 Prenatal development toxicity study with *O*-isopropyl ethyl thiocarbamate, the treatment regimen was decreased by 10 - 100-fold (relative to the dose-range finding study), and there were some, albeit minor indications of adverse effects on the pups, including a significant decrease in mean pup weight, a significant increase in a wide range of skeletal variations but also a significant increase in the malformation, misshapen humeri. Although the DS noted the biological significance of some of these findings was uncertain, the DS suspects these toxicological effects would be more pronounced if dams were dosed with a higher concentration than the top dose of 30 mg/kg bw/day.

The dossier submitter notes that the observed effects occurred in the absence of substantial maternal toxicity and are therefore not considered to be a secondary non-specific consequence to other toxic effects.

In the OECD 422, Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test with *O*-isopropyl ethylthiocarbamate, there was a statistically significant increase in post implantation loss and birth index at ≥ 31mg/kg bw/day and a statistically significant decrease in the total number of pups born and live pups at ≥ 103 mg/kg bw/day. There was also a biologically significant decrease in the viability index at 103 mg/kg bw/day. There was 100% litter loss at 309 mg/kg bw/day and no pups available for any assessments on PND 1, thus the viability index was 0%. The DS also notes that these effects were in the presence of maternal toxicity observed at both the mid and top dose groups as evidenced by statistically significant reductions in mean body weight gain during the pre-mating and gestation periods and body weight (uncorrected) during gestation. Due to insufficient data for gravid weight and pup weight at ≥ 103 mg/kg bw/day, it was not possible to carry out an accurate comparison of the corrected mean maternal body weights and it was not possible to conclude if the effects seen were solely due to maternal toxicity (i.e., unable to judge severity of maternal toxicity), or if they were a result of intrauterine toxicity. However, even in the presence of this maternal toxicity, the DS considers there is clear evidence of primary adverse effects on development, which are not considered to be secondary non-specific consequences of the maternal toxicity.

Based on the available information, the dossier submitter considers that classification into category 1B is warranted for effects on development.

Category 2 is not proposed based on the clear severity of the effects and evident dose response observed across multiple independent studies.

10.10.7 Adverse effects on or via lactation

In an OECD 422 Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test, at 309 mg/kg bw/day, there were no surviving pups and therefore there was no data available for the lactation period to be assessed at this dose. There was no information reported for the lactation index. There was no other data available in relation to effects on or via lactation. For further details see section: 10.10.4 Adverse effects on development.

10.10.8 Conclusion on classification and labelling for reproductive toxicity

Based on the available data, classification of *O*-isopropyl ethylthiocarbamate as a reproductive toxicant category 1B for effects on development is proposed.

10.11 Specific target organ toxicity-single exposure

Not evaluated as part of this dossier.

10.12 Specific target organ toxicity-repeated exposure

We understand that STOT RE is not under assessment in its own right in this present submission. The information and studies referred to are here purely to present supporting information for potential reproductive effects.

Table 25: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
OECD 408; Repeated Dose 90-day Oral Toxicity Study in Rodents. Rat Wistar Crl:WI (Han),male and female, 10/sex/group. GLP Compliant. Deviation from OECD 408: - There were no thyroid hormone assessments carried out.	IPETC (tradename of *O*-isopropyl ethylthiocarbamate). Purity: 95.7% Oral gavage, once daily. 0, 30, 100 and 300 mg/kg bw/day. Vehicle: Corn oil. Animals were treated 1/day for 90 days. Reliability: 1, reliable without restrictions.	**Top dose: 300 mg/kg bw/day:** **- Mortality: Females:** 1/10 euthanised on day 80 for ethical reasons. Cause of death was reported as a "*random event."* **-Clinical signs: Females:** 10/10 ataxia. **-Males bw:** ↓ in mean bw from day 8, with statistical significance achieved on days 71, 78 and 90. There was a 11% ↓ on day 90. ↓ in mean bw gain from day 1-8 with statistical significance achieved on days 1-8, 29-36, 43-50, 85-90 and on days 1-90. There was a 36% ↓ in mean bw gain on days 1-90. There was a 12% statistically significance ↓ in terminal bw. There were no effects seen in female mean bw, bw gain or terminal bw. **-Clinical chemistry:** **-Both sexes**: statistically significance ↑ **alkaline phosphatase** (AP) (males 81% ↑ and females 85% ↑). **-Males**: statistically significance ↑ in **alanine aminotransferase** (ALAT)(76%) and **total bilirubin** (TBIL) (113%). **- Females**: statistically significance ↑ in **total cholesterol** (39%) and ↓ in **aspartate-aminotransferase (ASAT)** (23%). **-Organ weights:** **-Males**: statistically significance ↓ in mean **absolute** organ weight; **prostate with seminal vesicles and coagulation glands** (24%), **brain** (9%) and **spleen** (29%) and mean **relative spleen weight** (11%). Statistically significance ↑ **relative kidney** (17%), **liver** (25%) and **heart** (7%) weight. **-Females:** statistically significance ↑ in mean **absolute and relative liver** (30% and 37%, respectively) and **absolute and relative ovary weight** (25% and 17%, respectively). **- Pathology**: **-Males**: 7/10 abnormal colour in kidneys. **- Histopathology:** **-Both sexes:** Centrilobular hepatocellular hypertrophy of the liver in 9/10 males and 8/10 females. Diffuse follicular cell hypertrophy/hyperplasia of the thyroid in 5/10 males and 4/10 females. **-Males:** Centrilobular hepatocellular vacuolation of the liver in 4/10 males.	Anonymous, 2017b

