BASF DocID: 2020/2081825

BASF Response Public Consultation on the Proposal for Harmonised Classification and Labelling of Mepiquat-Chloride According to Regulation (EC) No 1272/2008

Background

The hazard classification of mepiquat-chloride (CAS No. 24307-26-4) according to Dangerous Substances Directive (DSD) 67/548/EEC was agreed in the November 1995 meeting of the Commission Working Group on the C&L of Dangerous Substances. The Group agreed to the classification as: Xn; R22-52/53.

In a CLH report (Version 2, Dated 5.2.2020) submitted to ECHA, the dossier submitter (DS), Finland, proposes the following classifications:

Acute Tox. 3, H301; Toxic if swallowed
Acute Tox. 4, H332; Harmful if inhaled
Repr. 2, H361d; Suspected of damaging the unborn child
STOT SE 2, H371; May cause damage to organs
Aquatic Chronic 3, H412

The dossier submitter bases their proposal for Repr. 2, H361d on single events of fetal malformations, namely hydrocephalus and anophthalmia, in developmental toxicity studies. BASF submit that the CLP criteria for Repr. 2, H361d are not met. The observation of isolated occurrences of anophthalmia and hydrocephaly cited by the DS in support of this classification are clearly spontaneous findings that fall within the historical control range and are therefore unrelated to treatment with mepiquat-chloride. There are no treatment-related adverse effects on development in the developmental toxicity studies and the indications of developmental delay in the 2-generation reproductive toxicity study are clearly associated with marked toxicity to the dams, especially during lactation, indicating that they are non-specific secondary consequences of maternal toxicity.

As a basis for the proposal for STOT SE 2, H371, the DS focused on what they consider to be evidence of neurotoxicity across a range of studies, including effects seen after repeat dosing. The criteria for classification with STOT-SE 2 are not met as there is no convincing or reproducible weight of evidence to indicate that mepiquat-chloride can cause specific target organ toxicity (in this case neurotoxicity) after a single exposure at doses that are not associated with the classification for acute toxicity. The effects cited as supportive of this classification, many of which occur after repeated dosing, occur at doses that cause mortality. The effects seen in acute studies by the oral and inhalation routes are adequately described by the proposed classifications for acute toxicity i.e. Acute Tox. 3, H301 and Acute Tox. 4, H332

This document outlines in detail the weight of evidence that supports the position that the CLP criteria for Repr. 2 H361d and STOT-SE2 are not met.

Proposal for H361d (Suspected of damaging the unborn child): No Classification is Required as the CLP Criteria are Not Met for Developmental Toxicity

In a comparison with the CLP criteria, the CLH report states the following (p. 75): "*There is evidence from reliable developmental toxicity studies in two species that mepiquat causes fetal malformations, namely, hydrocephalus and anophthalmia. These findings are supported by similar developmental malformations found in pups of the 2-generation reproductive toxicity study. Even though these malformations are somewhat rare, they do not show a clear dose response pattern. Some maternal toxicity was present mostly demonstrated by decreased body weight gain. However, it is unlikely that this had a significant impact on these types of malformations. Therefore, classification* ***Repr. 2; H361d*** *(Suspected of damaging the unborn child) is proposed.*"

The CLP criteria for Repr. 2, H361d are not met. There is overwhelming evidence that mepiquat-chloride does not cause hydrocephalus or anophthalmia in the rat or rabbit. The incidence of these findings clearly follows a pattern that is consistent with isolated spontaneous occurrence with no relationship to treatment. The findings of the developmental and reproductive toxicity studies are reviewed here in detail with regard to the weight of evidence supporting a lack of any specific effects on development.

Two-Generation Reproductive Toxicity Study in Rats BASF Doc ID 1993/10983

The CLH report cites the observation of isolated incidences of anophthalmia and hydrocephaly in the two-generation reproductive toxicity study (in-life phase of study conducted in 1991) as being supportive of their proposal to classify with H361d (p. 74). As acknowledged by the Dossier Submitter (DS), the single incidences of anophthalmia and hydrocephaly both occurred in the same pup at the mid-dose and was only seen in the F1b litter but not the F1a or F2 litters. There were no other incidences of these malformations in any other dose group. Although not stated by the DS in the CLP report, the incidence of both findings was within the range of historical control data (HCD) for the test laboratory which cover the period from 1987 to 1992 (see Table 1; HCD are provided in the study report; date of individual study conduct for the HCD is provided in BASF DocID 2019/2053249 in Appendix 1). The incidence of hydrocephaly at the mid-dose of 1500 ppm was 1/25 litters (4.0%) and 1/364 fetuses (0.3%) compared to a historical control range of 0-4.2% with a mean of 0.1% (1/754) for litter incidence and 0-0.3% with a mean of 0.01% (1/9647) for fetal incidence. The incidence of anophthalmia at 1500 ppm was 1/25 litters (4.0%) and 1/364 fetuses (0.3%) with a historical control range of 0-4.5% with a mean of 0.4% (3/754) litter incidence and 0-1.1% with a mean of 0.05% (5/9647) for fetal incidence.

Table 1: Incidence of Hydrocephaly and Anophthalmia in F1b litter and Historical Control Data for Rat Two Generation Reproductive Toxicity Study (BASF Doc ID 1993/10983)

	Control	**500 ppm n (%)**	**1500 ppm n (%)**	**5000 ppm n (%)**	**HCD from Study Report (data from 1987-1992)**
Hydrocephaly	F – 0/382 L – 0/25	F – 0/337 L – 0/24	F – 1/364 (0.3%) L – 1/25 (4.0%)	F – 0/341 L – 0/25	F - 0.01% (0-0.3%) L – 0.1% (0-4.2%)
Anophthalmia	F – 0/382 L – 0/25	F – 0337 L – 0/24	F – 1/364 (0.3%) L – 1/25 (4.0%)	F – 0/341 L – 0/25	F - 0.05% (0-0.1%) L – 0.4% (0-4.5%)

F = fetal incidence; L = litter incidence

These two malformations (single incidence of hydrocephaly and a single incidence of anophthalmia) co-occurred in the same pup indicating that, in all probability, they were genetic in origin and unrelated to treatment. This spontaneous observation provides no supporting weight of evidence for classification with H361d.

In addition to the spontaneous finding outlined above, other offspring findings the CLH report noted (p. 74) in the high dose group of the two generation reproductive toxicity were the reduction in mean body weight gain of high dose F1a, F1b and F2 pups; a lower number of F1a, F1b and F2 pups reaching the criteria of auditory canal opening and eye opening and gripping reflex; an increased number of F1a pups died and were cannibalised and F1 pups had lower viability and lactation indices. These findings are considered to be secondary non-specific consequences of the marked maternal toxicity that was observed at the top dose in this study.

The maternal toxicity observed at the high dose was most marked during lactation when severe clinical signs of toxicity, including tremors and hypersensitivity, and insufficient or no nesting activity were observed. During lactation, at 5000 ppm 17/20 F0 dams of the F1a litter, 15/23 F0 dams of the F1b litter and 15/20 F1 dams of the F2 litter exhibited tremors and/or hypersensitivity, the onset of which was coincident with reduced food consumption and body weight gain. Maternal food consumption at the top dose was decreased markedly during lactation of the F1a, F1b and F2 litters, (by 23, 21 and 21%, respectively) resulting in maternal body weight losses (0.2, 2.0 and 3.3 g losses compared to gains of 21.0, 10.7 and 7.9 g in controls for the F1a, F1b and F2 litters respectively) during this critical phase of pup development (Table 2). This is reflected by the fact that Day 1 pup weights at 5000 ppm were only marginally lower than controls with the effect on pup weight becoming much more pronounced (22-28%) by Day 7, prior to any consumption of test diet by the pups, indicating that the observed maternal toxicity during lactation had a direct secondary non-specific consequence upon pup growth and development (Table 3). There were no effects on maternal body weight or clinical condition in the mid and low dose groups and consequently there were no effects on pup weight or development indicating that the effects at the high dose are a secondary non-specific consequence of maternal toxicity.

Table 2: Rat Two Generation Reproductive Toxicity Study (BASF Doc ID 1993/10983) Parental Food Consumption and Body Weight Gain During Lactation (% decrease compared to control weight gain in parentheses)

Parameter	Control	500 ppm	1500 ppm	5000 ppm
Mean Parental Food Consumption				
Lactation F1a (days 0-14)	46.2	48.7	47.5	35.7 (23%)
Lactation F1b (days 0-14)	48.5	49.8	47.3	38.3 (21%
Lactation F2 (days 0-14)	46.2	46.0	48.1	36.6 (21%)
Mean Parental Weight Gain				
Lactation F1a, days 0-21	21.0	25.2	18.3	-0.2** (Weight loss)
Lactation F1b, days 0-21	10.7	12.5	9.8	-2.0* (Weight loss)
Lactation F2, days 0-21	7.9	7.1	2.5	-3.3* (Weight loss)

* Significantly different from control, $p<0.05$. **Significantly different from control, $p<0.01$.

Table 3: Rat Two Generation Reproductive Toxicity Study (BASF Doc ID 1993/10983) Day 1 and Day 14 Mean Pup Weights and Mean Pup Body Weight Gain Days 1-4 and Days 4-21 for the F1a, F1b and F2 litters (% decrease compared to control weight gain in parentheses)

	F1a				F1b				F2			
	0	**500 ppm**	**1500 ppm**	**5000 ppm**	**0**	**500 ppm**	**1500 ppm**	**5000 ppm**	**0**	**500 ppm**	**1500 ppm**	**5000 ppm**
Males												
Day 1 Mean Bwt	6.5	6.6	6.5	6.1* (6.1%)	6.6	6.8	6.6	6.1* (7.6)	6.4	6.5	6.5	6.3
Day 7 Mean Bwt	15.3	15.1	15.3	11.1** (27.5)	15.7	16.1	15.6	11.8** (24.8)	14.4	13.6	14.5	11.2** (22.2)
Day 14 Mean Bwt	33.2	33.0	33.2	24.1** (27.4)	33.9	34.6	33.5	24.2** (28.6%)	31.7	30.4	31.6	23.9** (24.6%)
Gain Days 1-4	2.7	2.8	2.7	1.3* (52%)	2.9	3.1	2.7	1.6* (45%)	2.4	2.4	2.6	1.61** (33%)
Gain Days 4-21	45.5	44.9	44.2	27.5* (40%)	46.3	46.6	44.9	29.1* (37%)	43.1	41.0	41.9	27.2* (37%)
Females												
Day 1 Mean Bwt	6.2	6.3	6.2	5.8	6.2	6.4	6.3	5.9	6.1	6.3	6.1	6.1
Day 7 Mean Bwt	14.8	14.8	14.8	11.0** (25.7)	15.0	15.5	15.0	11.4** (24.0)	14.0	13.8	13.9	11.6** (17.1)
Day 14 Mean Bwt	32.2	32.4	32.7	23.5** (26,2)	33.0	33.8	32.6	23.4** (29.1%)	30.7	30.4	30.3	23.7** (22.8%)
Gain Days 1-4	2.6	2.7	2.6	1.2* (54%)	2.8	3.0	2.8	1.6* (43%)	2.5	2.4	2.5	1.71** (32%)
Gain Days 4-21	43.2	43.4	41.7	26.4* (39%)	43.8	44.5	42.8	28.0* (36%)	40.7	40.1	39.5	26.1* (36%)

* Significantly different from control, p<0.05. **Significantly different from control, p<0.01

The were some slight indications of developmental delay at the top dose with statistically significant reductions in the number of pups reaching the development criteria for auditory canal opening and eye opening and gripping reflex (see Table 4). For pinna unfolding at 5000 ppm, the % of pups achieving this landmark was 65%, 73% and 81% for the F1a, F1b and F2 litters compared to respective control values of 94%, 93% and 93% and a historical range (studies conducted 1987 to 1992) of 74-100%. For auditory canal opening at 5000 ppm, the % of pups achieving this landmark was 67%, 72% and 92% for the F1a, F1b and F2 litters compared to respective control values of 99%, 97% and 96% and a historical range of 81-100%. For eye opening at 5000 ppm, the % of pups achieving this landmark was 99%, 73% and 81% for the F1a, F1b and F2 litters compared to respective control values of 100%, 95% and 99% and a historical range of 85-100%. For gripping reflex at 5000 ppm, the % of pups achieving this landmark was 99%, 94% and 97% for the F1a, F1b and F2 litters compared to control values of 100% for all litters and a historical range of 98-100%. For pupil constriction at 5000 ppm, the % of pups achieving this landmark was 99%, 95% and 98% for the F1a, F1b and F2 litters

compared to respective control values of 99%, 100%, and 100% for the F1a, F1b and F2 litters and a historical range of 95-100%.

These delays in development are secondary consequences of the effects on pup weight (22-28% decrease by post-natal Day 7) caused by the marked maternal toxicity seen during lactation.

