

## **Annex I to CLH report**

### **Proposal for Harmonised Classification and Labelling**

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

#### **Chemical name:**

**2-ethylhexanoic acid, monoester with propane-1,2-diol**

**EC Number: 285-503-5**

**CAS Number: 85114-00-7**

**Index Number: n.a.**

**Contact details for dossier submitter: Ministry of Health  
Paseo del Prado, 18-20  
28071 - Madrid  
Spain**

**Version number: 2      Date: 23 /05/2022**

## CONTENTS

<b>1</b>	<b>PHYSICAL HAZARDS</b> .....	<b>3</b>
<b>2</b>	<b>TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)</b> .....	<b>3</b>
<b>3</b>	<b>HEALTH HAZARDS</b> .....	<b>3</b>
3.1	ACUTE TOXICITY - ORAL ROUTE.....	3
3.2	ACUTE TOXICITY - DERMAL ROUTE .....	3
3.3	ACUTE TOXICITY - INHALATION ROUTE.....	3
3.4	SKIN CORROSION/IRRITATION .....	3
3.5	SERIOUS EYE DAMAGE/EYE IRRITATION .....	3
3.6	RESPIRATORY SENSITISATION .....	3
3.7	SKIN SENSITISATION.....	3
3.8	GERM CELL MUTAGENICITY .....	3
3.9	CARCINOGENICITY .....	3
3.10	REPRODUCTIVE TOXICITY .....	3
3.10.1	<i>Animal data</i> .....	3
3.10.2	<i>Human data</i> .....	25
3.10.3	<i>Other data (e.g. studies on mechanism of action)</i> .....	25
3.11	SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE.....	25
3.12	SPECIFIC TARGET ORGAN TOXICITY – REPEATED EXPOSURE.....	25
3.13	HAZARD CLASS NOT ASSESSED IN THIS DOSSIER. ....	25
3.14	ASPIRATION HAZARD.....	25
3.15	HAZARD CLASS NOT ASSESSED IN THIS DOSSIER. ....	25
<b>4</b>	<b>ENVIRONMENTAL HAZARDS</b> .....	<b>25</b>

## TABLES

TABLE 3–1: FEMALE BODY WEIGHT, GD 5-18 (ANONYMOUS, 2020).....	6
TABLE 3–2: SUMMARY OF FOOD CONSUMPTION (ANONYMOUS, 2020).....	7
TABLE 3–3: PREGNANT FEMALES, CORPORA LUTEA, IMPLANTATION SITES, IMPLANTATION LOSS (ANONYMOUS, 2020)	8
TABLE 3–4: PRE-IMPLANTATION LOSS, EARLY-, LATE- AND TOTAL RESORPTIONS (ANONYMOUS, 2020) .....	8
TABLE 3–5: POST-IMPLANTATION LOSS, DEAD AND LIVE FETUSES (ANONYMOUS, 2020).....	9
TABLE 3–6: FETAL WEIGHT (ANONYMOUS, 2020).....	9
TABLE 3–7: OVERVIEW OF THE FETAL VARIATION FINDINGS INCLUDING HISTORICAL LEVELS (ANONYMOUS, 2020)...	11
TABLE 3–7 (CONTINUED): OVERVIEW OF FETAL VARIATIONS FINDINGS, INCLUDING HISTORICAL LEVELS (ANONYMOUS, 2020).....	12
TABLE 3–8: OBSERVATIONS REGARDING MALFORMATIONS (ANONYMOUS, 2020).....	13
TABLE 3–9: OVERVIEW OF NOTABLE ABNORMALITIES IN FETUSES/LITTERS (TABLE PRODUCED FROM THE REPORTING IN TABLE 4.2, TABLE 4.4 AND TABLE 8.10 IN ANONYMOUS, 2020).....	14
TABLE 3–10: HISTORICAL CONTROL DATA FOR MALFORMATIONS (ANONYMOUS, 2020) .....	15
TABLE 3–11: BODY WEIGHT CHANGE - GROUP MEAN VALUES (G) FOR FEMALES DURING GESTATION (ANONYMOUS, 2016).....	18
TABLE 3–12: FOOD CONSUMPTION - GROUP MEAN VALUES (G/ANIMAL/DAY) - FOR FEMALES DURING GESTATION (ANONYMOUS, 2016).....	19
TABLE 3–13: LITTER DATA - GROUP MEAN VALUES ON DAY 20 OF GESTATION (ANONYMOUS, 2016) .....	20
TABLE 3–14: PLACENTAL, LITTER AND FETAL WEIGHTS - GROUP MEAN VALUES (G) ON DAY 20 OF GESTATION (ANONYMOUS, 2016).....	21
TABLE 3–15: OBSERVATIONS REGARDING MAJOR ANOMALIES (ANONYMOUS, 2016) .....	22
TABLE 3–16: OBSERVATIONS REGARDING MINOR SKELETAL ABNORMALITIES (ANONYMOUS, 2016) .....	23
TABLE 3–17: OBSERVATIONS REGARDING MINOR VISCERAL SKELETAL ABNORMALITIES AND NECROPSY FINDING (ANONYMOUS, 2016).....	24

## **1 PHYSICAL HAZARDS**

Hazard classes not assessed in this dossier.

## **2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)**

No data identified.

## **3 HEALTH HAZARDS**

### **3.1 Acute toxicity - oral route**

Hazard class not assessed in this dossier.

### **3.2 Acute toxicity - dermal route**

Hazard class not assessed in this dossier.

### **3.3 Acute toxicity - inhalation route**

Hazard class not assessed in this dossier.

### **3.4 Skin corrosion/irritation**

Hazard class not assessed in this dossier.

### **3.5 Serious eye damage/eye irritation**

Hazard class not assessed in this dossier.

### **3.6 Respiratory sensitisation**

Hazard class not assessed in this dossier.

### **3.7 Skin sensitisation**

Hazard class not assessed in this dossier.

### **3.8 Germ cell mutagenicity**

Hazard class not assessed in this dossier.

### **3.9 Carcinogenicity**

Hazard class not assessed in this dossier.

### **3.10 Reproductive toxicity**

#### **3.10.1 Animal data**

##### **3.10.1.1 Anonymous, 2020.**

##### ***Study reference:***

Anonymous (2020).

(See Annex II, confidential information).

##### ***Detailed study summary and results:***

##### ***Test type***

OECD Test Guideline 414, Oral (gavage) prenatal developmental toxicity study in mouse.

## ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

---

EPA OPPTS 870.3700 (Prenatal Developmental Toxicity Study).