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
		Mid dose: 100 mg/kg bw/day: **-Clinical signs: Both sexes: ≥ 100 mg/kg bw/day;** all animals had the following clinical signs; salivation and disturbance of bedding. **- Organ weights:** **-Males: ≥ 100 mg/kg bw/day,** statistically significance ↓ in mean **absolute** (28% and 50% at 100 and 300 mg/kg bw/day, respectively) and **relative thymus weight** (30% and 50% at 100 and 300 mg/kg bw/day, respectively). **-Females: ≥ 100 mg/kg bw/day,** statistically significance ↓ in mean **relative thymus weight** (10% and 50% at 100 and 300 mg/kg bw/day, respectively). **Histopathology:** **-Both sexes:** Centrilobular hepatocellular hypertrophy of the liver in 4/10 males and 2/10 females. **-Males:** Diffuse follicular cell hypertrophy/hyperplasia of the thyroid in 2/10 males. **Low dose: 30 mg/kg bw/day:** **- Mortality: Males:** 1/10 died on day 77. Cause of death determined as a dosing accident. **-Organ weights:** **-Females**: **≥ 30 mg/kg bw/day,** statistically significance ↓ in mean **absolute thymus weight** (27% - 48%).	
OECD 422; Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test. GLP Compliant. Rat, CD® / Crl: CD(SD), male and female, 10/sex/group. Deviations from OECD 422: -10 females instead of 12-13. -No information on oestrous cycle monitoring. -Females were treated until lactation day (LD) 3. -Testing lasted for 59 days rather than 63.	IPETC or DanafloatTM262 (tradename of *O*-isopropyl ethylthiocarbamate). Purity: 95.7% Oral gavage, once daily. 0, 31, 103 and 309 mg/kg bw/day. Vehicle: Corn oil. Males were treated once daily, treatment commenced two weeks pre-mating and lasted for at least 28 days. Females were treated once daily, treatment commenced two weeks pre-mating and lasted until at least LD 3. Reliability: 2, reliable with	**Top dose: 309 mg/kg bw/day:** **-Female:** 1/10 died on test day 3. All other animals survived to scheduled sacrifice. **-Clinical signs:** **-Both sexes:** ↑ in salivation in males in pre-mating, mating and post-mating period and in females in gestation period. **Females**: piloerection during pre-mating period. **-Clinical Chemistry:** **-Males**: statistically significant ↑ in **bile acids** (9.2%), **total cholesterol** (27%), **total protein** (7%) and a statistically significant ↓ in c**hloride** (2%). **-Females:** statistically significant ↑ in **total cholesterol** (64%) and a non- statistically significant ↑ in **bile acids** (17.2%) and	Anonymous, 2012a

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
-There were no thyroid hormone assessments carried out. -There was no historical control data reported.	restrictions.	**alkaline phosphatase** (32%). **- Histopathology: Males:** interstitial lymphocytic infiltrate and mononuclear cell infiltration of the epididymis was observed in 3/5 and 5/5 males, respectively. **Organ weight:** **-Males:** statistically significant ↑ in **absolute liver weight** (24%) and a biologically significant ↓ in **absolute** (22%) **and relative** (11%) **spleen weight.** **-Females:** statistically significant ↓ in **absolute brain weight** (8%) and **relative right adrenal weight** (20%) a statistically significant ↑ in **relative heart weight** (18%) and **relative right kidney weight** (15%). A biologically significant ↓ in **absolute spleen weight** (17%). **<u>Mid dose: 103 mg/kg bw/day</u>:** **- Both sexes**; ↓ in motility from mating to gestation period and prone position during pre-mating period. **-Haematology:** **-Males**: statistically significant differences observed for haemoglobin content, red blood cells, haematocrit mean corpuscular haemoglobin concentration (MCHC). **Organ weight:** **-Males: ≥ 103 mg/kg bw/day:** statistically significant ↑ in **relative liver weight** (19% and 37% at 103 and 309 mg/kg bw/day, respectively), **absolute left kidney weight** (13% at 103 and 309 mg/kg bw/day), **relative left kidney weight** (24% at 103 and 309 mg/kg bw/day) and **relative right kidney weight** (16% and 22% at 103 and 309 mg/kg bw/day, respectively). **At 103 mg/kg bw/day:** statistically significant ↑ in **relative brain weight** (10%), **relative heart weight** (14%) and **absolute right kidney weight** (13%). **-Females: ≥ 103 mg/kg bw/day:** A statistically significant ↑ in **relative brain weight** (13% at 103 and 309 mg/kg bw/day) and in **absolute right adrenal weight** (40% at 103 and 309 mg/kg bw/day). A statistically significant ↓ in **absolute liver weight** (28% and 19% at 103 and 309 mg/kg bw/day, respectively). **At 103 mg/kg bw/day:** statistically significant ↓ in **relative liver weight** (20%).	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
		Low dose: 31 mg/kg bw/day: **Organ weight:** **-Males: ≥ 31 mg/kg bw/day:** ↑ in the left (7-12% with statistical significance at 309 mg/kg/bw/day) and right (7-20% with statistical significance at ≥31 mg/kg/bw/) relative epididymides weights and an ↑ (7-19% with statistical significance at ≥ 103 mg/kg/bw/day) in the right relative gonad weights. **At 31 mg/kg bw/day:** statistically significant ↑ in absolute brain (5%). **- Females: ≥ 31 mg/kg bw/day:** statistically significant ↓ in **absolute** (34-47%) **relative thymus weights** (30% at 31, 103 and 103 mg/kg bw/day). For information on body weight, food and water consumption and sexual function and fertility related parameters, please refer to Table 9: Summary table of animal studies on adverse effects on sexual function and fertility. For information on development related parameters, please refer to Table 13: Summary table of animal studies on adverse effects on development.	