Table 4: Rat Two Generation Reproductive Toxicity Study (BASF Doc ID 1993/10983) Selected Pup Physical Development and Reflex Data for the F1a, F1b and F2 Litters

Parameter	F1a				F1b				F2				HCD from Study Report (data from 1987-1992)
	0 ppm	500 ppm	1500 ppm	5000 ppm	0 ppm	500 ppm	1500 ppm	5000 ppm	0 ppm	500 ppm	1500 ppm	5000 ppm	
Pinna unfolding (n/%)	310 94%	286 96%	330 96%	157* 67%	329 93%	321* 99%	330* 98%	236* 72%	255 93%	215 88%	260 91%	182 92%	74-100%
Auditory canal opening (n/%)	188 99%	174** 95%	191 99%	88* 65%	194 97%	186 97%	189 99%	141* 73%	162 96%	140* 88%	170 94%	105** 81%	81-100%
Eye opening (n/%)	190 100%	182 99%	187 100%	102* 99%	189 95%	191* 100%	189 99%	141* 73%	168 99%	152* 96%	159** 88%	116** 89%	85-100%
Gripping reflex (n/%)	190 100%	182 99%	192 100%	135 99%	199 100%	191 100%	190 100%	181* 94%	169 100%	159 100%	180 100%	126* 97%	98-100%
Pupil constriction (n/%)	189 99%	182 99%	192 100%	134 99%	199 100%	190 99%	189 99%	184* 95%	169 100%	158 99%	179 99%	128 98%	95-100%

* Significantly different from control, $p<0.05$. **Significantly different from control, $p<0.01$

The values for lactation and viability were, with one exception (F1a litter) within the historical control range (studies conducted 1987 to 1992) and were not statistically significantly different from concurrent controls indicating that there are no treatment-related effects on these end points. Although lactation index was marginally lower than controls for the F1a litter at 5000 ppm (95% in controls compared to 91% at 5000 ppm; historical range 95-100%), this was not evident in the F1b or F2 litters (Table 5).

Table 5: Rat Two Generation Reproductive Toxicity Study (BASF Doc ID 1993/10983) Viability and Lactation Index for F1a, F1b and F2 pups

Parameter	F1a				F1b				F2				HCD from Study Report (data from 1987-1992)
	0 ppm	500 ppm	1500 ppm	5000 ppm	0 ppm	500 ppm	1500 ppm	5000 ppm	0 ppm	500 ppm	1500 ppm	5000 ppm	
Number of litters	25	23	25	20	25	24	25	25	23	22	23	20	
Viability index	96	95	94	89	95	98	94	96	96	93	96	93	89-99
Lactation index	95	99	100	91	100	99	99	97	93	98	100	90	95-100

The high number of pups cannibalized and higher number of pup deaths on days 1-4 at the top dose of 5000 ppm is a secondary consequence of marked maternal toxicity, especially during lactation. The lower total

number of pups delivered at the top dose in the F1a and F2 litters reflects the lower total number of litters in these groups with no differences seen in these end-points in the F1b litter.

It is concluded that the offspring effects seen only at the top dose in the two generation reproductive toxicity study occur as a secondary non-specific consequence of maternal toxicity which was particularly marked during lactation as was evident by severe clinical signs of toxicity and body weight loss.

The two generation reproductive toxicity study in rats does not provide any weight of evidence for effects on development that meet the criteria for classification with H361d.

Developmental Toxicity in the Rat (BASF Doc ID 92/10331)

Female Wistar rats were dosed with mepiquat-chloride by gavage at 0 (distilled water), 50, 150 and 300 mg/kg bw/day, from days 6 to 15 (inclusive) of gestation. At the high dose there were marked clinical signs of toxicity including tremor, unsteady gait, piloerection and hypersensitivity were observed between days 6 to 14 of gestation and ataxia was seen on days 7-9 of gestation. At the top dose, body weight gain was statistically significantly decreased during gestation by around 13-16% and food consumption was also significantly reduced by 10-19% compared to controls.

The percentage litter incidence of hydrocephaly was higher in controls than in the high dose group with 2/20 (10%) litters affected in controls versus 2/23 (8.7%) at the top dose (see Table 6). Similarly the fetal incidence of hydrocephaly was also higher in controls than in the high dose group with 2/129 (1.6%) fetuses affected in controls versus 2/151 (1.3%) fetuses in the high dose group. Historical control data (HCD; BASF DocID 2019/2075940, see Appendix 1) from the test laboratory covering the period 1991 to 1995 (in-life phase of study was conducted in April 1991) indicate that one fetus out of 3664 (0.03%) had hydrocephaly. The CLH report inaccurately states the historical incidence to be one case out of 3901 (0.03%) fetuses (p. 62). The incidence of hydrocephaly in the high dose and the control group was higher than the historical control range. **The proposal that the incidence of hydrocephaly observed in this study is related to treatment with mepiquat-chloride lacks biological plausibility as the % incidence is higher in controls than in treated animals.**

A single incidence of anophthalmia was observed in the mid-dose group but not in any other treated group nor controls. Anophthalmia was not reported in the HCD (studies conducted from 1991-1995) although one case of microphthalmia was observed out of 7606 fetuses examined. The CLH report inaccurately states the historical incidence as being one out of 8105 fetuses (p. 62). **The single incidence of anophthalmia in the mid-dose group represents a spontaneous finding that is unrelated to treatment with mepiquat chloride.**

The CLH report states that the total fetal and litter incidence of soft tissue variations and the fetal incidence of dilated renal pelvis were higher in the mid and high dose groups compared to controls (p. 62). However, there were no statistically significant differences from control for these observations which occur with a high spontaneous frequency as reflected by the HCD from 1991-1995 (see Table 6). The litter incidence of total soft tissue variations was 50%, 50%, 57% and 61% in concurrent controls and the respective dose groups compared with the historical control range (studies conducted from 1991-1995) of 33.3-80% The fetal incidence of soft tissue variations was 11%, 11%, 13% and 14% in the concurrent control and respective dose groups compared to the historical control range of 4.9-33.1%. The litter incidence of dilated renal pelvis was 50%, 50%, 57% and 61% in concurrent controls and the respective dose groups compared with the historical control range of 33.3-80%. The fetal incidence of dilated renal pelvis was 11%, 11%, 13% and 14% in the concurrent control and respective dose groups compared to the historical control range of 4.9-33.1%.

Table 6: Incidence of Selected Fetal Findings and Historical Control Data for Rat Developmental Toxicity Study (BASF Doc ID 92/10331)

	Control n (%)	50 mg/kg bw/d n (%)	150 mg/kg bw/d n (%)	300 mg/kg bw/d n (%)	HCD (BASF Doc ID 2019/2075940) Studies from 1991-1995
Hydrocephaly	F – 2 (1.6%) L – 2 (10.0%)	F – 1 (0.7%) L – 1 (4.5%)	F – 0 L – 0	F – 2 (1.3 %) L – 2 (8.7%)	F - 0.03% (0-0.9%) L – 0.2% (0-5.6%)
Anophthalmia	F – 0 L – 0	F – 0 L – 0	F – 1 (0.3%) L – 1 (4.3%)	F – 0 L – 0	F – 0% L – 0%
Total Soft Tissue Variations	F – 14 (11%) L – 10 (50%)	F – 17 (11%) L – 11 (50%)	F – 18 (13%) L – 13 (57%)	F – 21 (14%) L – 14 (61%)	F – 14.7% (4.9-33.1%) L –51.5% (33.3-80.0%)
Dilated renal pelvis	F – 14 (%) L – 10 (50%)	F – 17 (11%) L – 11 (50%)	F – 18 (13%) L – 13 (57%)	F – 21 (14%) L – 14 (61%)	F – 14.7% (4.9-33.1%) L –51.5% (33.3-80.0%)

F = fetal incidence; L = litter incidence

There are no treatment-related findings in the rat developmental toxicity study (BASF Doc ID 92/10331) to indicate that mepiquat-chloride has any adverse effects on development. The study findings do not meet the CLP criteria for classification with H361d.

Developmental Toxicity in the Rabbit (BASF Doc ID 1998/10497)

Himalayan rabbits were dose with mepiquat-chloride by gavage doses of 0 (distilled water), 50, 100 and 150 mg/kg bw/day, from day 7 to day 19 of gestation; the in-life phase of the study was May-July 1997. At the high dose body weight loss was observed during days 7 - 19 of gestation with a mean body weight loss of 50 grams over the entire treatment period compared to a weight gain of 44.6 g in controls. There was also a 42% reduction in food consumption during gestation in the high dose group and two animals were observed to have blood in their bedding on Days 23-27.

The litter is the conventional unit for assessment of developmental defects since findings may be due to genetics of the dams. Hydrocephaly occurred in 1 fetus (1/92 = 1.1%) at the low dose and 2 fetuses (2/102 = 2.0%) from the same litter at the high dose; a dose causing marked body weight loss during treatment (see Table 7). There were no statistically significant differences between the groups for the incidence of hydrocephaly. The historical control incidence of hydrocephaly, from studies conducted during 1995-2000, (see BASF Doc ID 2019/2075941, see Appendix 1) was one case reported out of 1230 fetuses/189 litters examined (mean of 0.08% with a range of 0-0.6% for fetal incidence and a mean of 0.5% with a range of 0-4.2% for litter incidence). The CLH report inaccurately states the historical control incidence as being one case out of 2459. **The absence of any hydrocephaly in the mid-dose together with the fact that the two incidences of hydrocephaly at the top dose were observed in the same litter indicates that these are spontaneous observations unrelated to treatment with mepiquat-chloride.**

The litter (64%, 87%, 73% and 86% in control and treated groups) and fetal incidence (17%, 20%, 22% and 25%) of total skeletal variations is well within the spontaneous background incidence, as reflected by the historical control data (mean litter incidence of 87.8% with a range of 58.8-100% and mean fetal incidence of 48.3% with a range of 11.5-73.5%) and there were no statistically or biologically relevant differences between the concurrent control and treated animals indicating that there is no treatment-related effect. **There is no justification for hazard classification based on the prenatal developmental toxicity study in rabbits.**

Table 7: Incidence of Hydrocephaly and Total Skeletal Variations and Historical Control Data in Rabbit Developmental Toxicity Study (BASF Doc ID 1998/10497)

	Control	**50 mg/kg bw/d**	**100 mg/kg bw/d**	**150 mg/kg bw/d**	**HCD (BASF Doc ID 2019/2075941) Data from 1995-2000**
Hydrocephaly	F – 0.0 L – 0.0	F – 1.0 (1%) L – 1.0 (6.7%)	F – 0.0 L – 0.0	F – 2 (2.0%) L – 1 (7.1%)	F – 0.08% (0-0.6%) L – 0.5% (0-4.2%)
Total skeletal variations	F – 16 (17%) L – 9 (64%)	F – 19 (20%) L – 13 (87%)	F – 23 (22%) L – 11 (73%)	F – 25 (25%) L – 12 (86%)	F – 48.3% (11.5-73.5%) L – 87.8% (58.8-100%)

F = fetal incidence; L = litter incidence

There are no treatment-related findings in the rabbit developmental toxicity study (BASF Doc ID 1998/10497) to indicate that mepiquat-chloride has any adverse effects on development. The study findings do not meet the CLP criteria for classification with H361d.

Overall Conclusion Regarding proposal for H361d

In conclusion, the CLP criteria for classification for developmental toxicity (H361d) are not met. The observation of isolated occurrences of anophthalmia and hydrocephaly cited by the DS in support of classification are clearly isolated spontaneous findings that within the historical control range and are therefore unrelated to treatment with mepiquat-chloride. The DS proposal that these observations are related to treatment has no biological plausibility. Also, there are no treatment-related adverse effects on development in the developmental toxicity studies and the indications of developmental delay in the 2-generation reproductive toxicity study are clearly associated with marked toxicity to the dams, especially during lactation, indicating that they are non-specific secondary consequences of maternal toxicity

Specific Target Organ Toxicity after a Single Exposure; the CLP Criteria are Not Met

Classification with STOT-SE is applicable to substances that have produced non-lethal toxicity in humans, or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant non-lethal toxicity in humans following a single exposure. The Dossier Submitter (DS) focused on what they consider to be evidence of neurotoxicity across a range of studies, including effects seen after repeat dosing, as the basis for STOT-SE2. However, the findings that the DS state in their justification (p. 87) for STOT-SE2 occur at doses causing mortality and are already addressed through classification for acute toxicity. Guidance on the application of the CLP Criteria states (3.8.2.5): "care should be taken not to assign each class for the same effect, in other words a double classification for the same effect has to be avoided". There is no evidence of specific target organ toxicity to the peripheral or central nervous system.

The four studies cited by the DS in support of STOT-SE2 are the acute neurotoxicity study in the rat, acute oral toxicity (LD50) studies in the rat and mouse and the acute inhalation study in the rat.