GLP compliant.

Reliability of 1 (reliable without restriction).

### ***Test substance***

The test substance: 2-Ethylhexanoic acid, monoester with propane-1,2-diol

Degree of purity: see Annex II, confidential information.

### ***Test animals***

Mice /CrI: CD-1(ICR)/ female.

24 females/group (a total of 96 animals included).

Mated at age 8-10 weeks old, when weight at least 25 g.

Weighed between 27.1-37.5 g at the start of dosing.

### ***Administration/exposure***

Oral (gavage)

The substance was administered once daily from GD (Gestation Day) 6 to GD17 (animals were maintained until GD 18, on which they were sacrificed).

Vehicle: Corn oil was used both as the vehicle and control article.

High dose: 1000 mg/kg bw/day. Based on a previous dose range-finding study.

Intermediate-dose level: 300 mg/kg bw/day. Anticipated to represent a No observed Adverse Effect Level (NOAEL) for both maternal and fetal development.

Low dose: 100 mg/kg bw/day. Anticipated to represent a No Observed Effect level (NOEL) for both maternal and fetal development.

A control group of 24 animals was included.

A dose volume of 5 mL/kg was used. Dose volumes were based on individual body weights.

### ***Test substance formulation***

Formulations were prepared on a weekly basis (formulations of 10 and 200 mg/mL were previously found stable and homogenous for 16 days when refrigerated (2-8°C)). The test article was formulated as a suspension in corn oil following dispensary standard operating procedure and the formulation method. Formulations were stored and refrigerated (2-8 °C) in a sealed container protected from light.

One control animal was sacrificed on GD 1 due to poor health (squinting eyes; thin body condition; hunched posture; fast respiration and abnormal colour, yellow skin of the uro-genital area).

### ***Description of test design***

According to OECD TG 414.

Animals were individually housed.

At the time of mating, females were 8-10 weeks old and weighing at least 25 g. Mating was confirmed by the presence of a vaginal plug *in situ*, or other not further described evidence of mating, if necessary. The day on which mating was confirmed was noted as GD 0.

Animals were exposed once daily from GD 6 to 17 and sacrificed on GD 18.

## ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

---

### **Maternal examinations**

Daily physical examinations from the start of dosing until necropsy.

Post dose observations.

Individual body weight on GD 5, 6, 7, 8, 9, 12, 15, 17 and 18.

Food consumption on GD 6-7, 7-8, 8-9, 9-12, 12-15, 15-17 and 17-18 (unit: g/animal/day).

When sacrificed, animals were examined macroscopically.

Blood was drawn from the intracardiac region prior to necropsy and analysed for thyroid hormones.

Ovaries and uteri were removed and examined with following data being recorded: Pregnancy status; gravid uterus weight; body weight (recorded for adjusted gravid uterus weight calculations and not reported); number of corpora lutea; number and intrauterine position of implantations subdivided into live fetuses, early intrauterine deaths, late intrauterine deaths and dead fetuses.

The uterus of any apparently non-pregnant female was immersed in a 10% ammonium sulfide solution to reveal any evidence of implantation.

Thyroids from schedule sacrifice females were dissected, weighed post-fixation and retained in 10% buffered formalin.

### **Fetal examinations**

Live fetuses were sacrificed by a subcutaneous injection of sodium pentobarbitone. Dead fetuses were classified as those which appeared to have died shortly before necropsy.

Number of dead and live fetuses, body weight, sex determination and anogenital distance were recorded.

One half of the fetuses from each litter were dissected and examination of viscera and heads by the Wilson sectioning method were conducted.

The other half of the fetuses from each litter were examined for skeletal abnormalities in 50% glycerol.

Fetal abnormalities were classified as *malformations* when rare and/or potentially lethal defects, or as *variations* when commonly occurring as non-lethal abnormality.

### **Results and discussion**

In this GLP compliant OECD TG 414 study, groups of 24 female mice were administered *2-ethyl hexanoic acid, monoester with propane-1,2-diol* at dose levels of 0, 100, 300 or 1000 mg/kg bw/day by oral gavage administration, from day 6 until and including day 17, after mating.

Historical Control Data were included in the data analysis of fetal pathology and malformations.

Samples prepared for use on the first and last day of dosing were analysed for achieved concentration. The mean concentration on the first and last day of dosing was within 10% of the nominal concentration, indicating acceptable accuracy of the formulations.

#### **Maternal toxicity:**

Few clinical observations were recorded for all groups, including controls, of which none were substance related.

Corrected weight changes for animals administered 1000 mg/kg bw/day were 29% higher than control animals; however, statistical significance was not achieved. The non-significant changes of corrected weight changes were observed with no substance-related effects on gravid uterus weights, carcass weights, or weight changes, and the corrected weight changes were thus considered incidental and unrelated to the test substance.

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

Table 3-1: Female body Weight, GD 5-18 (Anonymous, 2020)

Test Article		Control	2-Ethylhexanoic acid, monoester with propane-1,2-diol				
Group	Dose level (mg/kg/day)	1	2	3	4		
		0	100	300	1000		
Data Presented in "g"							
Group/ Sex	Phase Day	GE					
		5	6	7	8	9	12
1/F	Mean	31.5	31.9	32.3	33.0	33.6	38.7
	SD	2.33	2.42	2.38	2.37	2.47	2.96
	N	23	23	23	23	23	23
2/F	Mean	31.8	32.1	32.6	33.2	34.1	39.8
	SD	2.54	2.49	2.53	2.70	2.83	3.35
	N	19	19	19	19	19	19
3/F	Mean	31.8	32.0	32.5	33.1	33.8	39.6
	SD	1.51	1.84	1.74	1.85	1.87	2.40
	N	24	24	24	24	24	24
4/F	Mean	31.1	31.5	32.0	32.4	33.2	39.1
	SD	2.59	2.44	2.48	2.62	2.74	3.22
	N	21	21	21	21	21	21
Statistics		X1	A	A	A	A	A

GE = Gestation  
X1 = No analysis required  
A = ANOVA and Dunnett's

Summary of Body Weight

Test Article		Control	2-Ethylhexanoic acid, monoester with propane-1,2-diol		
Group	Dose level (mg/kg/day)	1	2	3	4
		0	100	300	1000
Data Presented in "g"					
Group/ Sex	Phase Day	GE			
		15	17	18	
1/F	Mean	46.9	55.0	58.6	
	SD	4.05	5.49	6.37	
	N	23	23	23	
2/F	Mean	48.2	56.1	59.2	
	SD	4.36	6.30	7.19	
	N	19	19	19	
3/F	Mean	48.1	55.4	59.6	
	SD	3.35	4.35	5.03	
	N	24	24	24	
4/F	Mean	47.3	53.4	57.3	
	SD	4.05	5.00	4.88	
	N	21	21	21	
Statistics		A	A	A	

GE = Gestation  
A = ANOVA and Dunnett's

Statistically significant increase was observed in food consumption on GD 6-7 in animals administered 100 mg/kg bw/day. Significantly increased body weight changes were observed in animals administered 300 mg/kg bw/day on GD 9-12, and on GD 9-12 of animals administered 1000 mg/kg bw/day. At GD 15-17 a significantly decrease body weight change was found at 1000 mg/kg bw/day. However, these variations were transient, and thus considered unrelated to the test substance.