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Study #01: OECD TG 408 Repeated Dose 90-day Oral Toxicity Study in Rodents. (*Anonymous, 2017b*).

In the OECD 408; Repeated Dose 90-day Oral Toxicity Study in Rodents, 10 Wistar Crl:WI (Han) rats per sex per dose group were administered 0, 30, 100 and 300 mg/kg bw/day, *O*-isopropyl ethylthiocarbamate. Males and females were treated 7 days/ week for 90 days.

There was one male death observed, at 30 mg/kg bw/day on treatment day 77 and 1 female death at 300 mg/kg bw/day, the animal being euthanised on treatment day 80 for ethical reasons. Neither of these deaths was considered treatment related.

Increased salivation and moving of bedding was observed in both sexes at ≥ 100 mg/kg bw/day and ataxia was observed in females at 300 mg/kg bw/day.

There was a decrease in mean body weight, mean body weight gain and terminal body weight in males at 300 mg/kg bw/day. The mean body weight was decreased from treatment day 8 and statistical significance was achieved on treatment days 71, 78 and 90. On treatment day 90, there was an 11% decrease in mean body weight at 300mg/kg bw/day, compared to the control males. There was a decrease in mean body weight gain from treatment days 1 - 8 with statistical significance achieved on days 1 - 8, 29 - 36, 43 - 50, 85 - 90 and 1 -

90. There was a 36% decrease in mean body weight gain over days 1 - 90. There was a small 12% statistically significance decrease in mean terminal body weight (368, 384, 355 and 323g at 0, 30, 100 and 300 mg/kg bw/day, respectively). There were no effects seen in female mean body weight, body weight gain or terminal body weight.

Adverse liver effects were indicated by a statistically significant increase observed in alkaline phosphatase (81% and 85% in males and females at 300 mg/kg bw/day, respectively), alanine aminotransferase (76%), total bilirubin (113%) (males at 300 mg/kg bw/day) and total cholesterol (39%) (females at 300 mg/kg bw/day). There was a statistically significant decrease in aspartate-aminotransferase (23%) observed in females at 300 mg/kg bw/day.

In males, there was a statistically significant decrease observed in mean absolute (28% and 50% at 100 and 300 mg/kg bw/day, respectively) and relative thymus (30% and 50% at 100 and 300 mg/kg bw/day, respectively) weights at ≥ 100 mg/kg bw/day. There was a statistically significant decrease observed in males' mean absolute prostate with seminal vesicles and coagulation glands (24%), absolute brain (9%) and absolute spleen (29%) weights and mean relative spleen weight (11%) at 300 mg/kg bw/day. At the same concentration, there was a statistically significant increase in males' mean relative kidney (17%), liver (25%) and heart (7%) weights. In females, there was statistically significant decrease in mean absolute thymus weight (27 – 48% at ≥30 mg/kg bw/day) and relative thymus weight (10% and 50% at 100 and 300 mg/kg bw/day, respectively) and a statistically significant increase in mean absolute and relative liver (30% and 37%, respectively) and absolute and relative ovary weight (25% and 17%, respectively, at 300 mg/kg bw/day).

In males at 300 mg/kg bw/day, there were 7/10 incidences of abnormal colour in the kidneys. There were no pathological effects observed in the reproductive organs.

There was further evidence that the liver is the target organ; histopathological changes were observed in the liver and thyroid in both sexes. Incidences of centrilobular hepatocellular hypertrophy of the liver was observed in 0/10, 0/10, 4/10 and 9/10 males and in 0/10, 0/10, 2/10 and 8/10 females at 0, 30, 100 and 300 mg/kg bw/day, respectively. Centrilobular hepatocellular vacuolation of the liver was also observed in 4/10 males at 300 mg/kg/bw/day. Incidences of diffuse follicular cell hypertrophy/hyperplasia of the thyroid was observed in 0/10, 0/10 2/10 and 5/10 males at 0, 30, 100 and 300 mg/kg bw/day, respectively and in 4/10 females at 300 mg/kg bw/day.

There were no effects observed in functional observation battery (FOB), food consumption, haematology and blood coagulation and urinalysis.

Study #02: OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (*Anonymous, 2012a*).

In the OECD 422 Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test, 10 CD® / Crl: CD(SD) rats per sex per dose were administered 0, 31, 103 and 309 mg/kg bw/day of *O*-isopropyl ethylthiocarbamate. Males were treated once daily, treatment commenced 2 weeks pre-mating and continued for at least 28 days. Females were treated once daily, treatment commenced 2 weeks pre-mating and continued until at least LD 3.

At 309 mg/kg bw/day 1/10 females was found dead on test day 3 and all other animals survived to scheduled sacrifice.

There was a reduction in motility observed in both sexes, at ≥ 103 mg/kg bw/day, during the pre-mating period, at 309 mg/kg bw/day during mating and in females at 309 mg/kg bw/day during gestation. Prone position was

observed in both sexes at 309 mg/kg bw/day during pre-mating. At 309 mg/kg bw/day, salivation (graded slight to extreme) was observed in males during pre-mating and mating/post-mating period and in 6/9 females during gestation. In females, at 309 mg/kg bw/day, piloerection was observed during premating.

