Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

2,3-epoxypropyl isopropyl ether

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

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

Index Number: **-**

Contact details for dossier submitter:

Swedish Chemicals Agency

Esplanaden 3A, P.O Box 2

SE-172 13 Sundbyberg, Sweden

kemi@kemi.se

+46 8 519 41 100

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

CONTENTS

1 PHYSICAL HAZARDS

Not evaluated in this dossier.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No studies are available.

3 HEALTH HAZARDS

Acute toxicity

3.1 Acute toxicity - oral route

Not evaluated.

3.2 Acute toxicity - dermal route

Not evaluated.

3.3 Acute toxicity - inhalation route

Not evaluated.

3.4 Skin corrosion/irritation

Not evaluated.

3.5 Serious eye damage/eye irritation

Not evaluated.

3.6 Respiratory sensitisation

Not evaluated.

3.7 Skin sensitisation

Not evaluated.

3.8 Germ cell mutagenicity

Not evaluated.

3.9 Carcinogenicity

Not evaluated.

3.10 Reproductive toxicity

3.10.1 Animal data

3.10.1.1 Study report 2017

Study Report, 2017, summarised in registration dossier on ECHA's dissemination site.

Test type

Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD TG 422, GLP compliant. The study ended on Day 5 instead of Day 13, as stated in the guideline.

Test substance

- 2,3-epoxypropyl isopropyl ether
- EC number: 223-672-9
- CAS number: 4016-14-2
- Degree of purity – information flagged as confidential.
- Impurities – no information available
- Batch number – information available in Study Report 2017
- Doses: 0, 100, 300, 600 mg/kg bw/day

Detailed study summary and results:

Details on mating procedure:

- M/F ratio per cage: 1/1

- Length of cohabitation: until evidence of successful mating, for a period of up to fourteen days

- Proof of pregnancy: Cage tray-liners were checked each morning for the presence of ejected copulation plugs and each female was examined for the presence of a copulation plug in the vagina. A vaginal smear was prepared for each female and the stage of estrus or the presence of sperm was recorded. The presence of sperm within the vaginal smear and/or vaginal plug in situ was taken as positive evidence of mating (Day 0 of gestation)

- After successful mating each pregnant female was caged (how): Mated females were housed individually during the period of gestation and lactation.

- Any other deviations from standard protocol: none stated

Details on analytical verification of doses or concentrations:

The stability and homogeneity of the test item formulations were determined by the laboratories' Analytical Services as part of this study. Results showed that the formulations were stable for at least twenty-one days. Formulations were therefore prepared fortnightly and stored at approximately 4 ºC in the dark. Representative samples of test item formulations were taken and analyzed for concentration of IPGE (CAS No. 4016-14-2 ; EC No. 223-672-9). The results indicated that the prepared formulations were within ± 4% of the nominal concentration, confirming the accuracy and suitability of the formulation procedure.

Duration of treatment / exposure:

Groups of twelve male and twelve female animals were treated daily at the appropriate dose level throughout the study (except for females during parturition where applicable). The first day of dosing was designated as Day 1 of the study.

Males were terminated after 43 or 44 days. At Day 5 post partum, all surviving females and surviving offspring were killed, and females were hence dosed 14 days prior to pairing, during pairing and pregnancy, and 4 days afterwards.

Details on study design:

- Dose selection rationale: Based on preliminary dose range-finding test

- Rationale for animal assignment: The animals were randomly allocated to treatment groups using a stratified body weight randomization procedure and the group mean body weights were then determined to ensure similarity between the treatment groups. The cage distribution within the holding rack was also randomized.

Examinations

Parental animals: Observations and examinations:

CAGE SIDE / CLINICAL OBSERVATIONS:

- Time schedule: All animals were examined for overt signs of toxicity, ill-health and behavioral change immediately before dosing, soon after dosing, and one hour after dosing (except for females during parturition where applicable). All observations were recorded.

BODY WEIGHT:

- Time schedule for examinations: Individual body weights were recorded on Day 1 (prior to dosing) and then weekly for males until termination and weekly for females until pairing. During pairing phase females were weighed daily until mating was confirmed. Body weights were then recorded for females on Days 0, 7, 14 and 20 post coitum, and on Days 1 and 4 post partum. Body weights were also recorded at terminal kill.