In the rat acute neurotoxicity study (BASF Doc ID 2002/1004002), there was significant toxicity at the top dose of 697 mg/kg bw as indicated by the death of 1 male on the day of administration and a 22% decrease in body weight gain by Day 7 post exposure in top dose males (Table 8). There were a range of signs of toxicity observed in the top dose either prior to or during the FOB tests (abdominal position, slight/half closure of eyelids, piloerection, squatting and abdominal posture, gasping/respiratory sounds, slight or moderate tremors, impairment of coordination and unsteady or shuffling gate) and a range of effects on functional activity, rearing and motor activity which are all considered to reflect generalised toxicity (i.e. reduced activity of rats experiencing peri-lethal toxicity and feeling unwell) and are not specific indications of neurotoxicity (Tables 8-11). There were no effects on neuropathology. Although there was a slight decrease in motor activity in males at the mid dose of 174 mg/kg bw/d which was statistically significant for intervals 1 and 2 , this was not seen in females, was considered not to be toxicologically adverse and, in all likelihood, is unrelated to treatment. The statistically significant differences in rearing and grip strength observed in the mid-dose are unrelated to treatment with mepiquat-chloride.

Table 8: Acute Neurotoxicity Study (BASF Doc ID 2002/1004002) in Rats Body Weight Gain (% Difference Compared to Control Weight Gain in Parentheses)

	Control	58 mg/kg a.s. bw	174 mg/kg a.s. bw	697 mg/kg a.s. bw#
Males				
Day 7	40.6	37.0	38.6	31.5*
Day 14	74.7	65.6	70.8	64.1
Females				
Day 7	14.8	15.7	16.8	16.0
Day 14	29.3	28.9	30.2	29.3

* Significantly different from control, $p<0.05$. #Clinical signs of toxicity observed in the top dose were abdominal position, slight/half closure of eyelids, piloerection, squatting and abdominal posture, gasping/respiratory sounds, slight or moderate tremors, impairment of coordination and unsteady or shuffling gate

Table 9: Acute Neurotoxicity Study (BASF Doc ID 2002/1004002) in Rats Motor Activity (Sum Interrupts of Intervals 1-12 for Males and Females; % difference compared to control weight gain in parentheses)

	Control	58 mg/kg a.s. bw	174 mg/kg a.s. bw	697 mg/kg a.s. bw#
Males				
Day -7	284.9	292.7	313.4	323.3
Day 0	231.8	280.9	189.5	26.0*
Day 7	290.0	306.8	336.3	397.3
Day 14	356.3	320.5	338.4	378.6
Females				
Day -7	318.1	308.0	333.5	319.6
Day 0	281.3	252.1	285.3	65.3*
Day 7	308.8	286.7	333.3	373.0
Day 14	360.1	310.0	368.8	319.7

* Significantly different from control, p<0.05. * Significantly different from control, p<0.05. #Clinical signs of toxicity observed in the top dose were abdominal position, slight/half closure of eyelids, piloerection, squatting and abdominal posture, gasping/respiratory sounds, slight or moderate tremors, impairment of coordination and unsteady or shuffling gate

Table 10: Acute Neurotoxicity Study(BASF Doc ID 2002/1004002) in Rats Incidence of Rearing

	Control	58 mg/kg a.s. bw	174 mg/kg a.s. bw	697 mg/kg a.s. bw#
Males				
Day -7	3.5	3.9	4.7	4.0
Day 0	1.6	3.1	3.8*	0.2**
Day 7	3.2	2.5	2.0	3.7
Day 14	3.6	2.4	3.7	3.0
Females				
Day -7	10.2	8.6	10.2	9.5
Day 0	10.1	9.8	9.3	0.1**
Day 7	12.8	11.0	9.3	11.7
Day 14	13.4	12.5	13.3	13.0

* Significantly different from control, p<0.05. **Significantly different from control, p<0.01. * Significantly different from control, p<0.05. #Clinical signs of toxicity observed in the top dose were abdominal position, slight/half closure of eyelids, piloerection, squatting and abdominal posture, gasping/respiratory sounds, slight or moderate tremors, impairment of coordination and unsteady or shuffling gate

Table 11: Acute Neurotoxicity Study (BASF Doc ID 2002/1004002) in Rats Hindlimb Grip Strength in Females

	Control	58 mg/kg a.s. bw	174 mg/kg a.s. bw	697 mg/kg a.s. bw#
Day -7	2.7	2.5	2.6	2.7
Day 0	2.5	2.5	2.6	2.3
Day 7	2.5	2.4	2.4	2.4
Day 14	2.9	2.9	2.7	2.5*

* Significantly different from control, p<0.05. **Significantly different from control, p<0.01. * Significantly different from control, p<0.05. #Clinical signs of toxicity observed in the top dose were abdominal position, slight/half closure of eyelids, piloerection, squatting and abdominal posture, gasping/respiratory sounds, slight or moderate tremors, impairment of coordination and unsteady or shuffling gate

Overall the acute neurotoxicity study provides no specific indications of a neurotoxic effect at non-lethal doses and none of the study findings meet the criteria for classification with STOT-SE.

In the acute oral toxicity study in rats (BASF Doc ID 89/0462), mortality (2/5 males and 3/5 females) occurred at doses of 270 mg/kg bw of mepiquat-chloride and above with no signs of toxicity observed at doses below this (58 & 115 mg/kg bw; see Table 12). Thus, the clinical signs of toxicity (poor general state, dyspnea, apathy, abdominal position, staggering, twitching, compulsory gnawing and cyanosis) that the DS noted at 270 mg/kg bw and above only occurred at doses causing lethality. Similarly in the **mouse acute oral toxicity study (BASF Doc ID 89/0463)**, clinical signs of toxicity were only observed at doses causing mortality (270 mg/kg bw and above).

Table 12: Mortality and Clinical Signs of Toxicity in Rat (BASF Doc ID 89/0462) and Mouse (BASF Doc ID 89/0463) Acute Oral Studies

Rat Acute Oral Toxicity			Mouse Acute Oral Toxicity		
Dose (mg/kg bw)	**Mortality**	***Clinical signs of Toxicity**	**Dose (mg/kg bw)**	**Mortality**	**#Clinical signs of Toxicity**
Males			**Males**		
58	0/5	None	**58**	0/5	None
115	0/5	None	**115**	0/5	None
270	2/5	Yes	**270**	2/5	Yes
851	5/5	Yes	**851**	5/5	Yes
1245	5/5	Yes	**1245**	4/5	Yes
Females			**Females**		
58	0/5	None	**58**	0/5	None
115	0/5	None	**115**	0/5	None
270	3/5	Yes	**270**	2/5	Yes
851	5/5	Yes	**851**	3/5	Yes
1245	5/5	Yes	**1245**	4/5	Yes

*Poor general state, dyspnea, apathy, abdominal position, staggering, twitching, compulsory gnawing and Cyanosis. #Poor general state, dyspnoea, apathy, abdominal position, lateral position, staggering, twitching, clonic convulsions, exsiccosis and additionally at 1245 mg/kg bw tremor, piloerection and weight reduction

Therefore the acute oral toxicity study findings in the rat and mouse do not meet the criteria for classification with STOT-SE. The mortality and associated clinical signs of toxicity in this study are addressed by the proposed Acute Tox. 3, H301 classification.

In the rat acute inhalation toxicity study (BASF Doc ID 91/10505), the clinical signs indicative of toxicity (poor general state, dyspnea, apathy, abdominal position, staggering, twitching, compulsory gnawing and cyanosis) were only observed at a concentration causing mortality (i.e. 2.84 mg/l). At the lower concentration, (1.50 mg/l) the only clinical signs observed were those associated with the experimental procedure which were irregular, accelerated and intermittent respiration and eyelid closure seen in all animals during exposure and ruffled fur, accelerated and intermittent respiration were seen in the first day post exposure (Table 13). These are common findings very frequently recorded in acute inhalation studies which, like other acute toxicity studies, do not have a control group and involve restraint of the animals within restraining tubes in order to allow for nose-only exposure.

Table 13: Findings in Acute Inhalation Study (BASF Doc ID 91/10505) in Rats

Concentration (mg/l a.s.)	Mortality	*Clinical signs of Toxicity During Exposure	#Clinical signs of Toxicity Post Exposure Day
Males			
1.50	0/5	Irregular, accelerated and intermittent respiration and eyelid closure	Ruffled fur, accelerated and intermittent respiration; resolved after Day 1 post exposure
2.84	1/5	Irregular, accelerated and intermittent respiration, eyelid closure and gasping respiration	Accelerate respiration, ruffled fur, intermittent respiration, respiratory sounds, abdominal, lateral or squatting position in individual animals, tonic-clonic convulsions and discoloured fur. All resolved after Day 6
Females			
1.50	0/5	Irregular, accelerated and intermittent respiration and eyelid closure	Ruffled fur, accelerated and intermittent respiration; resolved after Day 1 post exposure
2.84	2/5	Irregular, accelerated and intermittent respiration, eyelid closure and gasping respiration	Accelerate respiration, ruffled fur, intermittent respiration, respiratory sounds, abdominal, lateral or squatting position in individual animals, tonic-clonic convulsions and discoloured fur. All resolved after Day 6

*Irregular, accelerated and intermittent respiration and eyelid closure at both concentrations and gasping respiration at the high concentration. # Ruffled fur, accelerated and intermittent respiration were seen in the first day post exposure.

None of the findings in this study meet the criteria for STOT-SE2. The mortality and associated clinical signs of toxicity in this study are addressed by the proposed Acute Tox. 4, H332 classification.

In addition to the studies above, the DS also cite the following studies as providing information relevant to their STOT-SE2 proposal (p. 80-86):

In the rat sub-chronic neurotoxicity study (BASF Doc ID 2002/1011417), rats were administered dietary dose levels up to 13,000 ppm (517 and 617 mg/kg bw/d in males and females respectively). The decreases in body weight gain in top dose males and females were marked, particularly during the first month of the study indicating a marked degree of systemic toxicity in these animals (see Table 14). After two weeks of dosing, body weight gain in males at the top dose was 46% lower than controls and in females weight gain was 57% lower. Weight gain continued to be significantly decreased throughout the study and was 28-29% lower than controls in both sexes at the end of the study.

Table 14: Body weight gain (g) of males and females (% decrease compared to control weight gain in parentheses) in Sub-Chronic Neurotoxicity Study (BASF Doc ID 2002/1011417) in Rats

	Males				Females			
Day	**0 ppm**	**1625 ppm**	**6500 ppm**	**13000 ppm**	**0 ppm**	**1625 ppm**	**6500 ppm**	**13000 ppm**
7	45.4	46.2	38.0	17.0** (63%)	21.6	14.5 (33%)	16.1 (25%)	1.9** (91%)
14	75.0	77.7	66.9 (11%)	40.3** (46%)	36.8	29.6 (20%)	28.1* (24%)	15.9** (57%)
28	117.8	122.0	106.3	73.1** (38%)	54.6	48.6 (11%)	45.1* (17%)	32.8** (60%)
56	174.3	178.7	159.1	119.7** (31%)	78.4	75.6	71.3	55.7** (29%)
84	213.5	218.0	195.8	155.2** (27%)	96.4	90.6	82.6 (14%)	67.9** (30%)
91	216.7	220.2	198.0	155.8** (28%)	98.6	94.1	87.8 (11%)	70.0** (29%)

* Significantly different from control, $p<0.05$. **Significantly different from control, $p<0.01$.

Group mean body weight and food utilization were also decreased at the top dose. Consequently, the occasional statistically significant decreases in grip strength and systemic toxicity are attributable to marked systemic toxicity. There were no statistically significant differences in motor activity.

Similar reductions in grip strength and clinical signs of toxicity were seen in the 90 day rat study conducted at a doses of 12,000 ppm (826/951 mg/kg bw/d) which caused a 32% reduction in mean body weight in males and 17% reduction in females. The moderate multifocal muscle fibre degeneration with reactive myositis observed in the gastrocnemius muscle of a single top dose male, the single incidence of axonal degeneration in sciatic nerve and two incidences in the proximal tibial nerve were considered to be spontaneous findings unrelated to treatment.

There were no effects on the functional observational battery, hindlimb grip strength or histopathology of neurological tissue in a 24 month chronic toxicity study in rats up to doses of 826-951 mg/kg bw/d in males and females respectively.

Neither the sub-chronic neurotoxicity study nor 3 month sub-chronic toxicity study in rats provide any evidence of specific target organs toxicity even after multiple doses. The observed effects only occur at doses causing significant systemic toxicity and therefore reflect non-specific secondary consequences of such repeated-dose toxicity. The findings of these repeat dose studies are not applicable to the criteria for STOT-SE nor do they provide evidence of neurotoxicity.