There were statistically significant differences observed for haemoglobin content, red blood cells, haematocrit mean corpuscular haemoglobin concentration (MCHC) in males at 103 mg/kg/bw. There were no effects observed in females or in males at 0, 31 and 309 mg/kg bw/day.

At 309 mg/kg bw /day, there were statistically significant increase in total cholesterol (27% and 64% in males and females, respectively), bile acids (9% in males) and total protein (7% in males) and a statistically significant decrease in chloride (2% in males). At the same dose, there was a biologically significant increase in bile acids (18%) and alkaline phosphatase (32%) in females.

There were significant changes in absolute and relative organ weights observed in both sexes, statistically significant changes in absolute and relative brain weights, absolute and relative liver weights, relative heart and kidney weight and biologically significant changes in absolute and relative spleen weights. In males, there were significant changes observed in left and right relative epididymides weights, right relative gonad weights and absolute and relative kidney weights. In females, statistically significant changes were observed in absolute and relative adrenal and thymus weight and relative right kidney weights. For further details see Table 25: Summary table of animal studies on STOT RE. Further details on the organ weight effects observed in this study are provided in Annex I to this report.

In males at 309 mg/kg bw/day there were incidences of interstitial lymphocytic infiltrate (3/5) and mononuclear cell infiltration (5/5) of the epididymis observed.

10.12.2 Comparison with the CLP criteria

Not evaluated as part of this dossier. The information is provided as supportive information for the reproductive toxicity assessment (see section 10.10).

10.12.3 Conclusion on classification and labelling for STOT RE

Not evaluated as part of this dossier. The repeated dose toxicity studies are provided as information only for non-reproductive, repeated-dose effects.

10.13 Aspiration hazard

Not evaluated as part of this dossier.

11 ENDOCRINE DISRUPTION FOR HUMAN HEALTH

Not evaluated as part of this dossier.

12 EVALUATION OF AQUATIC HAZARDS UNDER CLP ANNEX I, 4.1

12.1 Rapid degradability of organic substances (CLP Annex I, 4.1)

Table 26: Summary of relevant information on rapid degradability

Method/ Study type	Test material and purity	Results	Remarks/Reliability	Reference
OECD 301D - Ready Biodegradability: Closed Bottle Test	Danafloat™ 262 (IPETC) Purity: 95.7%	Not considered readily biodegradable. Biodegradation was less than 60% of ThOD for the duration of this 28-day test.	GLP compliant study. Key study. Reliable without restriction. No deviations reported.	Anonymous, 2012b.

12.1.1 Ready biodegradability

The ready biodegradability of *O*-isopropyl ethylthiocarbamate, also known as Danafloat™ 262 (IPETC) was evaluated in a GLP compliant OECD 301D Ready Biodegradability Closed Bottle Test (*Anonymous, 2012b*). The inoculum used in this 28-day study was secondary effluent collected from a municipal wastewater treatment plant in Denmark, which predominantly receives domestic sewage. The medium was aerated to an initial oxygen concentration of approximately 9 mg O_2 per litre and inoculated with 0.5 ml secondary effluent per litre. An aqueous stock solution of the test product was prepared in Milli-Q water and then added to the test medium to achieve a nominal concentration of approximately 2.2 mg/L. The test was conducted at a temperature of 20.0 ± 0.3 °C. The pH at the start of the test was 7.3 - 7.5 and was 7.1 - 7.5 at the end of the test. As a toxicity control, the test product and reference substance were added to the inoculated medium at the same test concentrations as when tested individually, 2.2 mg/L and 2.0 mg/L, respectively. The degradation of the test product was expressed as the percentage Biological Oxygen Demand (BOD) of the Theoretical Oxygen Demand (ThOD).

For a ready biodegradability test to be considered valid, a value of ≥ 60% biodegradation must be obtained for the reference standard within a 14-day window (starting when the reference substance yields 10% biodegradation and ending 14 days later). A value of 72.6% biodegradation of the reference substance (sodium benzoate), was obtained on Day 14; therefore, the test is considered valid. The total oxygen consumption in the inoculum control was 0.56 mg O_2/L after 28 days, which is below the threshold of 1.5 mg O_2/L and the oxygen concentration in the test bottles was not at any time below 0.5 mg O_2/L. A test substance is considered readily biodegradable if a 14-day window value of ≥ 60% biodegradation is obtained within 28 days. For the test substance, Danafloat™ 262, at 2.2 mg/L, values of 3.3%, 2.4%, 6.7% and 2.1% biodegradation were obtained on Days 7, 14, 21 and 28, respectively; therefore, the test substance is not considered readily biodegradable at 2.2 mg/L.

The toxicity reference standard showed oxygen depletion, indicating that the test substance and reference materials were not toxic to the microbes in the inoculum (table 14, Annex I).

According to the criteria specified in OECD 301D, the test product is not readily biodegradable. The pass level for ready biodegradability (i.e., 60%) was not reached after 28 days, the reported degradation by this time being 2.1 %.

The dossier submitter considers this 28-day Ready Biodegradability Closed Bottle Test to be relevant and reliable without restriction. The validity criteria of the test, as stipulated in OECD 301D were fulfilled and,

under the conditions reported, Danafloat™ 262 (*O*-isopropyl ethylthiocarbamate, IPETC) is not considered readily biodegradable for classification purposes.