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–2: Summary of food Consumption (Anonymous, 2020)**

Test Article		Control	2-Ethylhexanoic acid, monoester with propane-1,2-diol				
Group	Dose level (mg/kg/day)	1	2	3	4		
		0	100	300	1000		
Data Presented in "g/animal/day" Interval X to X							
Group/ Sex	Phase Day	GE					
		6 - 7	7 - 8	8 - 9	9 - 12	12 - 15	15 - 17
1/F	Mean	5.1	6.4	5.4	5.4	5.7	7.1
	SD	1.57	2.07	1.35	0.97	0.97	1.19
	N	23	23	22	23	23	22
2/F	Mean	7.0*	6.9	6.5	5.9	5.2	6.9
	SD	2.68	3.65	2.25	1.46	1.31	1.29
	N	17	19	19	19	19	19
3/F	Mean	6.0	6.3	6.0	5.7	6.0	7.6
	SD	1.36	2.78	1.50	1.02	0.92	1.21
	N	24	24	24	24	24	24
4/F	Mean	5.9	6.2	6.0	5.9	6.2	7.6
	SD	1.36	1.40	2.76	1.98	1.04	2.17
	N	20	21	20	21	21	20
Statistics		AT	A	A	A	A	A

\* P<=0.05  
 \*\* P<=0.01  
 \*\*\* P<=0.001  
 GE = Gestation  
 A = ANOVA and Dunnett's  
 T = Rank-transformed data

Summary of Food Consumption

Test Article		Control	2-Ethylhexanoic acid, monoester with propane-1,2-diol		
Group	Dose level (mg/kg/day)	1	2	3	4
		0	100	300	1000
Data Presented in "g/animal/day" Interval X to X					
Group/ Sex	Phase Day	GE			
		17 - 18	6 - 18		
1/F	Mean	8.5	6.1		
	SD	2.70	1.00		
	N	23	21		
2/F	Mean	7.5	6.2		
	SD	2.19	0.94		
	N	19	17		
3/F	Mean	9.0	6.4		
	SD	2.17	0.91		
	N	24	24		
4/F	Mean	8.3	6.2		
	SD	2.52	0.70		
	N	21	18		
Statistics		A	A		

GE = Gestation  
 A = ANOVA and Dunnett's

No maternal toxicity related to the test substance was observed throughout the study up to the limit dose of 1000 mg/kg bw/day.

*Reproductive parameters:*

Litter data as assessed by live and dead fetuses, sex ratio, pup weight, mean corpora lutea, implantations, early, late and total resorptions, sex ratio and pre- and post-implantation loss, for animals receiving 100, 300 and 1000 mg/kg bw/day were not adversely affected by treatment. One animal administered 1000 mg/kg bw/day was pregnant on GD 18 but had no viable fetus. This was an isolated finding and thus considered

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

incidental. In all dose groups placental and litter weight were similar to controls and were not affected by the administration.

**Table 3–3: Pregnant females, corpora lutea, implantation sites, implantation loss (Anonymous, 2020)**

Group	Control	100 mg/kg	300 mg/kg	1000 mg/kg
<b>Summary of Cesarean Section Data - Excluding Females with No Viable Fetuses</b>				
Number of females pregnant at cesarean section	(n) 23	19	24	21
Corpora Lutea	(n) 23	19	24	21
	Mean 15.6	15.7	15.0	16.1
	SD 2.59	2.33	2.24	2.43
Implantation Sites	(n) 23	19	24	21
	Mean 14.1	14.6	14.3	14.8
	SD 2.55	2.34	1.94	1.37
Pre-implantation Loss	(n) 23	19	24	21
	Mean 1.5	1.2	0.7	1.3
	SD 1.38	2.43	0.95	1.85

**Table 3–4: Pre-implantation loss, early-, late- and total resorptions (Anonymous, 2020)**

Group	Control	100 mg/kg	300 mg/kg	1000 mg/kg
<b>Summary of Cesarean Section Data - Excluding Females with No Viable Fetuses</b>				
Pre-implantation Loss (%)	(n) 23	19	24	21
	Mean 9.33	6.48	4.35	7.38
	SD 8.590	12.406	5.695	8.471
Early Resorptions	(n) 23	19	24	21
	Mean 0.8	0.5	0.7	0.7
	SD 1.41	0.96	0.91	0.90
Late Resorptions	(n) 23	19	24	21
	Mean 0.3	0.2	0.1	0.3
	SD 0.45	0.42	0.45	0.73
Total Resorptions	(n) 23	19	24	21
	Mean 1.0	0.7	0.8	1.0
	SD 1.40	0.99	1.05	1.24



ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–5: Post-implantation loss, dead and live fetuses (Anonymous, 2020)**

	Group	Control	100 mg/kg	300 mg/kg	1000 mg/kg
<b>Summary of Cesarean Section Data - Excluding Females with No Viable Fetuses</b>					
Dead Fetuses	(n)	23	19	24	21
	Mean	0.0	0.3	0.0	0.0
	SD	0.00	1.16	0.00	0.22
Post-implantation Loss	(n)	23	19	24	21
	Mean	1.0	1.1	0.8	1.1
	SD	1.40	1.39	1.05	1.26
Post-implantation Loss (%)	(n)	23	19	24	21
	Mean	7.13	7.23	5.51	7.20
	SD	9.044	9.452	6.890	8.245
Live Fetuses	(n)	23	19	24	21
	Mean	13.3	13.5	13.4	13.7
	SD	2.53	2.63	1.74	1.55