FOOD CONSUMPTION AND COMPOUND INTAKE:

During the pre-pairing period, weekly food consumption was recorded for each cage of adults. This was continued for males after the mating phase. For females showing evidence of mating, food consumption was recorded for the periods covering post coitum Days 0-7, 7¬14 and 14-20. For females with live litters, food consumption was recorded on Days 1 and 4 post partum.

FOOD EFFICIENCY:

Food efficiency (the ratio of body weight change/dietary intake) was calculated retrospectively for males throughout the study period (with the exception of the mating phase) and for females during the pre-pairing phase. Due to offspring growth and milk production, food efficiency could not be accurately calculated during gestation and lactation.

WATER CONSUMPTION AND COMPOUND INTAKE:

- Time schedule for examinations: Water intake was observed daily by visual inspection of water bottles for any overt changes.

HAEMATOLOGY:

- Time schedule for collection of blood: Hematological and blood chemical investigations were performed on five males and five females selected from each test and control group prior to termination (Day 42 for males and Day 4 post partum or Day 25 post coitum for females). Blood samples were obtained from the lateral tail vein. Where necessary repeat samples were taken by cardiac puncture at termination. Animals were not fasted prior to sampling.

- Animals fasted: No

- How many animals: five males and five females selected from each test and control group.

The following parameters were measured on blood collected into tubes containing potassium EDTA anti-coagulant:

Hemoglobin (Hb), Erythrocyte count (RBC), Hematocrit (Hct), Erythrocyte indices (mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC)), Total leukocyte count (WBC), Differential leukocyte count (neutrophils (Neut), lymphocytes (Lymph), monocytes (Mono), eosinophils (Eos), basophils (Bas)), Platelet count (PLT), Reticulocyte count (Retic) (Methylene blue stained slides were prepared but reticulocytes were not assessed), Prothrombin time (CT) was assessed by 'Innovin' and Activated partial thromboplastin time (APTT) was assessed by 'Actin FS' using samples collected into sodium citrate solution (0.11 mol/L).

CLINICAL CHEMISTRY:

- Time schedule for collection of blood: Hematological and blood chemical investigations were performed on five males and five females selected from each test and control group prior to termination (Day 42 for males and Day 4 post partum or Day 25 post coitum for females). Blood samples were obtained from the lateral tail vein. Where necessary repeat samples were taken by cardiac puncture at termination. Animals were not fasted prior to sampling.

- Animals fasted: No

- How many animals: five males and five females selected from each test and control group.

The following parameters were measured on plasma from blood collected into tubes containing lithium heparin anti-coagulant: Urea, Glucose, Total protein (Tot.Prot.), Albumin, Albumin/Globulin (A/G) ratio (by calculation), Sodium (Na+), Potassium (K+), Chloride (Cl-), Calcium (Ca++), Inorganic phosphorus (P), Aspartate aminotransferase (ASAT), Alanine aminotransferase (ALAT), Alkaline phosphatase (AP), Creatinine (Creat), Total cholesterol (Chol), Total bilirubin (Bili), Bile acids

NEUROBEHAVIOURAL EXAMINATION:

Functional Observations

Prior to the start of treatment and at weekly intervals thereafter, all animals were observed for signs of functional/behavioral toxicity. Functional performance tests were also performed on five selected males and females from each dose level, prior to termination, together with an assessment of sensory reactivity to various stimuli.

Behavioral Assessment

Detailed individual clinical observations were performed for each animal using a purpose built arena. The following parameters were observed: Gait, Tremors, Twitches, Convulsions, Bizarre/Abnormal/Stereotypic behavior, Salivation, Pilo-erection, Exophthalmia, Lachrymation, Hyper/Hypothermia, Skin color, Respiration, Palpebral closure, Urination, Defecation, Transfer arousal, Tail elevation

This test was developed from the methods used by Irwin (1968) and Moser et al (1988). The scoring system used is outlined in The Key to Scoring System and Explanation for Behavioral Assessments and Sensory Reactivity Tests.

Functional Performance Tests

Motor Activity. Purpose-built 44 infra-red beam automated activity monitors were used to assess motor activity. Animals were randomly allocated to the activity monitors. The tests were performed at approximately the same time on each occasion (at least two hours after dosing), under similar laboratory

conditions. The evaluation period was thirty minutes for each animal. The percentage of time each animal was active and mobile was recorded for the overall thirty minute period and also during the final 20% of the period (considered to be the asymptotic period, Reiter and Macphail, 1979).