12.1.2 BOD_5/COD

No data available.

12.1.3 Hydrolysis

No data available.

12.1.4 Other convincing scientific evidence

No data available.

12.1.4.1 Field investigations and monitoring data (if relevant for the hazard class)

No data available.

12.1.4.2 Inherent and enhanced ready biodegradability tests

No data available.

12.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

No data available.

12.1.4.4 Photochemical degradation

No data available.

12.2 Environmental transformation of metals or inorganic metals compounds

No data available.

12.3 Environmental fate and other relevant information

No data available.

12.4 Bioaccumulation (CLP Annex I, 4.1)

No data available.

12.4.1 Estimated bioaccumulation

No data available.

12.4.2 Measured partition coefficient and bioaccumulation test data

The partition coefficient of *O*-isopropyl ethylthiocarbamate was determined experimentally in an OECD Partition Coefficient (n-octanol/water) study (OECD TG 117) which reported a partition coefficient value of Log K_{ow} 2.3 at 30°C (ECHA dissemination site, 2013).

Aquatic bioaccumulation studies to determine the bioconcentration of *O*-isopropyl ethylthiocarbamate in aquatic species are not available.

According to the CLP Regulation (EC) No. 1272/2008, "a cut-off value of Log $K_{ow} \geq 4$ is intended to identify only those substances with a real potential to bioconcentrate". For classification purposes, the Log K_{ow} value is used when an experimentally determined BCF is not available. As there are no experimental BCF studies reported in the registration dossier, the bioaccumulation potential of Danafloat™ 262 (IPETC) was determined by comparing the experimentally derived Log K_{ow} value with the CLP cut-off criteria. As the experimentally derived Log K_{ow} of 2.3 is less than the CLP cut-off value of ≥ 4 Danafloat™ 262 (IPETC) is considered to have a low bioaccumulation potential.

The dossier submitter considers *O*-isopropyl ethylthiocarbamate to have a low bioconcentration potential and is not considered bioaccumulative for classification purposes.

12.5 Acute aquatic hazard (CLP Annex I, 4.1)

Table 27: Summary of relevant information on acute aquatic toxicity for *O*-isopropyl ethylthiocarbamate (IPETC).

Method/ Study type	Test material and purity	Results[1]	Remarks/Reliability	Reference
OECD 203 Fish Acute Toxicity Test (96 hr Static renewal)	Danafloat™ 262 (IPETC) Purity: 95.7 % w/w Nominal concentrations: 0, 7.5; 15; 30; 60 and 120 mg/L	LC_{50} (96 hr, semi-static): 70.0 mg/L	GLP compliant study. Key study. Only partial chemical analysis was carried out on test concentrations. Reliable with restriction.	Anonymous, 2013a.
OECD 202 Acute toxicity to invertebrates (48 hr semi-static) *Daphnia magna*	Danafloat™ 262 (IPETC) Purity: 95.7 % w/w Nominal concentrations: 0; 2.0; 5.0; 10; 20; 50 and 100 mg/L.	LC_{50} (48hr) 54.67 mg/L (95% C.I. 21.26 – 425.19 mg/L)	GLP compliant study. Key study. Reliable without restriction.	Anonymous, 2013b.
OECD 201 Algal Growth Inhibition Test *Pseudokirchneriella subcapitata*	Danafloat™ 262 (IPETC) Purity: 95.7 % w/w Nominal concentrations: 0; 1.0; 2.0; 5.0; 10; 20; 50 and 100 mg/L.	70.25-hour E_rC_{50} of 20.7 mg/L (95% C.I. 19.3 to 22.3 mg/L). 70.25-hour E_yC_{50} of 3.2 mg/L (95% C.I. 2.9 to 3.8 mg/L).	GLP compliant study. Key study. Test not carried out for full 72-hours. Reliable, without restriction.	Anonymous, 2013c.

[1] All results are based on nominal concentrations.

12.5.1 Acute (short-term) toxicity to fish

The acute toxicity of *O*-isopropyl ethylthiocarbamate was assessed in one GLP compliant static renewal 96-hour test in accordance with test guideline OECD 203 (*Anonymous, 2013a*). The test was performed as a static

renewal test (i.e., all test media was renewed after 48 hours) with zebra fish commercially purchased in Denmark. The test was carried out at 23.4 ± 0.2 °C in a climate room with normal laboratory light having a daily light/dark period of 14:10 hours. Temperature, pH and dissolved oxygen were measured daily, before and after renewal of test medium and at the start and at the end of the test.

A 48-hour test with the reference substance potassium dichromate ($K_2Cr_2O_7$) was performed to verify the sensitivity of the test organisms. The reference test was performed at the following concentrations: 0 (control), 50, 100, 200, 300 and 400 mg/L. The test product was tested at the following nominal concentrations: 0 (control), 7.5, 15, 30, 60 and 120 mg/L. Ten fish were exposed to each concentration, mortality was recorded after 2, 24, 48, 72 and 96 hours. No mortality was observed in the control, or in the 7.5, 15, or 30 mg/L test concentrations at 96 hours. There was 10% mortality in the 60 mg/L test concentration and 100% mortality in the 120 mg/L at 96 hours. The study summary reported the 96-hour LC_{50} for IPETC as 70 mg/L, confidence intervals could not be determined.