**Table 3–6: Fetal weight (Anonymous, 2020)**

	Group	Control	100 mg/kg	300 mg/kg	1000 mg/kg
<b>Summary of Mean Fetal Data</b>					
Mean Fetal Weight (g)	(n)	22@	19	24	21
	Mean	1.359	1.347	1.367	1.164
	Adj Mean	1.354	1.352	1.365	1.167#H
	SD	0.1034	0.1053	0.0943	0.1026
Mean Weight - Male Fetuses (g)	(n)	21@ <sup>a</sup>	19	24	21
	Mean	1.387	1.378	1.399	1.194
	Adj Mean	1.382	1.382	1.397	1.197#H
	SD	0.1177	0.1131	0.1020	0.1076
Mean Weight - Female Fetuses (g)	(n)	21@ <sup>a</sup>	19	24	21
	Mean	1.333	1.319	1.340	1.128
	Adj Mean	1.328	1.324	1.338	1.131#H
	SD	0.1031	0.0924	0.0920	0.1000

@ Number examined reduced due to excluded data

#H = Dunnett Exact Homogeneous Test Significant: 0.001 level

<sup>a</sup> Sex not recorded for fetuses assigned for skeletal exams for Female M0001 (Group 1); therefore female excluded from mean calculations

*Fetal toxicity:*

*1000 mg/kg bw/day (group 4)*

At this dose level a statistically significant ( $p < 0.001$ ) lower mean fetal weight (adjusted for litter size) compared with controls was observed (males: -13%, females: -15%, combined: -14%). The adverse finding is regarded as a test substance related effect.

*Malformations:*

High incidences of fetal malformations of the head, skull and brain in litters at dose group administered 1000 mg/kg bw/day were recorded. Skull malformations were observed in a total of six fetuses versus none observed in the control group. However, the malformations observed in the skull of the fetuses did not show any statistical differences from the control group. Malformations of the brain were reported to be a disorganisation of the cranial cavity structures. Such malformations were observed in five fetuses of two

## ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

---

different litters, versus no malformations in controls and the other dose levels. However, the malformation of the brain was not statistically significant.

A significant difference between control and 1000 mg/kg bw/day was observed in:

- head malformation, exencephaly, (statistically significant difference was obtained in litters with  $p < 0.005$ ).

### *Variations:*

Furthermore, increased incidences of skeletal variations at 1000 mg/kg bw/day were observed, primarily unossified or incomplete ossification of the skeleton (in skull, sternebra, cervical central arch, thoracic centrum and limbs). Most of the observed incidences of skeletal variations were reported higher than Historical Control Data ranges or not previously observed in the Historical Control Data ranges to cover the period of the conducted study. Significant skeletal variations were only identified in fetuses maternally exposed to 1000 mg/kg bw/day and not when dosed 100 or 300 mg kg bw/day.

A significant difference between control and 1000 mg/kg bw/day was observed in:

- Bipartite ossification of the sternebra (statistically significant difference obtained in % litter with  $p < 0.05$ )
- Supernumerary rib present in the sternebra (statistical differences were obtained in both in % litter and % fetal with  $p < 0.05$  and  $p < 0.001$ , respectively)
- Unossified vertebra – cervical centrum (statistically difference was obtained both in % litter and % fetal, both with  $p < 0.001$ ).

Other notable fetal variations in 1000 mg/kg bw/day were observed in skull, sternebra, vertebra, forelimb and hindlimb.

### *300 mg/kg bw/day (group 3):*

No adverse developmental effects were reported.

### *100 mg/kg bw/day (group 2)*

Exencephaly and skull malformation were observed in one fetus. An incidence of such malformation was however reported within Historical Control Data, and together with the absence of a dose-response (no incidences of such malformations dosing 300 mg/kg bw/day), the incidence of malformation in the head observed was considered to be incidental for this one fetus.

Tabulated overviews of the observed fetal variations and malformations is given below in table 3-7, table 3-8 and table 3-9:

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–7: Overview of the fetal variation findings including historical levels (Anonymous, 2020)**

Variation	Control	0	100	300	1000	Historical control range Mean (SD) / range [No. affected]
<b>Skull</b>						
Hyoid - incomplete ossification	%Litter	0	0	0	10	0.80 (1.79) / 0 to 4 [1]
	%Fetal	0	0	0	1.47	0.17 (0.39) / 0 to 0.87 [1]
	Number of Litters/Fetus	0	0	0	2/2	
-Hyoid - unossified	%Litter	0	0	0	5	Not present in the historical control data
	%Fetal	0	0	0	2.38	
	Number of Litters/Fetus	0	0	0	1/3	
Mandible - incomplete ossification	%Litter	0	0	4	5	0.14 (0.3) / 0 to 0.68 [1]
	%Fetal	0	0	0.69	4.76	1 (2.24) 0 to 5 [1]
	Number of Litters/Fetus	0	0	1/1	1/6	
Parietal - incomplete ossification	%Litter	0	0	0	5	2 (2.74) / 0 to 5 [2]
	%Fetal	0	0	0	0.68	0.26 (0.37) / 0 to 0.79 [2]
	Number of Litters/Fetus	0	0	0	1/1	
Supraoccipital - incomplete ossification	%Litter	0	0	0	10	3 (4.47) / 0 to 10 [3]
	%Fetal	0	0	0	1.28	0.4 (0.6) / 0 to 1.36 [3]
	Number of Litters/Fetus	0	0	0	2/2	
Zygomatic arch - incomplete ossification	%Litter	0	0	0	5	Not present in the historical control data
	%Fetal	0	0	0	0.79	
	Number of Litters/Fetus	0	0	0	1/1	
<b>Sternebra</b>						
Bipartite ossification	%Litter	0	5	4	19*	6 (5.48) / 0 to 40 [6]
	%Fetal	0	0.88	1.04	3.74	1 (1.05) / 0 to 2.5 [8]
	Number of Litters/Fetus	0	1/1	1/2	4/5	
Incomplete ossification	%Litter	0	0	4	14	4.8 (3.56) / 0 to 10 [5]
	%Fetal	0	0	0.69	2.15	1.02 (0.63) / 0 to 1.45 [7]
	Number of Litters/Fetus	0	0	1/1	3/3	
Misaligned ossification centers	%Litter	13	21	8	33	46.2 (10.01) / 35 to 60 [48]
	%Fetal	1.71	4.00	1.22	5.81	10.32 (2.41) / 7.25 to 12.65 [71]
	Number of Litters/Fetus	3/3	4/5	2/2	7/8	
Supernumerary rib present	%Litter	57	32	71	90*	71.33 (14.57) / 55 to 83 [46]
	%Fetal	16.85	9.65	24.00	42.15#	34.18 (114.49) / 22.38 to 45.34 [139]
	Number of Litters/Fetus	13/25	6/14	17/39	19/62	

\* Fisher 1 tail Ascending Test significant at the 0.05 level.