In the **2-Generation reproductive toxicity study in rats (BASF Doc ID 93/10983)**, the top dose of 5000 ppm (circa 520 mg/kg bw/day) produced marked toxicity in the dams, particularly during lactation where maternal body weight loss was observed (Table 15). During mating, food consumption was decreased (9-15% in males and 5-11% in females) in both sexes at 5000 ppm with corresponding reduction in body weight gain (13% in males and 11% in females. During gestation body weight gain was 10-17% lower at 5000 ppm and during lactation food consumption was 21-23% lower than controls and dams lost body weight with a 0.2-3.3 g loss in body weight compared to gains of 7.9-21 g.

Although tremor and hypersensitivity and reduced forelimb grip strength were observed in most high dose dams of both generations (no clinical signs of toxicity were observed in males), these findings only occurred during lactation when there was clear evidence of marked systemic toxicity including maternal weight loss. In neurofunctional tests no abnormalities were detected for both sexes. The hot-plate test values did not show statistically significant differences between treated and control groups. It should also be noted that before reaching the lactation phase on this study, animals would have been dosed for at least 90 days or more hence any observations during lactation cannot be considered to be a consequence of a single exposure.

Table 15: Parental Food Consumption and Body Weight Gain During Lactation in 2-Generation Study (BASF Doc ID 93/10983; % decrease compared to control weight gain in parentheses)

Parameter	0 ppm	500 ppm	1500 ppm	5000 ppm
Mean Parental Food Consumption				
Lactation F1a (days 0-14)	46.2	48.7	47.5	35.7 (23%)
Lactation F1b (days 0-14)	48.5	49.8	47.3	38.3 (21%
Lactation F2 (days 0-14)	46.2	46.0	48.1	36.6 (21%)
Mean Parental Weight Gain				
Lactation F1a, days 0-21	21.0	25.2	18.3 (13%)	-0.2** (weight loss)
Lactation F1b, days 0-21	10.7	12.5	9.8	-2.0* (weight loss)

Parameter	0 ppm	500 ppm	1500 ppm	5000 ppm
Lactation F2, days 0-21	7.9	7.1 (10%)	2.5 (68%)	-3.3* (weight loss)

* Significantly different from control, p<0.05. **Significantly different from control, p<0.01.

The findings of the 2-Generation reproductive toxicity study in rats reflect marked maternal toxicity after repeated exposure and do not provide any evidence of specific target organ toxicity that would meet the criteria for classification with STOT-SE2

In the **developmental neurotoxicity study in rats (BASF Doc ID 2006/1031894;** in-life phase from March 2005 to May 2005**)**, doses of 15, 30 and 60 mg/kg bw/day were administered to pregnant females from gestation day 6 to post-natal day 21 with pups dosed directly from day 11 to day 21 post-partum. Upon commencement of direct dosing of pups there was significant pup mortality at the top dose (see Table 16) with 22 pup deaths seen from days 5-14 post-partum. The auditory startle maximum amplitude and startle time to peak amplitude were as decreased in male pups in all dose groups compared to control which was due to a high average maximum amplitude value in controls exceeding the historical control range (studies dated from 1997-2003) as one control male had an exceptionally high value. Values for auditory startle maximum amplitude (sub-set 2) on post-partum day 24 were 549, 356, 391 and 354 for the control and respective dose groups. This compared to the historical range of 352-434 for day 24 post-partum. However, on post-partum day 60 values were 1669, 1620, 2104 and 1549 (historical range 629-1758) indicating the variable nature of this end-point. Similarly, in females on post-partum days 24 (411, 454, 384 and 425; historical range 294-507) and 60 (919, 1062, 1167 and 955; historical range 243-1688) values were generally higher than control, again reflecting variability in these measurements. Values (msec) for time to peak amplitude in males were 34.9, 28.9, 30.8 and 28.1 in controls and respective dose groups day 24 post-partum (historical range 24.6-35.4) and 42.6, 36.6. 37.7 and 36.3 on day 60 post-partum (historical range 30.2-42.5). In females time to peak amplitude values for post-partum day 24 were 32.5, 30.3, 29.8 and 26.9 for controls and the respective dose groups (historical range 27.5-36.1) and for post-partum day 60 were 31.9, 30.4, 34.4 and 29.8 (historical range 29.1-38.5). None of these observations are treatment related.

Table 16: Selected Litter Data from DNT Study (BASF Doc ID 2006/1031894)

Parameter	Control	15 mg/kg bw/day	30 mg/kg bw/day	60 mg/kg bw/day
Total number of litters	32	34	37	38
Litters with liveborn pups (%)	100	100	100	100
Litters with stillborn pups (%)	6.3	5.9	5.4	2.6
Pups delivered -total -mean	302 9.4	298 8.8	344 9.3	331 8.7
Pups sacrificed moribund (%)	0	0.7	0.6	0
Pups dead (n) -days 1-4 -days 5-10 -days 11-14 -days 15-21	0 1 0 0	1 0 0 2	0 0 2 0	0 0 15 7

In a follow-up study (BASF DocID 2006/1031827) to investigate pup mortality during direct dosing on Days 11-21 post-partum, to replicate the conditions of the DNT study, pups were dosed at 0, 30, 60, 120 and 2000 mg/kg bw/d. Acute mortality and marked clinical signs were observed in pups at 120 and 200 mg/kg bw/d. Mortality at 60 mg/kg bw/d was comparable to that seen in controls (Table 17). There were no effects at 30 mg/kg bw/d.

Table 17: Selected Litter Data from Study of Pup Mortality (BASF DocID 2006/1031827)

	Control	30 mg/kg bw/day	60 mg/kg bw/day	120 mg/kg bw/day	200 mg/kg bw/day
Total number of litters	9	10	10	10	2
Litters with liveborn pups (%)	100	100	100	100	100
Pups dead (n)					
-days 1-4	1	2	0	1	0
-days 5-10	0	0	0	0	0
-days 11-14	3	0	3	39	16
-days 15-21	0	1	0	4	0
Viability index (days 0-4)	99	98	100	99	100

The DNT study provides no evidence of any neurological findings or any other finding that would support classification with STOT-SE2.

The DS cite the observation of sedation at the top dose of 3000 ppm in the non-GLP **3-month dog study** conducted in 1977 (BASF DocID 77/035) as part of the justification for STOT-SE2. This was seen initially in all dogs for up to 4 weeks and then in 3/8 dogs on occasional study days thereafter. However, sedation was not observed in either of the two more recent **1-year dog studies** (top doses of 1800 or 8000/6000 ppm; BASF Doc IDs 89/0357 & 94/10282) nor in the **28 day dog study** (top dose 12,000 ppm; BASF DocID 94/10283), indicating that this was not a reproducible finding. **The observation of sedation in a study judged "Supportive" does not provide a weight of evidence to support classification with STOT-SE2.**

The DS also cite the observation of salivation in the **28 day** (BASF Doc ID 94/10283) **and 1 year dog studies (**BASF Doc ID 94/10282**)** in support of the STOT-SE proposal (p. 85-86). Salivation observed at 2-6 hours post dosing in **28 day** (BASF Doc ID 94/10283) and **1 year** (BASF Doc ID 94/10282) **dog studies** at doses of 6000 ppm (166 mg/kg bw/d) and above. No incidence of salivation was recorded in the **3-month dog study** (BASF Doc ID 77/035) up to a dose of 3000 ppm nor in the other **1 year dog study** (BASF Doc ID 89/0357) up to a dose of 1800 ppm. The observation of salivation in the **1 year dog study** occurred at a dose that caused deaths in 3 dogs (1/6 males and 2/6 females) which required the top dose to be reduced from 8000 ppm to 6000 ppm. Thereafter, marked clinical signs of toxicity were observed in 1 female at 6000 ppm from Day 7 onwards which required the animal to be sacrificed prematurely. **Within the context of the mortality seen at 8000/6000 ppm in the 1-year dog study, the observation of post dose salivation, which in itself is a frequent observation in dog feeding studies, is not considered to indicate significant or severe toxicity after a single exposure and therefore does not meet the criteria for STOT-SE2.**

Overall Conclusion Regarding proposal for STOT-SE2

In conclusion, the criteria for classification with STOT-SE2 are not met as there is no convincing or reproducible weight of evidence to indicate that mepiquat-chloride can cause specific target organ toxicity (in this case neurotoxicity) after a single exposure at doses that are not associated with the classification for acute toxicity. The effects cited as supportive of this classification, many of which occur after repeated dosing, occur at doses that cause mortality. The effects seen in acute studies by the oral and inhalation routes are adequately described by the proposed classifications for acute toxicity i.e. Acute Tox. 3, H301 and Acute Tox. 4, H332.

Proposal for No Classification for Carcinogenicity:

BASF agree with the opinion of the DS that Mepiquat-chloride is not carcinogenic in the rat or mouse and therefore does not meet the criteria for classification for carcinogenicity:

- In both the 24 month chronic toxicity study and 24 month carcinogenicity study, there were no treatment-related increases in tumour incidence either individually or overall
- There is no evidence of any pre-neoplastic lesions that suggest the potential for a tumour outcome
- The observed tumour incidence is within the spontaneous background range of historical control data from the test laboratory
- There are no indications of genotoxicity

Appendix 1

In the following the Historical control data from test facility for rat and rabbit prenatal developmental toxicity studies.

BASF DocID 2019/2075940: page 18 ff

BASF DocID 2019/2075941: page 39 ff

BASF DocID 2019/2053249: page 60

10-DEC-19

TABLE :
01-JAN-91 to 31-DEC-95

HISTORICAL CONTROL DATA

SPECIES: RAT
STRAIN: WISTAR
SUPPLIER: [redacted]
FILENAME: MEPI2019

Study No./Control Group		Start Date	End Date	Route of Administration
89117	1	4-MAY-93		GAVAGE
89118	1	21-JUN-93		GAVAGE
90077	1	29-JAN-91		GAVAGE
90088	1	28-FEB-91		GAVAGE
90104	1	4-JUN-91		GAVAGE
90116	1	17-JUL-91		GAVAGE
91030	1	15-OCT-91		GAVAGE
91070	1	27-APR-93		GAVAGE
91071	1	5-MAR-91		GAVAGE
91081	1	23-APR-92		GAVAGE
91096	1	8-SEP-92		GAVAGE
91101	1	6-NOV-92		GAVAGE
91122	1	15-JUN-93		GAVAGE
92063	1	14-APR-93		GAVAGE
92083	1	12-OCT-93		GAVAGE
92091	1	20-JAN-94		GAVAGE
93028	1	20-OCT-93		GAVAGE
93029	1	27-JAN-94		GAVAGE
93046	1	28-MAR-94		GAVAGE
93047	1	20-APR-94		GAVAGE
93059	1	14-MAR-95		GAVAGE
94014	1	6-JUL-94		GAVAGE
94014_A	1	6-JUL-94		GAVAGE
94017	1	15-NOV-94		GAVAGE
94050	1	10-OCT-95		GAVAGE

10-DEC-19

TABLE :
01-JAN-91 to 31-DEC-95

HISTORICAL CONTROL DATA
MEAN MATERNAL BODY WEIGHTS DURING GESTATION GRAMS

SPECIES: RAT
STRAIN: WISTAR
SUPPLIER: [redacted]

	NO. OF ANIMALS	MEAN	RANGE OF ACTUAL VALUES		95 % SPREAD 2.5%	97.5%
DAY 0	555	236.5	200.7	305.1	204.8	268.3
DAY 1	555	240.1	203.3	299.8	208.9	271.2
DAY 3	555	251.9	212.2	313.5	220.1	283.6
DAY 6	555	265.5	223.1	329.2	231.6	299.4
DAY 8	555	272.8	229.5	337.7	238.3	307.3
DAY 10	555	283.1	234.7	350.8	247.3	318.8
DAY 13	555	300.2	245.1	367.9	262.1	338.4
DAY 15	555	313.0	244.3	387.2	272.6	353.3
DAY 17	555	336.2	244.3	416.4	291.0	381.5
DAY 20	555	386.0	248.6	479.8	328.9	443.1

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR

REPRODUCTION DATA

SUPPLIER [redacted]

			RANGE (per study)	
Females Mated	N	595		
Pregnant	N	555		
	%	93		
Aborted	N	0		
Premature Births	N	0		
Dams with Viable Fetuses	N	553		
Dams with all Resorptions	N	2		
Female Mortality	N	0		
	%	0.0		
Pregnant at C-section	N	555		
	%	93		
Corpora Lutea	N	8920		
	MEAN	16.1	14.4	16.8
	S.D.	2.29		
Implantation Sites	N	8164		
	MEAN	14.7	11.9	16.0
	S.D.	3.17		
Preimplantation Loss	%	8.6	2.3	20.1
	S.D.	16.91		
Postimplantation Loss	%	7.3	4.4	15.7
	S.D.	9.89		
Dams with Resorptions	N	332		
	%	60		
Resorptions	N	555		
	MEAN	1.0	0.6	1.5
	S.D.	1.12		
	MEAN %	7.3	4.4	15.7
	S.D.	9.89		
Dead Fetuses	N	0		
Viable Fetuses	N	7606		
Litter Size	MEAN	13.7	11.1	14.9
	S.D.	3.23		
Viable Male Fetuses	N	3874		
	%	51		