The dossier submitter notes that only a sample of the test concentrations were analysed, and the range of concentrations as specified in the OECD guideline was not followed. However, as there was no mortality observed in the lower test concentrations (i.e., less than 30 mg/L) and as the test concentrations analysed (30, 60 and 120 mg/L) covered the observed mortality the reliability of the LC_{50} is not expected to be significantly compromised by this lack of analysis. The DS also notes that the nominal 30mg/L test concentration did not remain at 80% of the nominal concentration but as no mortality occurred at this concentration this does not affect the determination of the 96-hour LC_{50}. It was also noted that the 120 mg/L test concentration was only analysed at 0 hours and therefore actual concentration that the test species was exposed too for the duration of the test could not be confirmed. Based on analyses of other samples it is unlikely that the 120 mg/L test concentration varied more than 20% between the nominal and the measured concentration.

The dossier submitter considers this study to be valid and supports the use of the IPETC 96hr LC_{50} of 70 mg/L for classification of this trophic level.

12.5.2 Acute (short-term) toxicity to aquatic invertebrates

The acute toxicity of *O*-isopropyl ethylthiocarbamate to *Daphnia magna* was investigated in a GLP compliant study according to test guideline OECD 202 in a 48-hour semi-static test (*Anonymous, 2013b*). *O*-isopropyl ethylthiocarbamate was tested at the following nominal concentrations of the product: 0 (control), 2, 5, 10, 20, 50 and 100 mg/L. The chemical analysis showed a measured IPETC concentration of 80 - 95% of the estimated nominal concentration. As the test concentrations were maintained within ± 20% of the nominal concentrations, the statistical calculation was made using the nominal concentrations. Twenty animals were exposed at each concentration, five animals less than 24 hours old were transferred to each of 4 test beakers per concentration. The control group consisted of 30 animals, 6 beakers each containing 5 animals. After 24 hours of exposure, all test solutions were renewed. The number of immobile animals was recorded after 24 hours and 48 hours. On this basis, the effect concentrations (EC) were determined. Dissolved oxygen and pH were measured at 0 hours, at 24 hours before and after renewal of test solutions and at 48 hours. The test was run in a climate room at 20.1 ± 0.2 °C, in total darkness. In accordance with the test guideline, a 24-hour acute toxicity test on the reference substance potassium dichromate ($K_2Cr_2O_7$) was performed to check the sensitivity of the test animals. The validity criteria as specified in the methods are considered fulfilled. The study summary reported the 48-hour EC_{50} for IPETC as 60 mg/L with 95% confidence intervals of 52 – 73 mg/L.

The DS notes that immobility was only observed at the 100 mg/L test concentration at 24 hours while 5, 10, 20 and 95% immobility were observed at the 10, 20, 50 and 100 mg/L test concentrations at 48-hours. The study summary reported the 48-hour EC_{50} for IPETC as 60 mg/L with 95% confidence intervals of 52 – 73

mg/L, re-evaluation of the data could not reproduce this endpoint and the DS calculated the 48-hour EC_{50} for IPETC as 54.67 mg/L with 95% confidence intervals of 21.26 – 425.19 mg/L.

This finding does not impact the relevance or reliability of the test and the DS considers this study to be valid and supports the use of the IPETC 48hr EC_{50} of 54.67 mg/L for classification of this trophic level.

12.5.3 Acute (short-term) toxicity to algae or other aquatic plants

The acute toxicity of *O*-isopropyl ethylthiocarbamate to the freshwater algae *Pseudokirchneriella subcapitata*, was investigated according to OECD TG 201 (*Anonymous, 2013c*). The test was GLP compliant.

O-isopropyl ethylthiocarbamate was tested at the following nominal concentrations: 0 (control), 1. 2, 5, 10, 20, 50 and 100 mg/L. At the start of the test the cell density was approx. 8,300 cells/ml. The test design consisted of triplicate test flasks of each concentration, six controls (flasks with algae but no test product) and a blank of each concentration (flasks with test product but no algae). The algae were incubated for approximately 72 hours under continuous shaking at 23.1 ± 0.1 °C and constant illumination from a panel of fluorescent light with an intensity of approx. 60-120 µmol × m^{-2} × sec^{-1}.

To verify the tested concentrations, duplicate samples of each test concentration were taken at the initiation of the test, every 24 hours and at the termination of the test. According to the analytical test report, the chemical analysis of IPETC on test solutions with less than 2 mg/L IPETC cannot be considered valid as they were close to the limit of detection, no additional information was provided on why this was the case. The results from the IPETC analysis of the nominal test concentrations from 5.0 - 100 mg/L showed a measured IPETC concentration of 88 - 96% of the estimated nominal concentration. As the test concentrations 5.0 - 100 mg/L were maintained within ± 20% of the nominal concentrations, the same thing was assumed to apply for test concentrations below 5.0 mg/L, and the statistical calculation was based on the nominal concentrations.

Exposure of the algae to the test substance resulted in a 70.25-hours IPETC E_rC_{50} of 20.7 mg/L, with a 95% confidence interval of 19.3 to 22.3 mg/L, and a 70.25-hour IPETC E_yC_{50} of 3.2 mg/L, with a 95% confidence interval of 2.9 to 3.8 mg/L.