# Wilcoxon rank Sum Test Significant at the 0.001 level.

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–7 (continued): Overview of fetal variations findings, including historical levels (Anonymous, 2020)**

Variation	Control	0	100	300	1000	Historical control range Mean (SD) / range [No. affected]
Vertebra - cervical arch						
Additional ossification site	%Litter	0	5	4	14	Not present in the historical control data
	%Fetal	0	0.88	0.69	2.72	
	Number of Litters/Fetus	0	1/1	1/1	3/4	
Vertebra - cervical centrum						
Unossified	%Litter	26	26	29	95**	Not present in the historical control data
	%Fetal	9.16	6.42	8.37	60.71#	
	Number of Litters/Fetus	6/15	5/8	7/14	20/87	
Vertebra - thoracic centrum						
Unossified	%Litter	0	0	0	14	0.8 (1.79) / 0 to 4 [1]
	%Fetal	0	0	0	6.24	0.12 (0.28) / 0 to 0.62 [1]
	Number of Litters/Fetus	0	0	0	3/9	
Forelimb						
Metacarpal - unossified	%Litter	0	0	0	10	2.8 (4.090) / 0 to 9 [3]
	%Fetal	0	0	0	2.83	2.01 (2.76) / 0 to 5.07 [5]
	Number of Litters/Fetus	0	0	0	2/4	
Phalanx - unossified.	%Litter	0	0	0	5	23.4 (24.28) / 0 to 55 [25]
	%Fetal	0	0	0	4.08	10.59 (12.19) / 0 to 25.52 [50]
	Number of Litters/Fetus	0	0	0	1/6	
Hindlimb						
Metatarsal - unossified	%Litter	0	0	0	10	20 (28.06) / 0 to 65 [21]
	%Fetal	0	0	0	2.15	9.21 (12.46) / 0 to 24.83 [45]
	Number of Litters/Fetus	0	0	0	2/3	

\*\* Fisher 1 tail Ascending Test significant at the 0.001 level.

# Wilcoxon rank Sum Test Significant at the 0.001 level.

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–8: Observations regarding malformations (Anonymous, 2020)**

Dose Group	Maternal animal ID	Fetus ID / Sex	Tissue	Malformation
0 (Control)	M0005	R8 Female	Mouth	Cleft Palate
	M0007	R5 Male	Eye	Partially opened - right
	M0016	R16 Male	Blood Vessel Blood Vessel	Aortic arch - absent Subclavian artery - malpositioned left, arising from descending aorta
100 mg/kg/day	M0108	L1 Female	Head	Exencephaly
			Skull	Frontal - misshapen - bilateral
			Skull	Interparietal - misshapen
			Skull	Interparietal - split
			Skull	Orbital socket - small - bilateral
			Skull	Parietal - misshapen - bilateral
			Skull	Presphenoid - absent
300 mg/kg/day	M0114	L2 Male	Eye	Partially opened - left
	M0202	L2 Male	Sternebra	Misshapen - 4, 5
	M0224	L4 Male	Limb Paw	Malrotated hindlimb - right ankle joint Polydactyly hindlimb - right - one additional digit

  

Dose Group	Maternal animal ID	Fetus ID / Sex	Tissue	Malformation		
1000 mg/kg/day	M0301	R10 Male	Brain	Cranial cavity structures - disorganized		
			Head	Exencephaly		
		R12 Female	Brain	Cranial cavity structures - disorganized		
			Head	Exencephaly		
	M0302	R10 Male	Mouth	Cleft palate		
	M0304	R10 Female	Eye	Open - bilateral		
			Head	Exencephaly		
			Skull	Frontal - misshapen - bilateral		
			Skull	Interparietal - misshapen		
			Skull	Orbital socket - small - bilateral		
			Skull	Parietal - misshapen - bilateral		
			Skull	Presphenoid - absent		
			Skull	Squamosal - misshapen - bilateral		
			Skull	Supraoccipital - split		
			M0309	L4 Female	Head	Exencephaly
					Skull	Frontal - misshapen - bilateral
					Skull	Interparietal - misshapen
	Skull	Orbital socket - small - bilateral				
	Skull	Parietal - misshapen - bilateral				
	Skull	Presphenoid - absent				
	Skull	Squamosal - misshapen - bilateral				
	Skull	Supraoccipital - absent				
	L6 Male	Brain			Cranial cavity structures - disorganized	
		Head			Exencephaly	
	L7 Male	Brain	Cranial cavity structures - disorganized			
		Eye	Open, left			
	R9 Female	R9 Female	Head	Exencephaly		
			Brain	Cranial cavity structures - disorganized		
			Eye	Open - bilateral		
	M0322	L6 Male	Head	Exencephaly		
			Rib	Fused - right, 7/8, proximal		
	M0324	L1 Male	Skull	Suture - sutural bone - large - interfrontal		
			Skull	Suture - wide - interfrontal		
	L3 Female	L3 Female	Eye	Open - bilateral		
			Head	Exencephaly		
			Mouth	Palate - high arched		
			Skull	Frontal - misshapen - bilateral		
			Skull	Interparietal - absent		
			Skull	Nasal - misshapen - bilateral		
			Skull	Orbital socket - small - bilateral		
Skull			Palatine - malpositioned - bilateral			
Skull			Palatine - small			
Skull			Parietal - misshapen - bilateral			
Skull			Presphenoid - absent			
Skull			Squamosal - misshapen - bilateral			
Skull			Supraoccipital - split			
R10 Male			R10 Male	Skull	Suture - sutural bone - large - interfrontal	
				Skull	Suture - wide - interfrontal	
R13 Female			R13 Female	Vertebra	Cervical arch misshapen - right - 2 - neural arch	
				Skull	Suture - wide - interfrontal	

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

Table 3-9 below gives a condensed overview regarding the abnormal findings.