10-DEC-19

TABLE :

SPECIES RAT

STRAIN WISTAR

SUPPLIER [redacted]

HISTORICAL CONTROL DATA

PLACENTA WEIGHTS -- GRAMS

DATES: 01-JAN-91 - 31-DEC-95

	NO. OF LITTERS	MEAN	RANGE OF ACTUAL VALUES		95 % SPREAD 2.5%	97.5%
MALES	552	0.45	0.34	0.74	0.35	0.55
FEMALES	550	0.44	0.32	0.66	0.34	0.53
BOTH	553	0.44	0.32	0.69	0.35	0.53

11-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR

SUPPLIER [redacted]

MEAN FETAL WEIGHTS -- GRAMS

	NO. OF LITTERS	MEAN	RANGE OF ACTUAL VALUES		95 % SPREAD 2.5%	97.5%
MALES	552	3.9	3.2	4.7	3.4	4.4
FEMALES	550	3.7	3.0	4.6	3.3	4.2
BOTH	553	3.8	3.3	4.6	3.4	4.3

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR

FETAL EXTERNAL MALFORMATIONS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %	%	%	%
NUMBER EVALUATED	7606				553						
Live	7606										
Dead	0										
M ANASARCA	3	0.04	0.0	0.6	3	0.5	0.0	9.1	0.0	0.0	0.6
M PROBOSCIS	1	0.01	0.0	0.3	1	0.2	0.0	4.0	0.0	0.0	0.3
M BRACHYGNATHIA	1	0.01	0.0	0.3	1	0.2	0.0	4.0	0.0	0.0	0.3
M AGLOSSOSTOMIA	1	0.01	0.0	0.3	1	0.2	0.0	4.0	0.0	0.0	0.3
M CLEFT PALATE	6	0.08	0.0	1.2	3	0.5	0.0	4.5	0.1	0.0	1.0
M MICROPHTHALMIA	1	0.01	0.0	0.3	1	0.2	0.0	4.2	0.0	0.0	0.6
M OPEN EYE	1	0.01	0.0	0.3	1	0.2	0.0	4.0	0.0	0.0	0.3
M MALPOSITION OF EYE(S)	1	0.01	0.0	0.3	1	0.2	0.0	4.0	0.0	0.0	0.3
M DISLOCATION OF EAR(S)	1	0.01	0.0	0.3	1	0.2	0.0	4.0	0.0	0.0	0.3
TOTAL FETAL EXTERNAL MALFORMATIONS	10	0.1	0.0	1.2	7	1.3	0.0	9.1	0.1	0.0	1.0

OBSERVATION CODE: M=Malformation

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR

FETAL EXTERNAL VARIATIONS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	7606				553						
Live	7606										
Dead	0										
TOTAL FETAL EXTERNAL VARIATIONS	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0	0.0	0.0

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR

FETAL EXTERNAL UNCLASSIFIED FINDINGS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	7606				553						
Live	7606										
Dead	0										
U PLACENTAE FUSED	13	0.2	0.0	0.6	12	2.2	0.0	9.1	0.2	0.0	0.6
TOTAL FETAL EXTERNAL UNCLASSIFIED FIND	13	0.2	0.0	0.6	12	2.2	0.0	9.1	0.2	0.0	0.6

OBSERVATION CODE: U=Unclassified

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR
SUPPLIER [redacted]

FETAL SOFT TISSUE MALFORMATIONS

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %	%	%	%
NUMBER EVALUATED	3664				551						
Live	3664										
Dead	0										
M HYDROCEPHALY	1	0.03	0.0	0.9	1	0.2	0.0	5.6	0.1	0.0	1.9
M DILATATION OF AORTIC ARCH AND AORTA DESC.	1	0.03	0.0	0.6	1	0.2	0.0	4.2	0.0	0.0	0.5
M DILATATION OF BOTH VENTRICLES (GLOBULAR SHAPED HEART)	4	0.1	0.0	0.7	4	0.7	0.0	4.3	0.1	0.0	0.7
M HEART: DILATATION OF RIGHT VENTRICLE	3	0.08	0.0	1.2	3	0.5	0.0	8.0	0.1	0.0	1.5
TOTAL FETAL SOFT TISSUE MALFORMATIONS	8	0.2	0.0	1.2	8	1.5	0.0	8.0	0.3	0.0	1.9

OBSERVATION CODE: M=Malformation

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR
SUPPLIER [redacted]

FETAL SOFT TISSUE VARIATIONS

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %	%	%	%
NUMBER EVALUATED	3664				551						
Live	3664										
Dead	0										
V DILATED RENAL PELVIS	538	14.7	4.9	33.1	283	51.4	33.3	80.0	15.4	4.9	35.1
V HYDROURETER	108	2.9	0.0	8.2	87	15.8	0.0	34.8	3.0	0.0	7.1
TOTAL FETAL SOFT TISSUE VARIATIONS	539	14.7	4.9	33.1	284	51.5	33.3	80.0	15.4	4.9	35.1

OBSERVATION CODE: V=Variation

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR

FETAL SOFT TISSUE UNCLASSIFIED FINDINGS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER %MEAN	RANGE (per study)	
	N	%	%	%	N	%	%		%	%	%
NUMBER EVALUATED	3664				551						
Live	3664										
Dead	0										
U BLOODY IMBIBITION OF KIDNEY(S)	3	0.08	0.0	0.7	3	0.5	0.0	4.3	0.1	0.0	0.7
TOTAL FETAL SOFT TISSUE UNCLASSIFIED FIND	3	0.08	0.0	0.7	3	0.5	0.0	4.3	0.1	0.0	0.7

OBSERVATION CODE: U=Unclassified

10-DEC-19

TABLE :

SPECIES RAT

STRAIN WISTAR
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SKELETAL MALFORMATIONS

DATES: 01-JAN-91 - 31-DEC-95

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN	AFFECTED FETUSES /LITTER %	RANGE (per study) %	RANGE (per study) %
NUMBER EVALUATED	3942				553						
Live	3942										
Dead	0										
M FETUS WITH MULTIPLE MALFORMATIONS OF RIBS AND VERTEBR. COL.	2	0.05	0.0	0.7	2	0.4	0.0	4.3	0.0	0.0	0.6
M MANDIBLE FUSED	1	0.03	0.0	0.7	1	0.2	0.0	4.3	0.0	0.0	0.5
M FETUS WITH MULTIPLE MALFORMATIONS (SKULL)	1	0.03	0.0	0.6	1	0.2	0.0	4.0	0.0	0.0	0.6
M EXOCCIPITAL BONE(S) FUSED WITH ATLAS	1	0.03	0.0	0.6	1	0.2	0.0	4.0	0.0	0.0	0.6
M VERTEBRAE FUSED AND/OR OF IRREGULAR SHAPE	2	0.05	0.0	1.1	1	0.2	0.0	4.3	0.0	0.0	1.0
M THORACIC VERTEBRAL BODY/BODIES DUMBBELL-SHAPED (ASYMMETR.)	120	3.0	0.0	8.8	98	17.7	0.0	39.1	3.1	0.0	7.6
M THORACIC VERTEBRAL BODY/BODIES BIPARTITE (ASYMMETRICAL)	26	0.7	0.0	1.9	25	4.5	0.0	13.0	0.6	0.0	1.9
M THORACIC VERTEBRA ABSENT	2	0.05	0.0	1.2	2	0.4	0.0	9.1	0.0	0.0	1.1
M LUMBAR VERTEBRA ABSENT	2	0.05	0.0	1.3	1	0.2	0.0	4.5	0.0	0.0	1.0
M DIFF.LUMB.VERTEBR.BOD. AND/OR ARCHES SEVERELY MALFORMED	1	0.03	0.0	0.6	1	0.2	0.0	4.3	0.0	0.0	0.7
M LUMBAR VERTEBRAL BODY/BODIES BIPARTITE (ASYMMETRICAL)	2	0.05	0.0	0.6	2	0.4	0.0	4.3	0.0	0.0	0.6
M LUMBAR VERTEBRAL BODY/BODIES DUMBBELL-SHAPED (ASYMMETR.)	1	0.03	0.0	0.6	1	0.2	0.0	4.0	0.0	0.0	0.5
M DEFORMED CLAVICLE	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.3

OBSERVATION CODE: M=Malformation

10-DEC-19

TABLE :

SPECIES RAT

STRAIN WISTAR
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SKELETAL MALFORMATIONS

DATES: 01-JAN-91 - 31-DEC-95

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN	AFFECTED FETUSES /LITTER %	RANGE (per study) %	RANGE (per study) %
NUMBER EVALUATED	3942				553						
Live	3942										
Dead	0										
M STERNEBRA(E) BIPARTITE, OSSIFICATION CENTERS DISLOCATED	27	0.7	0.0	2.7	26	4.7	0.0	20.0	0.6	0.0	2.7
M STERNEBRAE SEVERELY FUSED (BONY PLATE)	1	0.03	0.0	0.6	1	0.2	0.0	4.5	0.0	0.0	0.5
M MALPOSITIONED AND BIPARTITE STERNEBRA	2	0.05	0.0	2.7	2	0.4	0.0	20.0	0.0	0.0	2.7
M RIB(S) ABSENT	2	0.05	0.0	1.2	2	0.4	0.0	9.1	0.0	0.0	1.1
TOTAL FETAL SKELETAL MALFORMATIONS	172	4.4	0.0	10.1	134	24.2	0.0	43.5	4.4	0.0	8.7

OBSERVATION CODE: M=Malformation

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR

FETAL SKELETAL VARIATIONS

SUPPLIER [redacted]

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN	AFFECTED FETUSES /LITTER %	RANGE (per study) %	RANGE (per study) %
NUMBER EVALUATED	3942				553						
Live	3942										
Dead	0										
V EPACTAL BONE BETWEEN PARIETAL AND INTERPARIETAL BONES	5	0.1	0.0	1.2	5	0.9	0.0	8.7	0.1	0.0	1.3
V INCOMPLETE OSSIFICATION OF SKULL	2	0.05	0.0	2.7	2	0.4	0.0	20.0	0.0	0.0	2.7
V INCOMPLETE OSSIFICATION OF HYOID	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.3
V ACCESSORY THORACIC VERTEBRA	2	0.05	0.0	0.7	2	0.4	0.0	4.3	0.1	0.0	0.7
V DUMBBELL OSSIFICATION OF THORACIC CENTRUM	17	0.4	0.0	22.7	8	1.4	0.0	80.0	0.4	0.0	23.0
V INCOMPLETE OSSIFICATION OF THORACIC CENTRUM	6	0.2	0.0	8.0	4	0.7	0.0	40.0	0.1	0.0	8.2
V BIPARTITE OSSIFICATION OF THORACIC CENTRUM	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.3
V UNOSSIFIED THORACIC CENTRUM	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.4
V ACCESSORY LUMBAR VERTEBRA	3	0.08	0.0	0.7	3	0.5	0.0	4.3	0.1	0.0	2.2
V INCOMPLETE OSSIFICATION OF LUMBAR ARCH	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.4
V INCOMPLETE OSSIFICATION OF SACRAL VERTEBRA	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.4
V CLAVICULA DEFORMED	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.3
V STERNEBRA(E) OF IRREGULAR SHAPE	1387	35.2	0.0	44.0	491	88.8	0.0	100.0	35.3	0.0	46.2
V STERNEBRA(E) BIPARTITE	53	1.3	0.0	3.6	50	9.0	0.0	20.0	1.3	0.0	3.3

OBSERVATION CODE: V=Variation

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR
SUPPLIER [redacted]