The DS notes that the duration of the test was 70.25 hours, no information on why the test duration was reduced was included in the report. The guideline allows for a change in the normal 72-hour duration provided that all the validity criteria are met. A re-evaluation of the raw data by the DS highlighted that the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures exceed 7%. The test report recorded the CV mean Growth Rate as 4.9% but this value could not be replicated and was determined by the DS to be 7.8% when analysed by ToxRat Professional. Although this is a breach of the validation criteria the DS does not believe that this minor deviation invalidates the test or that this has had a significant impact on the results of the test. During re-evaluation of the raw data the DS determined the E_rC_{50} and the E_yC_{50} to be broadly in line with those in the test report. The DS considers this study to be valid and supports the use of the 70.25-hour IPETC E_rC_{50} of 20.7 mg/L, with a 95% confidence interval of 19.3 to 22.3 mg/L, and a 70.25-hour IPETC E_yC_{50} of 3.2 mg/L, with a 95% confidence interval of 2.9 to 3.8 mg/L for classification at this trophic level.

12.5.4 Acute (short-term) toxicity to other aquatic organisms

No data available.

12.6 Long-term aquatic hazard (CLP Annex I, 4.1)

Table 28: Summary of relevant information on the chronic aquatic toxicity of *O*-isopropyl ethylthiocarbamate, (IPETC).

Method/ Study type	Test material and purity	Results[1]	Remarks/Reliability	Reference
OECD 201 Algal Growth Inhibition Test *Pseudokirchneriella subcapitata*	Danafloat™ 262 (IPETC) Purity: 95.7 % w/w Nominal concentrations: 0; 1.0; 2.0; 5.0; 10; 20; 50 and 100 mg/L.	70.25-hour NOEC of 1 mg/L. E_rC_{10} 1.4 mg/L (95% C.I. 1.2 – 1.7 mg/L)	Key study. Test not carried out for full 72-hours. Reliable, without restriction.	Anonymous, 2013c. ECHA dissemination site, 2024.

[1] Results are based on the nominal concentrations.

12.6.1 Chronic toxicity to fish

No data available.

12.6.2 Chronic toxicity to aquatic invertebrates

No data available.

12.6.3 Chronic toxicity to algae or other aquatic plants

Please refer to section 12.5.3. for full study summary details.

In the study by *Anonymous, (2012d)*, the chronic toxicity of *O*-isopropyl ethylthiocarbamate to the freshwater algae *Pseudokirchneriella subcapitata*, was investigated according to OECD TG 201. The test was GLP compliant, and no deviations were reported.

Exposure of the algae to the test substance resulted in a 70.25-hours IPETC NOEC of 1 mg/L for both growth rate and yield and an E_rC_{10} of 1.4 mg/L.

The dossier submitter (DS) notes that the duration of the test was 70.25 hours, no information on why the test duration was reduced was included in the report. The guideline allows for a change in the normal 72-hour duration provided that all the validity criteria are met. A re-evaluation of the raw data by the DS highlighted that the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures exceed 7%. The test report recorded the CV mean GR as 4.9% but this value could not be replicated and was determined by the DS to be 7.8% when analysed by ToxRat Professional. Although this is a breach of the validation criteria the DS does not believe that this minor deviation invalidates the test or that this deviation has had a significant effect on the results of the test.

The DS considers this study to be valid and although the E_rC_{10} is available the DS considers the NOEC to be the most relevant endpoint for classification as, in this case, the NOEC is the most protective endpoint.

The DS supports the use of the 70.25-hour IPETC NOEC of 1 mg/L for classification of this trophic level.

12.6.4 Chronic toxicity to other aquatic organisms

No data available.

12.7 Comparison with the CLP criteria (CLP Annex I, 4.1)

12.7.1 Acute aquatic hazard

O-isopropyl ethylthiocarbamate is not acutely toxic to fish, invertebrates, and algae. In accordance with Table 4.1.0 of the CLP Regulation, where adequate toxicity data for three trophic levels is available, the lowest available toxicity value between and within the different trophic levels (i.e., fish, crustacea, algae/aquatic plants) should be used to define the appropriate hazard category.

Table 29: Aquatic acute classification category for substances hazardous to the aquatic environment - a summary of the most sensitive end points for Danafloat™ 262 (IPETC).

Criteria for acute environmental hazards	Danafloat™ 262 (IPETC)	Conclusion
Category Acute 1: $LC_{50}/EC_{50} \leq 1$ mg/L	**Fish:** LC_{50} (96 hr, semi-static): 70.0 mg/L (Zebra fish) **Invertebrates:** LC_{50} (48hr) 54.67 mg/L (*Daphnia magna*) **Algae:** E_rC_{50} of 20.7 mg/L E_yC_{50} of 3.2 mg/L (*Pseudokirchneriella subcapitata*)	**Criteria for classification not fulfilled**.

The study data demonstrates *O*-isopropyl ethylthiocarbamate is not acutely toxic to fish, invertebrates or algae and therefore does not fulfil the criteria for classification as Aquatic Acute 1.

12.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

There is no data available on the bioaccumulation potential of *O*-isopropyl ethylthiocarbamate. The measured (as per OECD TG 117) octanol-water partition coefficient for *O*-isopropyl ethylthiocarbamate is 2.3 which falls below the cut-off criteria of Log $K_{ow} \geq 4$ and therefore can be considered to have a low bioaccumulation potential for classification purposes.

As summarised in section 12.1. and according to the criteria specified in OECD 301D, the test product *O*-isopropyl ethylthiocarbamate is not readily biodegradable. The pass level for ready biodegradability (i.e., 60%

of ThOD) was not reached after 28 days, the reported degradation was 35.1 % of the ThOD. The dossier submitter considers *O*-isopropyl ethylthiocarbamate not to be readily biodegradable for classification purposes.