**Table 3–9: Overview of notable abnormalities in fetuses/litters (table produced from the reporting in table 4.2, table 4.4 and table 8.10 in Anonymous, 2020)**

Group Parameter	Fetuses (observed/total no. examined fetus)				Litter (observed/total no. examined litters)			
	1	2	3	4	1	2	3	4
<b>Malformations</b>								
<b>Exencephaly %</b>	0/305 0	1/257 0.44	0/322 0	8/288 3.04*	0/23 0	1/19 5	0/24 0	4/21 19*
<b>Skull, various malformations %</b>	0/152 0	1/129 0.77	0/161 0	6/143 26	0/23 0	1/19 5.3	0/24 0	3/21 14
<b>Brain, disorganised cranial structures %</b>	0/153 0	0/128 0	0/161 0	5/145 3.97	0/23 0	0/19 0	0/24 0	2/21 10
<b>Variations</b>								
<b>Bipartite ossification of the sternebra %</b>	0/152 0	1/129 0.88	2/161 1.04	5/143 3.74	0/23 0	1/19 5	1/24 4	4/21 19*
<b>Supernumerary rib present in the sternebra %</b>	25/152 16.85	14/129 9.65	39/161 24	62/143 42.15**	13/23 57	6/19 32	17/24 71	19/21 90*
<b>Unossified vertebra – cervical centrum %</b>	15/152 9.16	8/129 6.42	14/161 8.37	87/143 60.71**	6/23 26	5/19 26	7/24 29	20/21 95**

\*p<0.05 \*\*p<0.001

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–10: Historical Control Data for Malformations (Anonymous, 2020)**

Tissue	Malformation	Fetal Incidences Mean (SD) Ranges	Number of Fetuses	Litter incidences Mean (SD) Ranges	Number of Litters
Mouth	Cleft Palate	0.42% (0.41) 0 to 1.02%	7	6.14 % (5.38) 0 to 14%	1 7
Eye	Partially opened	0.31% (0.4) 0 to 0.83%	6	2.86% (3.93) 0 - 10%	4
Head	Exencephaly	0.05% (0.13) 0 to 0.33%	1	0.57% (1.51) 0 to 4%	1
Skull	Orbital socket - small - bilateral,	0.14% (0.3) 0 to 0.68%	1	1% (2.24) 0 to 5%	1
Skull	Supraoccipital - absent	0.12% (0.28) 0 to 0.62%	1	0.8% (1.79) 0 to 4%	1
Limb	Malrotated hindlimb - right ankle joint	0.14% (0.38) 0 to 1%	3	1.43% (3.87) 0 to 10%	2
<i>Not present in the Historical control data 2016 to 2020:</i>					
Vertebra	Cervical arch misshapen - right - 2 - neural arch				
Brain	Cranial cavity structures - disorganised				
Rib	Fused - right - 7/8 - proximal				
Paw	Polydactyly hindlimb - right - one additional digit				
Skull	Frontal - misshapen - bilateral				
Skull	Interparietal - misshapen				
Skull	Interparietal - split				
Skull	Parietal - misshapen - bilateral,				
Skull	Palatine - malpositioned - bilateral				
Skull	Palatine - small				
Skull	Presphenoid - absent				
Skull	Squamosal - misshapen - bilateral				
Skull	Supraoccipital - split				
Skull	Suture - sutural bone - large - interfrontal				
Skull	Suture - wide - interfrontal				
Skull	Nasal - misshapen - bilateral				
Sternebra	Misshapen - 4, 5				
Eye	Open				
Mouth	Palate - high arched				
Blood Vessel	Aortic arch - absent				
Blood Vessel	Subclavian artery - malpositioned - left - arising from descending aorta				

*Substance related findings:*

Overall, the statistically significant increased incidences of malformations, skeletal variations and lower fetal weight, observed in fetuses from animals administered 1000 mg/kg bw/day were considered to be treatment related.

**3.10.1.2 Anonymous, 2016.**

*Study reference:*

Anonymous (2016).

## ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

---

(See Annex II, confidential information)

### ***Detailed study summary and results:***

#### ***Test type***

According to OECD Test Guideline 414 (Prenatal Developmental Toxicity Study).

GLP compliance.

Reliability of 1 (reliable without restriction).

#### ***Test substance***

Test material: 2-Ethylhexanoic acid, monoester with propane-1,2-diol

Analytical purity: 95.8% (data from public available REACH registration of the substance)

#### ***Test animals***

Rat/ Sprague-Dawley CrI:CD<sup>®</sup>(SD)/females.

20 females/group.

Age: 70 days on Day 0 of gestation.

Weight at study initiation: 220-290 g.

#### ***Administration/exposure***

Oral (gavage).

Dosing from Day 6 to Day 19 (inclusive) after mating, once daily.

0 (group 1), 100 (group 2), 300 (group 3), 1000 mg/kg bw/day (group 4); actual doses.

Vehicle: corn oil.

Dose volume: 5 mL/kg.

Concentration in vehicle: 0, 20, 60 or 200 mg/mL.

Formulations from 10 mg/mL to 200 mg/mL were stable for up to 1 day at ambient temperature (nominally +21°C) and 16 days refrigerated (nominally +4°C).

#### ***Description of test design:***

According to OECD TG 414.

Cohoused with M/F ratio per cage: 1:1 with identified stock males

No pre-mating exposure.

Animals exposed from GD 6 to 19 (inclusive)

Animals sacrificed on GD 20

#### ***Maternal examination:***

Cage side observations at least twice daily. Detailed clinical observations GD Days 0, 5, 12, 18 and 20. Body weight measurement GD 0,3,6-20. Detailed necropsy and full macroscopic examination of the tissues were performed. All external features and orifices were examined visually. Based on observations required tissue samples preserved in appropriate fixative.

Ovaries and uterine content examined after termination including gravid uterus weight, number of corpora lutea, number of implantations, number of early resorptions and number of late resorptions.



## ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

---

### *Fetal examinations:*

Number of dead and life fetuses, M/F ratio, fetal weight, external examinations, soft tissue examinations, skeletal examinations (no head examinations).

### **Results and discussion**

In this GLP compliant OECD TG 414 study, groups of 20 female Sprague Dawley rats were administered 2-ethyl hexanoic acid, monoester with propane-1,2-diol at dose levels of 0, 100, 300 or 1000 mg/kg bw/day by oral gavage administration, from day 6 and including day 19 after mating.

### *Maternal toxicity:*

All females were pregnant. There were no signs at routine examination that could be associated with treatment and no signs were observed in association with dose administration. Body weight, gravid uterine weight, food consumption and macroscopic evaluation were not adversely affected by treatment up to 1000 mg/kg bw/day when compared with control animals. At 1000 mg/kg bw/day, slight mean body weight loss was recorded during days 6-7 of gestation and mean food consumption was slightly low during days 6-9.

### *Reproductive parameters:*

Litter data as assessed by mean corpora lutea, implantations, early, late and total resorptions, sex ratio and pre- and post- implantation loss, for animals receiving 100, 300 and 1000 mg/kg bw/day, were not adversely affected by treatment. Placental and litter weight were similar with controls and were not affected by the administration.