FETAL SKELETAL VARIATIONS

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %	%	%	%
NUMBER EVALUATED	3942				553						
Live	3942										
Dead	0										
V ACCESSORY STERNEBRA	5	0.1	0.0	0.7	5	0.9	0.0	4.5	0.1	0.0	0.7
V UNOSSIFIED STERNEBRA	7	0.2	0.0	9.3	4	0.7	0.0	40.0	0.2	0.0	8.9
V INCOMPLETE OSSIFICATION OF STERNEBRA	18	0.5	0.0	24.0	9	1.6	0.0	90.0	0.4	0.0	23.9
V UNILATERAL OSSIFICATION OF STERNEBRA	8	0.2	0.0	10.7	6	1.1	0.0	60.0	0.2	0.0	11.3
V MISSHAPEN STERNEBRA	29	0.7	0.0	38.7	10	1.8	0.0	100.0	0.7	0.0	39.1
V BIPARTITE OSSIFICATION OF STERNEBRA	2	0.05	0.0	2.7	2	0.4	0.0	20.0	0.0	0.0	2.7
V 13TH RIB(S) SHORTENED	366	9.3	0.0	20.8	204	36.9	0.0	75.0	9.4	0.0	21.0
V RUDIMENTARY CERVICAL RIB(S)	83	2.1	0.0	6.6	60	10.8	0.0	30.4	2.2	0.0	5.9
V ACCESSORY 14TH RIB(S)	41	1.0	0.0	4.1	34	6.1	0.0	16.0	1.0	0.0	3.4
V 13TH RIB(S) ABSENT	1	0.03	0.0	0.6	1	0.2	0.0	4.2	0.0	0.0	0.6
V FLYING RIB(S)	1	0.03	0.0	0.6	1	0.2	0.0	4.0	0.0	0.0	0.6
V SHORT RIB (13TH)	9	0.2	0.0	12.0	6	1.1	0.0	60.0	0.2	0.0	12.4
V CERVICAL RIB	2	0.05	0.0	2.7	1	0.2	0.0	10.0	0.1	0.0	3.3
V INCOMPLETE OSSIFICATION OF METACARPAL	2	0.05	0.0	2.7	2	0.4	0.0	20.0	0.0	0.0	2.7
V INCOMPLETE OSSIFICATION OF METATARSAL	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.4
V INCOMPLETE OSSIFICATION OF PUBIS	1	0.03	0.0	1.3	1	0.2	0.0	10.0	0.0	0.0	1.4

OBSERVATION CODE: V=Variation

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

DATES: 01-JAN-91 - 31-DEC-95

STRAIN WISTAR

FETAL SKELETAL VARIATIONS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
TOTAL FETAL SKELETAL VARIATIONS	1752	44.4	34.5	73.3	520	94.0	80.0	100.0	44.5	32.7	73.5

10-DEC-19

TABLE :

SPECIES RAT

STRAIN WISTAR
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SKELETAL RETARDATIONS

DATES: 01-JAN-91 - 31-DEC-95

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN	AFFECTED FETUSES /LITTER %	AFFECTED FETUSES /LITTER RANGE (per study) %	AFFECTED FETUSES /LITTER RANGE (per study) %
NUMBER EVALUATED	3942				553						
Live	3942										
Dead	0										
R SKULL INCOMPLETELY OSSIFIED	38	1.0	0.0	4.0	33	6.0	0.0	28.0	0.9	0.0	4.0
R HYOID BONE NOT OSSIFIED	4	0.1	0.0	1.2	4	0.7	0.0	8.7	0.1	0.0	1.0
R HYOID BONE INCOMPLETELY OSSIFIED	12	0.3	0.0	1.3	12	2.2	0.0	10.0	0.3	0.0	1.3
R INTERPARIETAL AND/OR PARIETAL BONES INCOMPLETELY OSSIFIED	9	0.2	0.0	2.9	5	0.9	0.0	12.5	0.2	0.0	2.9
R CERVICAL VERTEBRAL ARCH(ES) INCOMPLETELY OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.0	0.0	0.0	0.6
R THORACIC VERTEBRAL BODY/BODIES DUMBBELL-SHAPED (SYMMETR.)	464	11.8	0.0	25.6	271	49.0	0.0	82.6	12.2	0.0	30.7
R THORACIC VERTEBRAL BODY/BODIES INCOMPLETELY OSSIFIED	415	10.5	0.0	49.1	196	35.4	0.0	100.0	10.5	0.0	50.0
R THORACIC VERTEBR. BODY/BODIES-ONLY ONE OSSIFICATION CENTER	12	0.3	0.0	1.2	12	2.2	0.0	8.7	0.3	0.0	1.2
R THORACIC VERTEBRAL BODY/BODIES BIPARTITE (SYMMETRICAL)	3	0.08	0.0	0.6	3	0.5	0.0	4.5	0.1	0.0	1.1
R THORACIC VERTEBRAL BODY/BODIES NOT OSSIFIED	6	0.2	0.0	1.3	6	1.1	0.0	10.0	0.2	0.0	1.4
R THORACIC VERTEBRAL ARCH(ES) INCOMPLETELY OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.0	0.0	0.0	0.6
R THORACIC VERTEBRAL BODY/BODIES DUMBBELL-SHAPED	40	1.0	0.0	11.9	26	4.7	0.0	54.2	1.1	0.0	12.4

OBSERVATION CODE: R=Retardation

10-DEC-19

TABLE :

SPECIES RAT

STRAIN WISTAR
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SKELETAL RETARDATIONS

DATES: 01-JAN-91 - 31-DEC-95

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN	AFFECTED FETUSES /LITTER %	AFFECTED FETUSES /LITTER RANGE (per study) %	AFFECTED FETUSES /LITTER RANGE (per study) %
NUMBER EVALUATED	3942				553						
Live	3942										
Dead	0										
R THORACIC VERTEBRAL BODY/BODIES BIPARTITE	1	0.03	0.0	0.6	1	0.2	0.0	4.0	0.1	0.0	1.3
R LUMBAR VERTEBRAL BODY/BODIES NOT OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.3	0.0	0.0	0.5
R LUMBAR VERTEBRAL BODY/BODIES INCOMPLETELY OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.3	0.0	0.0	0.5
R LUMBAR VERTEBRAL BODY/BODIES DUMBBELL-SHAPED (SYMMETRICAL)	2	0.05	0.0	0.6	2	0.4	0.0	4.3	0.0	0.0	0.5
R LUMBAR VERTEBRAL BODY/BODIES-ONLY ONE OSSIFICATION CENTER	1	0.03	0.0	0.6	1	0.2	0.0	4.3	0.0	0.0	0.7
R LUMBAR VERTEBRAL ARCH(ES) INCOMPLETELY OSSIFIED	6	0.2	0.0	1.3	5	0.9	0.0	10.0	0.2	0.0	1.4
R SACRAL VERTEBRAL BODY/BODIES NOT OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.3	0.0	0.0	0.5
R SACRAL VERTEBRA(E) INCOMPLETELY OSSIFIED	3	0.08	0.0	1.3	3	0.5	0.0	10.0	0.1	0.0	1.4
R SACRAL VERTEBRA(E) NOT OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.3	0.0	0.0	0.5
R CAUDAL VERTEBRA(E) NOT OSSIFIED	2	0.05	0.0	0.6	2	0.4	0.0	4.3	0.0	0.0	0.6
R STERNEBRA(E) NOT OSSIFIED	269	6.8	0.0	13.0	183	33.1	0.0	56.0	6.6	0.0	12.1
R STERNEBRA(E) INCOMPLETELY OSSIFIED OR REDUCED IN SIZE	900	22.8	0.0	54.8	377	68.2	0.0	95.5	22.1	0.0	53.8

OBSERVATION CODE: R=Retardation

10-DEC-19

TABLE :

SPECIES RAT

HISTORICAL CONTROL DATA

STRAIN WISTAR

SUPPLIER [redacted]

FETAL SKELETAL RETARDATIONS

DATES: 01-JAN-91 - 31-DEC-95

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER RANGE (per study)		
	N	%	%	%	N	%	%	%MEAN %	%	%	%
NUMBER EVALUATED	3942				553						
Live	3942										
Dead	0										
R STERNEBRA(E)-ONLY ONE OSSIFICATION CENTER	453	11.5	0.0	19.2	260	47.0	0.0	69.6	11.5	0.0	19.8
R METACARPAL BONES INCOMPLETELY OSSIFIED	6	0.2	0.0	2.7	6	1.1	0.0	20.0	0.1	0.0	2.7
R HINDLIMB(S) INCOMPLETELY OSSIFIED	2	0.05	0.0	1.2	2	0.4	0.0	9.1	0.0	0.0	1.1
R HINDLIMB(S) NOT OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.5	0.0	0.0	0.5
R METATARSAL BONES INCOMPLETELY OSSIFIED	4	0.1	0.0	1.3	4	0.7	0.0	10.0	0.1	0.0	1.4
R METATARSAL BONES NOT OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.5	0.0	0.0	0.5
R OS PUBIS NOT OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.3	0.0	0.0	0.5
R OS ISCHIUM NOT OSSIFIED	1	0.03	0.0	0.6	1	0.2	0.0	4.3	0.0	0.0	0.5
R OS PUBIS INCOMPLETELY OSSIFIED	3	0.08	0.0	1.3	3	0.5	0.0	10.0	0.1	0.0	1.4
TOTAL FETAL SKELETAL RETARDATIONS	1943	49.3	0.0	72.0	507	91.7	0.0	100.0	49.0	0.0	71.5

OBSERVATION CODE: R=Retardation

11-DEC-19

TABLE :

HISTORICAL CONTROL DATA FOR TOTAL MALFORMATIONS AND TOTAL VARIATIONS 01-JAN-91 to 31-DEC-95

STUDIES INCLUDED IN HISTORICAL CONTROL

SPECIES: RAT
STRAIN: WISTAR
SUPPLIER: [redacted]

STUDY#/GROUP		NUMBER EXAMINED FETUSES	LITTERS
89117	1	329	23
89118	1	326	24
90077	1	282	23
90088	1	322	22
90104	1	333	25
90116	1	343	23
91030	1	293	21
91070	1	280	20
91071	1	338	24
91081	1	222	18
91096	1	312	23
91101	1	318	22
91122	1	326	24
92063	1	340	23
92083	1	316	23
92091	1	296	22
93028	1	337	25
93029	1	341	25
93046	1	333	25
93047	1	332	25
93059	1	335	25
94014	1	147	10
94014_A	1	147	10
94017	1	327	24
94050	1	331	24

11-DEC-19

TABLE :

HISTORICAL CONTROL DATA FOR TOTAL MALFORMATIONS AND TOTAL VARIATIONS 01-JAN-91 to 31-DEC-95

SPECIES: RAT
STRAIN: WISTAR
SUPPLIER: [redacted]

	FETUSES				LITTERS				AFFECTED FETUSES/LITTER		
	POOLED		BY STUDY		POOLED		BY STUDY		POOLED	BY STUDY	
	N	%	LO%	HI%	N	%	LO%	HI%	MEAN%	LO%	HI%
NUMBER EVALUATED	7606				553						
TOTAL FETAL MALFORMATIONS	183	2.41	0.30	5.67	141	25.50	4.00	43.48	2.43	0.31	4.80
TOTAL FETAL VARIATIONS	2291	30.12	23.37	46.26	535	96.75	88.00	100.0	30.57	23.57	46.02

10-DEC-19

TABLE :
01-JAN-95 to 31-DEC-00

HISTORICAL CONTROL DATA

SPECIES: RABBIT
STRAIN: HIMALAYAN RABBIT
SUPPLIER: [redacted]
FILENAME: MEPI2019

Study No./Control Group		Start Date	End Date	Route of Administration
92100	1	8-MAY-95		GAVAGE
93064	1	27-DEC-95		GAVAGE
94040	1	2-JAN-95		GAVAGE
96135	1	8-APR-97		GAVAGE
96153	1	6-OCT-97		GAVAGE
96159	1	5-JAN-98		GAVAGE
96180	1	19-APR-99		GAVAGE
96196	1	9-OCT-00		GAVAGE
97127	1	14-SEP-98		GAVAGE
98107	1	11-OCT-99		GAVAGE

10-DEC-19

TABLE :
01-JAN-95 to 31-DEC-00

HISTORICAL CONTROL DATA
MEAN MATERNAL BODY WEIGHTS DURING GESTATION GRAMS

SPECIES: RABBIT
STRAIN: HIMALAYAN RABBIT
SUPPLIER: [redacted]

	NO. OF ANIMALS	MEAN	RANGE OF ACTUAL VALUES		95 % SPREAD 2.5%	97.5%
DAY 0	217	2653	2210	3184	2256	3051
DAY 2	217	2698	2261	3205	2295	3102
DAY 4	217	2694	2236	3200	2287	3100
DAY 6	34	2769	2313	3143	2340	3199
DAY 7	183	2664	2221	3194	2265	3064
DAY 9	217	2680	2251	3204	2277	3084
DAY 11	217	2682	2252	3185	2276	3089
DAY 14	217	2702	2261	3210	2291	3114
DAY 16	217	2742	2300	3292	2331	3154
DAY 18	34	2829	2381	3176	2420	3238
DAY 19	183	2734	2293	3327	2321	3147
DAY 21	217	2746	2331	3322	2331	3162
DAY 23	216	2768	2293	3350	2357	3178
DAY 25	216	2815	2305	3344	2405	3225
DAY 28	147	2864	2471	3507	2461	3267
DAY 29	216	2888	2338	3476	2469	3307

10-DEC-19

TABLE :

SPECIES RABBIT

HISTORICAL CONTROL DATA

DATES: 01-JAN-95 - 31-DEC-00

STRAIN HIMALAYAN RABBIT

REPRODUCTION DATA

SUPPLIER [redacted]