Chronic toxicity data is only available for one trophic level, algae. The available chronic test data has demonstrated that *O*-isopropyl ethylthiocarbamate is toxic to this species and has a 70.25-hour NOEC of 1 mg/L.

Table 30: Aquatic chronic classification categories for substances hazardous to the aquatic environment - a summary of the most sensitive end points for Danafloat™ 262 (IPETC).

Criteria for chronic environmental hazards			**Danafloat™ 262 (IPETC)**	**Conclusion**
Rapid degradation	Half-life hydrolysis < 16 days Readily biodegradable in a 28-day test for ready biodegradability (> 70 % DOC removal or > 60 % theoretical oxygen demand, theoretical carbon dioxide)		Hydrolytically stable - biodegradation < 60% of ThOD.	**Not rapidly degradable**
Bioaccumulation	Log K_{ow} ≥ 4 BCF ≥ 500		Log K_{ow} 2.3 (measured)	**Low potential for bioaccumulation**
Aquatic toxicity	*Chronic toxicity:* Non-rapidly degradable substances: Cat. 1: EC_x or NOEC ≤ 0.1 mg/L Cat. 2: EC_x or NOEC ≤ 1 mg/L		Algae: NOEC 1 mg/L (70.25 hr growth rate) (*Pseudokirchneriella subcapitata)*	**Conclusion:** **Aquatic Chronic 2**

As outlined in Annex I, Table 4.1.0 of the CLP Regulation and as per the decision tree outlined in Figure 4.1.1 of the Guidance on the Application of the CLP Criteria when there is insufficient chronic toxicity data available for all three trophic levels, which is the case for *O*-isopropyl ethylthiocarbamate, the chronic data from one trophic level can be used to classify. The options in this case are to classify according to the criteria given in Table 4.1.0(b)(i) or 4.1.0(b)(ii) depending on information on rapid degradation, and if for the other trophic levels adequate acute toxicity data are available to classify according to the criteria given in Table 4.1.0(b)(iii). The classification must be the most stringent outcome of the two options.

In the case of *O*-isopropyl ethylthiocarbamate as the NOEC from the only available chronic study is 1 mg/L and as the substance is considered to be non-rapidly degradable, it fulfils the criteria for classification as Aquatic Chronic 2 as per Table 4.1.0(b)(i). As there is also adequate acute toxicity data available, classification is also possible as per the criteria given in Table 4.1.0(b)(iii). Following these criteria, as the available acute

toxicity endpoints fall within the range of > 10 to ≤ 100 mg/L, *O*-isopropyl ethylthiocarbamate would also fulfil the criteria for classification as Aquatic Chronic 3.

As classification must be the most stringent of the two options available, the substance *O*-isopropyl ethylthiocarbamate fulfils the criteria for classification as Aquatic Chronic 2, H411, *'Toxic to aquatic life with long lasting effects'* according to the CLP Regulation for non-rapidly degrading substances.

12.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR AQUATIC HAZARDS

In accordance with the CLP Regulation and based on the information as outlined above *O*-isopropyl ethylthiocarbamate does not fulfil the criteria for classification as Aquatic Acute 1. However, *O*-isopropyl ethylthiocarbamate does fulfil the criteria for classification as Aquatic Chronic 2: H411, *'Toxic to aquatic life with long lasting effects'* according to the CLP Regulation for non-rapidly degrading substances.

13 ENDOCRINE DISRUPTION FOR THE ENVIRONMENT

Not evaluated as part of this dossier.

14 PERSISTENT, BIOACCUMULATIVE AND TOXIC (PBT) OR VERY PERSISTENT, VERY BIOACCUMULATIVE (VPVB) PROPERTIES UNDER CLP ANNEX I, 4.3

Not evaluated as part of this dossier.

15 PERSISTENT, MOBILE AND TOXIC (PMT) OR VERY PERSISTENT, VERY MOBILE (VPVM) PROPERTIES UNDER CLP ANNEX I, 4.4

Not evaluated as part of this dossier.

16 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated as part of this dossier.

17 ADDITIONAL LABELLING

Not applicable.

18 REFERENCES

Anonymous (2012a), Combined Repeated Dose Toxicity Study with Reproduction/Developmental toxicity screening test of IPETC (Danafloat™ 262) in Rats by Oral Administration. (Unpublished report).

Anonymous. (2012b) Biodegradability of Danafloat™ 262 (IPETC) in the Closed Bottle Test (OECD 301D). (Unpublished report).

Anonymous. (2013a) Acute Toxicity of Danafloat™ 262 (IPETC) to zebra fish (Danio rerio) under static renewal conditions. (Unpublished report).

Anonymous. (2013b) Acute toxicity of Danafloat™ 262 (IPETC) in Daphnia magna. (Unpublished report).

Anonymous. (2013c) Algal growth inhibition test with Danafloat™ 262 (IPETC). (Unpublished report).

Anonymous (2016), Dose Range Finding Study for Prenatal Developmental Toxicity Study after Repeated Oral Administration in Wistar Rats with IPETC. (Unpublished report).

Anonymous (2017a), Prenatal Development Toxicity Study after repeated oral administration in Wistar Rats with IPETC. (Unpublished report).

Anonymous (2017b), 90-Day Repeated Dose Oral Toxicity Study in Wistar Rats with IPETC. (Unpublished report).

ECHA (2024). *O*-isopropyl ethylthiocarbamate REACH Registration dossier. (Accessed 2024). ECHA dissemination site .

19 ANNEXES

Annex I to the CLH report containing detailed study summaries for studies referenced in this report.