### *Fetal toxicity:*

#### *1000 mg/kg bw/day (group 4)*

Male, female and overall fetal weights were statistically significantly lower when compared with controls. At this level there were two fetuses in two litters with the major abnormality short/threadlike tail. There was an increased incidence of a wide spectrum of minor abnormalities/skeletal variants: large nasofrontal suture; thoracic vertebral abnormality; short supernumerary cervical rib and 14th rib; delayed/incomplete ossification/unossified cranial centres, cervical, thoracic and sacral caudal vertebrae, sternebra, pelvic bones, metacarpals/metatarsals and a decrease in ossified cervical vertebral centra; variation in lens shape; small/absent lobe of thyroid; partially undescended lobe of thymus; small/absent renal papilla and dilated ureter when compared with concurrent control and Historical Control Data with the exception of delayed/incomplete ossification/unossified cervical vertebrae.

According to the authors of the test report these findings indicate a treatment related disturbance of development which is potentially adverse.

#### *300 mg/kg bw/day (group 3)*

At 300 mg/kg bw/day there was an increased incidence of the minor abnormalities, large nasofrontal suture; thoracic vertebral abnormality; delayed/incomplete ossification/unossified thoracic vertebrae and a decrease in ossified cervical vertebral centra when compared with concurrent control and Historical Control Data with the exception of delayed/incomplete ossification/unossified thoracic vertebrae.

According to the authors of the test report these findings were considered not to represent an adverse effect on fetal development.

#### *100 mg/kg bw/day (group 2)*

At 100 mg/kg bw/day there was an increased incidence of the minor abnormalities, large nasofrontal suture and variation in lens shape, compared with concurrent control and Historical Control Data. According to the authors of the test report these findings are considered not to represent an adverse effect on fetal development.

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

Relevant data/ tables from Anonymous (2016) test report:

**Table 3–11: Body weight change - group mean values (g) for females during gestation (Anonymous, 2016)**

Group /Sex		Days 0-3	Days 3-6	Days 6-7	Days 7-8	Days 8-9	Days 9-10	Days 10-11	Days 11-12	Days 12-13	Days 13-14	Days 14-15	Days 15-16
Statistical test:		Av	Av	Wi	Wi	Wi	Wi	Wi	Sh	Wi	Wi	Wi	Wi
1F	Mean	18	13	0	6	3	5	8	6	2	5	8	9
	SD	5.1	6.1	5.2	4.8	4.4	6.5	5.1	4.9	5.4	4.9	5.1	5.1
	N	20	20	20	20	20	20	20	20	20	20	20	20
2F	Mean	19	10	3	4	5	6	8	4	4	6	9	9
	SD	5.6	5.4	4.4	4.1	4.3	4.7	4.0	2.7	3.2	3.9	4.5	3.6
	N	20	20	20	20	20	20	20	20	20	20	20	20
3F	Mean	19	12	1	5	5	6	7	5	6*	5	9	10
	SD	6.1	6.9	4.1	5.2	5.0	3.8	3.5	6.1	4.5	4.1	4.3	4.2
	N	20	20	20	20	20	20	20	20	20	20	20	20
4F	Mean	19	10	-4**	4	6	7	8	5	6**	6	8	9
	SD	6.6	6.3	5.0	4.7	5.4	5.5	5.0	5.3	3.6	3.4	4.0	4.3
	N	20	20	20	20	20	20	20	20	20	20	20	20

  

Group /Sex		Days 16-17	Days 17-18	Days 18-19	Days 6-19	Days 19-20
Statistical test:		Wi	Wi	Wi	Wi	Wi
1F	Mean	13	14	15	95	18
	SD	5.2	5.9	3.2	13.9	4.9
	N	20	20	20	20	19
2F	Mean	16	15	13	102	18
	SD	3.8	5.8	4.7	7.4	6.7
	N	20	20	20	20	19
3F	Mean	14	16	15	104*	20
	SD	5.3	4.3	5.4	14.5	4.5
	N	20	20	20	20	19
4F	Mean	15	15	16	103*	18
	SD	4.3	4.1	4.3	12.1	8.7
	N	20	20	20	20	19

**Table 3–12: Food consumption - group mean values (g/animal/day) - for females during gestation (Anonymous, 2016)**

Group /Sex		Day 0-2	Day 3-5	Day 6-9	Day 10-13	Day 14-17	Day 18-19
Statistical test:		Av	Av	Wi	Wi	Wi	Wi
1F	Mean	20	23	20	21	23	22
	SD	2.4	2.1	1.4	2.0	2.0	2.6
	N	20	20	20	20	20	20
2F	Mean	20	22	19	21	23	22
	SD	2.2	1.8	1.3	1.7	2.7	4.0
	N	20	20	20	20	20	20
3F	Mean	21	23	20	22	24	23
	SD	2.4	1.8	2.1	2.0	1.9	2.8
	N	20	20	20	20	20	20
4F	Mean	20	22	17**	22	24	22
	SD	2.2	2.8	2.4	1.8	2.7	2.7
	N	20	20	20	20	20	20

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–13: Litter data - group mean values on Day 20 of gestation (Anonymous, 2016)**

Group /Sex	Corpora Implantations		Resorptions			Live Young			Sex ratio (%M)	Implantation Loss (%)	
	Lutea	Early	Early	Late	Total	Male	Female	Total		Pre-	Post-
Statistical test:	Wi	Wi	Wc	Wc	Wc	Wi	Wi	Wi	Wa	Wa	Wa
1F Mean	16.4	15.7	1.4	0.0	1.4	8.0	6.3	14.3	57.1	4.5	8.9
SD	1.67	1.31				1.95	2.45	2.74			
N	20	20	20	20	20	20	20	20	20	20	20
2F Mean	17.3	16.2	0.8	0.4	1.2	7.8	7.3	15.0	52.7	6.1	7.4
SD	1.71	1.66				2.05	2.79	2.79			
N	20	20	20	20	20	20	20	20	20	20	20
3F Mean	17.4	16.5	0.8	0.0	0.8	7.1	8.6*	15.7	45.6**	6.0	4.5
SD	1.66	1.82				1.89	2.35	1.92			
N	20	20	20	20	20	20	20	20	20	20	20
4F Mean	17.2	16.6	0.6	0.1	0.7	8.4	7.6*	16.0*	52.8	3.7	3.9
SD	1.84	1.88				1.90	2.04	1.82			
N	20	20	20	20	20	20	20	20	20	20	20