			RANGE (per study)	
Females Mated	N	221		
Pregnant	N	217		
	%	98		
Aborted	N	1		
Premature Births	N	0		
Dams with Viable Fetuses	N	213		
Dams with all Resorptions	N	2		
Female Mortality	N	3		
	%	1.4		
Pregnant at C-section	N	215		
	%	97		
Corpora Lutea	N	1841		
	MEAN	8.6	8.0	8.9
	S.D.	1.73		
Implantation Sites	N	1554		
	MEAN	7.2	6.6	7.7
	S.D.	2.25		
Preimplantation Loss	%	16.0	7.0	25.6
	S.D.	19.57		
Postimplantation Loss	%	11.2	5.2	19.9
	S.D.	16.66		
Dams with Resorptions	N	105		
	%	49		
Resorptions	N	215		
	MEAN	0.7	0.2	1.2
	S.D.	1.01		
	MEAN %	11.1	5.2	19.9
	S.D.	16.67		
Dead Fetuses	N	1		
Viable Fetuses	N	1393		
Litter Size	MEAN	6.5	5.6	7.1
	S.D.	2.34		
Viable Male Fetuses	N	616		
	%	44		

10-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

PLACENTA WEIGHTS -- GRAMS

DATES: 01-JAN-95 - 31-DEC-00

	NO. OF LITTERS	MEAN	RANGE OF ACTUAL VALUES		95 % SPREAD 2.5%	97.5%
MALES	179	4.44	2.80	6.17	3.12	5.75
FEMALES	183	4.31	2.51	7.34	2.94	5.68
BOTH	213	4.42	2.81	7.34	2.99	5.85

10-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

MEAN FETAL WEIGHTS -- GRAMS

DATES: 01-JAN-95 - 31-DEC-00

	NO. OF LITTERS	MEAN	RANGE OF ACTUAL VALUES		95 % SPREAD 2.5%	97.5%
MALES	179	38.1	24.7	49.5	29.5	46.7
FEMALES	183	37.8	20.6	49.0	29.2	46.4
BOTH	213	38.0	23.9	52.6	29.4	46.7

10-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL EXTERNAL MALFORMATIONS

DATES: 01-JAN-95 - 31-DEC-00

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER %MEAN	RANGE (per study)	
	N	%	%	%	N	%	%		%	%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
M FETUS WITH MULTIPLE MALFORMATIONS	2	0.2	0.0	0.9	2	1.1	0.0	5.9	0.1	0.0	0.7
M ACRANIA	1	0.08	0.0	0.9	1	0.5	0.0	5.9	0.1	0.0	1.2
M ECTRODACTYLY	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.7
M MICROMELIA	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.7
M SHORT TAIL	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.8
TOTAL FETAL EXTERNAL MALFORMATIONS	5	0.4	0.0	1.7	5	2.6	0.0	11.8	0.4	0.0	1.9

OBSERVATION CODE: M=Malformation

10-DEC-19

TABLE :

SPECIES RABBIT

HISTORICAL CONTROL DATA

DATES: 01-JAN-95 - 31-DEC-00

STRAIN HIMALAYAN RABBIT

FETAL EXTERNAL VARIATIONS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
V PSEUDOANKYLOSIS (FORELIMB)	5	0.4	0.0	2.6	4	2.1	0.0	11.8	0.4	0.0	3.5
V PAW HYPERFLEXION	14	1.1	0.0	3.7	12	6.3	0.0	17.4	1.0	0.0	3.2
TOTAL FETAL EXTERNAL VARIATIONS	19	1.5	0.0	3.7	16	8.5	0.0	17.4	1.4	0.0	3.5

OBSERVATION CODE: V=Variation

10-DEC-19

TABLE :

SPECIES RABBIT

HISTORICAL CONTROL DATA

DATES: 01-JAN-95 - 31-DEC-00

STRAIN HIMALAYAN RABBIT

FETAL EXTERNAL UNCLASSIFIED FINDINGS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
U PLACENTA(E) NECROBIOTIC	2	0.2	0.0	0.9	2	1.1	0.0	5.9	0.2	0.0	0.7
U BLOOD COAGULUM AROUND PLACENTA	1	0.08	0.0	0.7	1	0.5	0.0	4.0	0.1	0.0	0.7
TOTAL FETAL EXTERNAL UNCLASSIFIED FIND	2	0.2	0.0	0.9	2	1.1	0.0	5.9	0.2	0.0	0.7

OBSERVATION CODE: U=Unclassified

11-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SOFT TISSUE MALFORMATIONS

DATES: 01-JAN-95 - 31-DEC-00

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
M FETUS WITH MULTIPLE MALFORMATIONS	1	0.08	0.0	0.9	1	0.5	0.0	5.9	0.1	0.0	0.7
M EFFERENT URINARY TRACT SEVERELY DILATED	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	0.7
M HYDROCEPHALY	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.4
M PERSISTENT TRUNCUS ARTERIOSUS	1	0.08	0.0	0.7	1	0.5	0.0	4.3	0.1	0.0	0.6
M MALPOSITIONED PULMONARY ARTERY	1	0.08	0.0	0.7	1	0.5	0.0	4.3	0.1	0.0	0.7
M MALPOSITIONED AORTA	1	0.08	0.0	0.7	1	0.5	0.0	4.3	0.1	0.0	0.7
M SEPTAL DEFECT	4	0.3	0.0	2.6	4	2.1	0.0	17.6	0.3	0.0	2.5
M MUSCULAR VENTRICULAR SEPTUM DEFECT	5	0.4	0.0	3.0	4	2.1	0.0	13.0	0.4	0.0	2.6
M MEMBRANOUS VENTRICULAR SEPTUM DEFECT	2	0.2	0.0	0.7	2	1.1	0.0	4.3	0.2	0.0	0.7
M HEART: SMALL VENTRICULAR CHAMBER	1	0.08	0.0	0.7	1	0.5	0.0	4.3	0.1	0.0	0.7
M SMALL LUNG	1	0.08	0.0	0.7	1	0.5	0.0	4.0	0.1	0.0	0.6
M HERNIA DIAPHRAGMATICA	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	0.7
M DIAPHRAGMATIC HERNIA	1	0.08	0.0	0.7	1	0.5	0.0	4.0	0.1	0.0	0.6
M SMALL SPLEEN	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.5
M AGENESIA OF GALLBLADDER	2	0.2	0.0	0.8	2	1.1	0.0	5.9	0.4	0.0	2.5
M ABSENT GALLBLADDER	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.8
M AGENESIA OF KIDNEY(S)	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	1.0

OBSERVATION CODE: M=Malformation

11-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SOFT TISSUE MALFORMATIONS

DATES: 01-JAN-95 - 31-DEC-00

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
M HYDRONEPHROSIS	1	0.08	0.0	0.7	1	0.5	0.0	4.0	0.1	0.0	0.8
M MALPOSITIONED KIDNEY	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.5
M AGENESIA OF ADRENAL(S)	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	1.0
M AGENESIA OF URETER(S)	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	1.0
M HYDROURETER	1	0.08	0.0	0.7	1	0.5	0.0	4.0	0.1	0.0	0.8
TOTAL FETAL SOFT TISSUE MALFORMATIONS	20	1.6	0.0	3.7	19	10.1	0.0	23.5	1.8	0.0	3.3

OBSERVATION CODE: M=Malformation

11-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SOFT TISSUE VARIATIONS

DATES: 01-JAN-95 - 31-DEC-00

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
V DILATED CEREBRAL VENTRICLE	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.6
V SEPARATED ORIGIN OF CAROTIDS	53	4.3	0.0	17.4	32	16.9	0.0	64.7	4.4	0.0	15.2
V MALPOSITIONED CAROTID BRANCH	92	7.5	0.0	18.3	61	32.3	0.0	70.8	7.4	0.0	17.2
V HEART: TRACES OF INTERVENTRIC.FORAMEN/SEPTUM MEMBRANACEUM	14	1.1	0.0	5.0	13	6.9	0.0	29.4	1.3	0.0	4.9
V HYPOPLASIA OF GALLBLADDER	1	0.08	0.0	1.0	1	0.5	0.0	6.7	0.1	0.0	0.7
V SMALL GALLBLADDER	2	0.2	0.0	1.2	2	1.1	0.0	8.3	0.2	0.0	1.3
TOTAL FETAL SOFT TISSUE VARIATIONS	161	13.1	5.2	20.0	104	55.0	26.1	82.4	13.0	5.3	19.8

OBSERVATION CODE: V=Variation

11-DEC-19

TABLE :

SPECIES RABBIT

HISTORICAL CONTROL DATA

DATES: 01-JAN-95 - 31-DEC-00

STRAIN HIMALAYAN RABBIT

FETAL SOFT TISSUE UNCLASSIFIED FINDINGS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %	%	%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
U FLUID-FILLED ABDOMEN	8	0.7	0.0	5.0	4	2.1	0.0	16.7	0.6	0.0	4.4
U LIVER: FOCAL NECROSIS	2	0.2	0.0	1.7	2	1.1	0.0	11.8	0.1	0.0	1.5
U INFARCT OF LIVER	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	1.0
U BLOOD COAGULUM AROUND URINARY BLADDER	7	0.6	0.0	3.1	5	2.6	0.0	13.3	0.5	0.0	2.6
TOTAL FETAL SOFT TISSUE UNCLASSIFIED FIND	18	1.5	0.0	6.2	12	6.3	0.0	20.8	1.3	0.0	5.8

OBSERVATION CODE: U=Unclassified

11-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SKELETAL MALFORMATIONS

DATES: 01-JAN-95 - 31-DEC-00

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN	AFFECTED FETUSES /LITTER %	RANGE (per study) %	RANGE (per study) %
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
M FETUS WITH MULTIPLE MALFORMATIONS	2	0.2	0.0	0.9	2	1.1	0.0	5.9	0.1	0.0	0.7
M SKULL BONES SEVERELY MALFORMED	1	0.08	0.0	0.9	1	0.5	0.0	5.9	0.1	0.0	1.2
M SUPERNUMERARY VERTEBRAL ARCH WITH UNILATERAL CENTER	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	1.0
M THORACIC CENTER, ARCH AND CORRESPONDING RIB ABSENT	2	0.2	0.0	0.7	2	1.1	0.0	4.3	0.2	0.0	1.0
M FUSED AND/OR MISSHAPEN CERVICAL VERTEBRA	1	0.08	0.0	0.7	1	0.5	0.0	4.0	0.1	0.0	0.8
M FUSED CERVICAL VERTEBRA	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.2	0.0	1.4
M THORACIC VERTEBRA ABSENT	1	0.08	0.0	0.9	1	0.5	0.0	5.9	0.1	0.0	0.8
M MISSHAPEN THORACIC VERTEBRA	1	0.08	0.0	0.7	1	0.5	0.0	4.3	0.1	0.0	0.5
M LUMBAR VERTEBRA ABSENT	1	0.08	0.0	0.9	1	0.5	0.0	5.9	0.1	0.0	0.8
M ABSENT LUMBAR VERTEBRA	5	0.4	0.0	1.3	4	2.1	0.0	8.3	0.4	0.0	1.6
M MISSHAPEN LUMBAR VERTEBRA	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.5
M MISSHAPEN SACRAL VERTEBRA	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.8
M MISSHAPEN SCAPULA	2	0.2	0.0	1.2	2	1.1	0.0	8.3	0.1	0.0	1.1
M STERNEBRAE SEVERELY FUSED (BONY PLATE)	4	0.3	0.0	2.0	4	2.1	0.0	12.0	0.4	0.0	2.6
M BONY PLATE (STERNEBRAE SEVERELY FUSED)	2	0.2	0.0	0.7	2	1.1	0.0	4.3	0.2	0.0	0.8

OBSERVATION CODE: M=Malformation

11-DEC-19

TABLE :

SPECIES RABBIT

HISTORICAL CONTROL DATA

STRAIN HIMALAYAN RABBIT

FETAL SKELETAL MALFORMATIONS

DATES: 01-JAN-95 - 31-DEC-00

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
M SEVERELY MALFORMED STERNUM	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.7
M BIFURCATED RIB(S)	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	1.0
M SUPERNUMERARY RIB	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	1.0
M BRANCHED RIB	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.7
M SEVERELY MALFORMED FORELIMB	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.7
TOTAL FETAL SKELETAL MALFORMATIONS	24	2.0	0.0	3.6	22	11.6	0.0	25.0	2.2	0.0	3.8

OBSERVATION CODE: M=Malformation

11-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SKELETAL VARIATIONS

DATES: 01-JAN-95 - 31-DEC-00

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN	AFFECTED FETUSES /LITTER %	RANGE (per study) %	RANGE (per study) %
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
V EPACTAL BONE BETWEEN NASAL AND FRONTAL BONES	21	1.7	0.0	5.8	18	9.5	0.0	35.3	1.7	0.0	5.5
V SPLITTING OF SKULL BONE(S)	12	1.0	0.0	5.0	11	5.8	0.0	29.4	1.1	0.0	5.2
V INCOMPLETE OSSIFICATION OF HYOID	117	9.5	0.0	24.5	72	38.1	0.0	76.0	10.4	0.0	29.1
V SPLITTING OF SKULL BONE	14	1.1	0.0	6.6	12	6.3	0.0	32.0	1.4	0.0	8.1
V INCOMPLETE OSSIFICATION OF PARIETAL AND/OR INTERPARIETAL	5	0.4	0.0	3.3	5	2.6	0.0	20.0	0.4	0.0	2.9
V EXTRA OSSIFICATION SITE (BETW. NASAL AND FRONTAL)	25	2.0	0.0	5.3	20	10.6	0.0	20.0	2.0	0.0	5.5
V PARIETAL HOLE(S)	9	0.7	0.0	3.0	9	4.8	0.0	20.8	1.1	0.0	6.6
V EXTRA OSSIFICATION SITE (BETW. PARIETALS)	1	0.08	0.0	0.7	1	0.5	0.0	4.3	0.1	0.0	0.5
V INCOMPLETE OSSIFICATION OF CERVICAL CENTRUM	55	4.5	0.0	9.8	36	19.0	0.0	43.5	4.8	0.0	11.6
V UNOSSIFIED CERVICAL CENTRUM	2	0.2	0.0	1.2	2	1.1	0.0	8.3	0.2	0.0	1.3
V DUMBBELL OSSIFICATION OF CERVICAL CENTRUM	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.5
V ACCESSORY THORACIC VERTEBRA	2	0.2	0.0	1.7	2	1.1	0.0	11.8	0.2	0.0	2.2
V INCOMPLETE OSSIFICATION OF THORACIC CENTRUM	8	0.7	0.0	4.0	7	3.7	0.0	20.0	0.6	0.0	3.2

OBSERVATION CODE: V=Variation

11-DEC-19

TABLE :

SPECIES RABBIT

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

HISTORICAL CONTROL DATA

FETAL SKELETAL VARIATIONS

DATES: 01-JAN-95 - 31-DEC-00

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN %	AFFECTED FETUSES /LITTER RANGE (per study) %	AFFECTED FETUSES /LITTER RANGE (per study) %	AFFECTED FETUSES /LITTER RANGE (per study) %
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
V DUMBBELL OSSIFICATION OF THORACIC CENTRUM	3	0.2	0.0	1.3	2	1.1	0.0	4.3	0.2	0.0	0.9
V SUPERNUMERARY THORACIC VERTEBRA	2	0.2	0.0	0.6	2	1.1	0.0	4.2	0.2	0.0	0.7
V INCOMPLETE OSSIFICATION OF LUMBAR ARCH	11	0.9	0.0	2.6	10	5.3	0.0	13.0	1.0	0.0	2.8
V SUPERNUMERARY LUMBAR VERTEBRA	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.7
V INCOMPLETE OSSIFICATION OF SACRAL ARCH	5	0.4	0.0	1.5	5	2.6	0.0	8.7	0.6	0.0	3.0
V STERNEBRA(E) OF IRREGULAR SHAPE	25	2.0	0.0	11.6	20	10.6	0.0	45.0	2.1	0.0	11.0
V STERNEBRAE FUSED	16	1.3	0.0	6.6	16	8.5	0.0	40.0	1.6	0.0	8.3
V ACCESSORY STERNEBRA	2	0.2	0.0	1.0	2	1.1	0.0	6.7	0.3	0.0	3.3
V UNOSSIFIED STERNEBRA	183	14.9	0.0	28.6	78	41.3	0.0	79.2	13.6	0.0	25.3
V INCOMPLETE OSSIFICATION OF STERNEBRA	189	15.4	0.0	29.2	95	50.3	0.0	87.5	15.5	0.0	31.6
V FUSED STERNEBRA	30	2.4	0.0	7.5	22	11.6	0.0	25.0	2.4	0.0	7.4
V MISSHAPEN STERNEBRA	31	2.5	0.0	6.6	26	13.8	0.0	33.3	2.4	0.0	6.1
V EXTRA STERNEBRAL OSSIFICATION SITE	5	0.4	0.0	2.0	4	2.1	0.0	8.3	0.4	0.0	2.0
V ACCESSORY 13TH RIB(S)	12	1.0	0.0	7.4	7	3.7	0.0	29.4	1.1	0.0	8.3
V RUDIMENTARY CERVICAL RIB(S)	2	0.2	0.0	0.9	2	1.1	0.0	5.9	0.1	0.0	0.8
V 12TH RIB(S) SHORTENED	1	0.08	0.0	0.9	1	0.5	0.0	5.9	0.1	0.0	0.8

OBSERVATION CODE: V=Variation

11-DEC-19

TABLE :

SPECIES RABBIT

HISTORICAL CONTROL DATA

DATES: 01-JAN-95 - 31-DEC-00

STRAIN HIMALAYAN RABBIT

FETAL SKELETAL VARIATIONS

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %	%	%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
V 12TH RIB(S) ABSENT	2	0.2	0.0	1.7	1	0.5	0.0	5.9	0.2	0.0	1.7
V FLYING RIB(S)	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	0.7
V SUPERNUMERARY RIB (13TH)	48	3.9	0.0	14.0	32	16.9	0.0	50.0	4.5	0.0	17.9
V CERVICAL RIB	2	0.2	0.0	0.7	2	1.1	0.0	4.3	0.1	0.0	0.5
V SHORT RIB (12TH)	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.1	0.0	0.5
V INCOMPLETE OSSIFICATION OF TALUS	7	0.6	0.0	2.2	6	3.2	0.0	8.7	0.5	0.0	2.0
V INCOMPLETE OSSIFICATION OF PUBIS	1	0.08	0.0	0.6	1	0.5	0.0	4.2	0.0	0.0	0.4
TOTAL FETAL SKELETAL VARIATIONS	594	48.3	11.5	73.5	166	87.8	58.8	100.0	49.2	14.8	73.7

OBSERVATION CODE: V=Variation

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TABLE :

SPECIES RABBIT

HISTORICAL CONTROL DATA

DATES: 01-JAN-95 - 31-DEC-00

STRAIN HIMALAYAN RABBIT
SUPPLIER [redacted]

FETAL SKELETAL RETARDATIONS

	FETUSES N	FETUSES %	%RANGE (per study) %	%RANGE (per study) %	LITTERS N	LITTERS %	%RANGE (per study) %	%RANGE (per study) %MEAN	AFFECTED FETUSES /LITTER %	AFFECTED FETUSES /LITTER RANGE (per study) %	AFFECTED FETUSES /LITTER RANGE (per study) %
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
R HYOID BONE INCOMPLETELY OSSIFIED	77	6.3	0.0	46.3	32	16.9	0.0	94.1	6.4	0.0	48.8
R SKULL INCOMPLETELY OSSIFIED	2	0.2	0.0	2.1	2	1.1	0.0	13.3	0.1	0.0	1.7
R INTERPARIETAL AND/OR PARIETAL BONES INCOMPLETELY OSSIFIED	8	0.7	0.0	4.3	6	3.2	0.0	23.5	0.7	0.0	5.9
R ENLARGED FRONTAL FONTANELLE	2	0.2	0.0	1.0	2	1.1	0.0	6.7	0.1	0.0	0.7
R CERVICAL VERTEBRAL BODY/BODIES INCOMPLETELY OSSIFIED	21	1.7	0.0	11.6	16	8.5	0.0	58.8	1.8	0.0	11.7
R THORACIC VERTEBRAL BODY/BODIES INCOMPLETELY OSSIFIED	2	0.2	0.0	1.7	2	1.1	0.0	11.8	0.2	0.0	1.8
R THORACIC VERTEBRAL BODY/BODIES DUMBBELL-SHAPED	1	0.08	0.0	0.9	1	0.5	0.0	5.9	0.1	0.0	1.2
R LUMBAR VERTEBRAL ARCH(ES) INCOMPLETELY OSSIFIED	2	0.2	0.0	0.9	2	1.1	0.0	5.9	0.1	0.0	0.7
R SACRAL VERTEBRAL ARCH(ES) INCOMPLETELY OSSIFIED	5	0.4	0.0	3.5	4	2.1	0.0	17.6	0.4	0.0	2.8
R SACRAL VERTEBRAL ARCH(ES) NOT OSSIFIED	1	0.08	0.0	0.9	1	0.5	0.0	5.9	0.1	0.0	0.6
R SCAPULA(E) INCOMPLETELY OSSIFIED	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	1.2
R STERNEBRA(E) NOT OSSIFIED	106	8.6	0.0	28.1	48	25.4	0.0	76.5	8.4	0.0	27.6
R STERNEBRA(E) INCOMPLETELY OSSIFIED OR REDUCED IN SIZE	121	9.8	0.0	34.4	56	29.6	0.0	93.3	9.4	0.0	35.2

OBSERVATION CODE: R=Retardation

11-DEC-19

TABLE :

SPECIES RABBIT

HISTORICAL CONTROL DATA

STRAIN HIMALAYAN RABBIT

FETAL SKELETAL RETARDATIONS

DATES: 01-JAN-95 - 31-DEC-00

SUPPLIER [redacted]

	FETUSES		%RANGE (per study)		LITTERS		%RANGE (per study)		AFFECTED FETUSES /LITTER	RANGE (per study)	
	N	%	%	%	N	%	%	%MEAN %		%	%
NUMBER EVALUATED	1230				189						
Live	1229										
Dead	1										
R RIB(S) INCOMPLETELY OSSIFIED	1	0.08	0.0	0.8	1	0.5	0.0	5.9	0.1	0.0	1.2
R TALUS INCOMPLETELY OSSIFIED	13	1.1	0.0	5.0	8	4.2	0.0	15.0	0.9	0.0	4.2
R OS PUBIS INCOMPLETELY OSSIFIED	3	0.2	0.0	1.7	3	1.6	0.0	11.8	0.2	0.0	1.3
TOTAL FETAL SKELETAL RETARDATIONS	283	23.0	0.0	83.5	68	36.0	0.0	100.0	22.7	0.0	84.3

OBSERVATION CODE: R=Retardation

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TABLE :

HISTORICAL CONTROL DATA FOR TOTAL MALFORMATIONS AND TOTAL VARIATIONS 01-JAN-95 to 31-DEC-00

STUDIES INCLUDED IN HISTORICAL CONTROL

SPECIES: RABBIT
STRAIN: HIMALAYAN RABBIT
SUPPLIER: [redacted]

STUDY#/GROUP		NUMBER EXAMINED FETUSES	LITTERS
92100	1	121	20
93064	1	114	17
94040	1	96	15
96135	1	121	17
96153	1	151	25
96159	1	166	24
96180	1	164	24
97127	1	135	23
98107	1	161	24

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TABLE :

HISTORICAL CONTROL DATA FOR TOTAL MALFORMATIONS AND TOTAL VARIATIONS 01-JAN-95 to 31-DEC-00

SPECIES: RABBIT
STRAIN: HIMALAYAN RABBIT
SUPPLIER: [redacted]

	FETUSES				LITTERS				AFFECTED FETUSES/LITTER		
	POOLED		BY STUDY		POOLED		BY STUDY		POOLED	BY STUDY	
	N	%	LO%	HI%	N	%	LO%	HI%	MEAN%	LO%	HI%
NUMBER EVALUATED	1229				189						
TOTAL FETAL MALFORMATIONS	42	3.42	0.00	6.14	38	20.11	0.00	29.41	3.82	0.00	6.20
TOTAL FETAL VARIATIONS	676	55.00	15.63	75.78	177	93.65	66.67	100.0	55.52	20.91	74.77

Supplemental information concerning the dates of the historical control studies provided in the study report for the 2-generation reproductive toxicity study (conducted in 1993; BASF DocID 1993/10983)

Study:	Reproduction toxicity study with Mepiquat-chloride in rats - Continuous dietary administration over 2 generations (2 litters in the first and 1 litter in the second generation) [redacted] 1993). BASF DocID 1993/10983

Historical control data are provided in the study report within Part 2 of the Volume IV Supplement (from Page 1681 of the report PDF document). However, although the study report provides the study numbers for the historical data, the date of conduct of the historical control studies is not presented. Details of the date of conduct of the historical control studies cited in the study report are therefore provided in the Table 1 below.

Table 1: Year of Conduct of Historical Control studies Cited in the 2-Generation Reproductive Toxicity Study in the Rat (BASF DocID 1993/10983)

Study No.	Year(s) of conduct
83078	1989/90
85121	1987/88
87099	1988
88032	1988/89
88053	1989
88076	1990
88098	1990
89046	1990
89058	1990
90019	1990
90064	1990
90102	1992
91022	1992