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–14: Placental, litter and fetal weights - group mean values (g) on Day 20 of gestation (Anonymous, 2016)**

Group /Sex		Placental Weight	Litter Weight	Litter Size	Male Fetal Weight	Female Fetal Weight	Overall Fetal Weight
Statistical test:		Wi	Sh	Wi	Wi	Sh	Wi
1F	Mean	0.55	53.13	14.30	3.82	3.58	3.72
	SD	0.065	10.469	2.736	0.270	0.319	0.282
	N	20	20	20	20	20	20
2F	Mean	0.56	56.73	15.00	3.85	3.62	3.74
	SD	0.057	12.443	2.791	0.427	0.430	0.412
	N	20	20	20	20	20	20
3F	Mean	0.54	58.48	15.70	3.84	3.65	3.73
	SD	0.047	7.116	1.922	0.230	0.223	0.224
	N	20	20	20	20	20	20
4F	Mean	0.54	52.53	15.95*	3.40**	3.19**	3.30**
	SD	0.073	6.168	1.820	0.239	0.224	0.231
	N	20	20	20	20	20	20

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–15: Observations regarding major anomalies (Anonymous, 2016)**

Group		Fetuses				Litters			
		1	2	3	4	1	2	3	4
Number Examined		286	300	314	319	20	20	20	20
Total Number Affected		1	0	0	2	1	0	0	2
<b>Lumbar (and abdominal)/Sacral/Caudal</b>									
Skeletal	Termination vertebral column lumbar region	0	0	0	1	0	0	0	1
Visceral	Omphalocele	1	0	0	0	1	0	0	0
External	Imperforate anus	0	0	0	1	0	0	0	1
	Short/thread like tail	0	0	0	2	0	0	0	2
<b>Appendicular</b>									
External	Malrotated hindlimb(s)	1	0	0	0	1	0	0	0

ANNEX I TO CLH REPORT FOR 2-ETHYLHEXANOIC ACID, MONOESTER WITH PROPANE-1,2-DIOL

**Table 3–16: Observations regarding minor skeletal abnormalities (Anonymous, 2016)**

Group		Fetuses				Litters			
		1	2	3	4	1	2	3	4
Number Examined		143	150	158	160	20	20	20	20
Minor skeletal abnormalities									
Cranial	sutural bone	1	2	0	2	1	2	0	2
	fissure(s)	0	1	1	0	0	1	1	0
	interparietal fissure(s)	0	0	1	2	0	0	1	1
Vertebral element abnormality	thoracic	0	0	4	3	0	0	4	2
	lumbar	0	0	0	1	0	0	0	1
Ribs	medially thickend/kinked	0	0	0	3	0	0	0	2
Costal cartilage	misaligned	0	0	1	0	0	0	1	0
Total affected by one or more of the above		1	3	5	9	1	3	5	5
Rib and vertebral configuration									
Cervical rib	short supernumerary	1	1	2	5	1	1	2	4
13th rib	short	3	0	0	0	3	0	0	0
	interrupted ossification	0	1	0	0	0	1	0	0
Number of 14th ribs	short supernumerary	9	15	15	54	8	8	8	17
	full supernumerary	1	0	1	0	1	0	1	0
	total	10	15	16	54	9	8	9	17
Thoracolumbar vertebra(e)	20	1	2	0	4	1	2	0	2
Pelvic girdle	unilateral caudal shift	0	0	0	1	0	0	0	1
Delayed/Incomplete ossification/unossified									
Cranial	cranial centres	13	8	10	47	7	7	6	15
	large nasofrontal suture	0	5	16	107	0	3	7	20
	presphenoid	0	0	0	1	0	0	0	1
	hyoid	19	9	21	22	10	4	7	11
Vertebrae	cervical	0	2	1	4	0	2	1	4
	thoracic	7	11	16	27	7	8	12	12
	lumbar	0	0	1	1	0	0	1	1
	sacrocaudal	8	5	11	68	6	5	7	18
	caudal	0	0	0	1	0	0	0	1
Sternebrae	5th and/or 6th	112	101	124	160	20	19	19	20
	other	14	9	10	38	8	8	8	15
	total	113	101	125	160	20	19	19	20
Ribs	any	0	0	0	2	0	0	0	2
Appendicular	pelvic bones	3	4	5	47	3	4	4	15
	long bones	0	0	1	0	0	0	1	0
	metacarpals	4	0	0	27	3	0	0	12
	metatarsals	3	1	1	55	3	1	1	14
Increased ossification									
Cervical vertebral centra	more than 4 ossified	8	14	1	0	3	6	1	0

Note: Individual fetuses/litters may occur in more than one category.

**Table 3–17: Observations regarding minor visceral skeletal abnormalities and necropsy finding (Anonymous, 2016)**

Group		Fetuses				Litters			
		1	2	3	4	1	2	3	4
Number Examined		143	150	156	159	20	20	20	20
Total Number Affected		20	36	22	57	12	16	11	18
Visceral abnormalities									
Brain	dilated interventricular foramen	0	1	1	0	0	1	1	0
Lens	variation in shape	2	5	1	13	2	3	1	10
Thyroid	small lobe	0	0	0	2	0	0	0	1
	absent lobe	0	0	0	2	0	0	0	2
Thymus	partially undescended lobe	3	3	3	11	3	3	3	8
	thymic remnant	0	0	0	1	0	0	0	1
Right subclavian artery	arises from aortic arch	0	1	0	1	0	1	0	1
Diaphragm	thinning with liver protrusion	2	2	0	0	2	2	0	0
Kidney(s)	small renal papilla	0	2	1	15	0	2	1	10
	absent renal papilla	0	0	0	2	0	0	0	2
Ureter(s)	dilated	1	2	1	4	1	1	1	4
Testis(es)	undescended	1	0	0	0	1	0	0	0
	malpositioned	4	1	0	1	4	1	0	1
Umbilical artery	left	2	1	2	2	2	1	2	2

Note: Individual fetuses/litters may occur in more than one category.



**3.10.2 Human data**

No data identified.

**3.10.3 Other data (e.g. studies on mechanism of action)**

No data identified.

**3.11 Specific target organ toxicity – single exposure**

Hazard class not assessed in this dossier.

**3.12 Specific target organ toxicity – repeated exposure**

**3.13 Hazard class not assessed in this dossier.**

**3.14 Aspiration hazard**

**3.15 Hazard class not assessed in this dossier.**

**4 ENVIRONMENTAL HAZARDS**

Hazard classes not assessed in this dossier.