Forelimb/Hindlimb Grip Strength. An automated meter was used. Each animal was allowed to grip the proximal metal bar of the meter with its forepaws. The animal was pulled by the base of the tail until its grip was broken. The animal was drawn along the trough of the meter by the tail until its hind paws gripped the distal metal bar. The animal was pulled by the base of the tail until its grip was broken. A record of the force required to break the grip for each animal was made. Three consecutive trials were performed for each animal. The assessment was developed from the method employed by Meyer et al (1979).

Sensory Reactivity

Each animal was individually assessed for sensory reactivity to auditory, visual and proprioceptive stimuli. This assessment was developed from the methods employed by Irwin (1968) and Moser et al (1988).

The following parameters were observed: Grasp response, Vocalization, Toe pinch, Tail pinch, Finger approach, Touch escape, Pupil reflex, Blink reflex, Startle reflex

Oestrous cyclicity (parental animals): Not monitored, estrous secured by sufficient pairing time

Sperm parameters (parental animals): Parameters examined in male parental generation: testis weight, epididymis weight. Detailed qualitative examination of the testes was undertaken, taking into account the tubular stages of the spermatogenic cycle. The examination was conducted in order to identify treatment-related effects such as missing germ cell layers or types, retained spermatids, multinucleated or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell-or stage-specificity of testicular findings was noted.

Litter observations:

PARAMETERS EXAMINED

The following parameters were examined in F1 offspring:

On completion of parturition (Day 0 post partum), the number of live and dead offspring was recorded. Offspring were individually identified within each litter by tattoo on Day 1 post partum. For each litter the following was recorded:

i. Number of offspring born

ii. Number of offspring alive recorded daily and reported on Days 1 and 4 post partum

iii. Sex of offspring on Days 1 and 4 post partum

iv. Clinical condition of offspring from birth to Day 5 post partum

v. Individual offspring weights on Days 1 and 4 post partum (litter weights were calculated retrospectively from this data)

GROSS EXAMINATION OF DEAD PUPS:

All adult animals and offspring, including those dying during the study, were subjected to a full external and internal examination, and any macroscopic abnormalities were recorded.

Postmortem examinations (parental animals):

SACRIFICE

- Male animals: All surviving animals on day 43 or 44.

- Maternal animals: All surviving animals on day 5 post partum.

GROSS PATHOLOGY:

Necropsy

Adult males were killed by intravenous overdose of suitable barbiturate agent followed by exsanguination on Day 43 or Day 44. Adult females were killed by intravenous overdose of suitable barbiturate agent followed by exsanguination on Day 5 post partum. Surviving offspring were terminated via intracardiac overdose of suitable barbiturate agent. Any females which failed to achieve pregnancy or produce a litter were killed on or after Day 25 post coitum.

For all females, the uterus was examined for signs of implantation and the number of uterine implantations in each horn was recorded. This procedure was enhanced; as necessary, by staining the uteri with a 0.5% ammonium polysulphide solution (Salewski 1964). The corpora lutea were also counted.

All adult animals and offspring, including those dying during the study, were subjected to a full external and internal examination, and any macroscopic abnormalities were recorded.

The following organs were dissected free from fat and weighed before fixation from five selected males and five selected females from each dose group. Tissues shown in bold were weighed from all remaining animals: Adrenals, Brain, Epididymides, Heart, Kidneys, Liver, Ovaries, Pituitary (post-fixation), Prostate and Seminal Vesicles, Spleen, Testes, Thymus, Thyroid (weighed post-fixation with Parathyroid), Uterus (weighed with Cervix)

HISTOPATHOLOGY:

Samples of the following tissues were removed from five selected males and five selected females from each dose group and preserved in buffered 10% formalin, except where stated. Tissues shown in bold were preserved from all remaining animals: Adrenals, Aorta (thoracic), Bone & bone marrow (femur including stifle joint), Bone & bone marrow (sternum), Brain (including cerebrum, cerebellum and pons), Caecum, Coagulating glandm, Colon, Duodenum, Epididymides (preserved in Modified Davidsons fluid), Esophagus, Eyes (fixed in Davidson’s fluid), Gross lesions, Heart, Ileum (including peyer’s patches), Jejunum, Kidneys, Liver, Lungs (with bronchi) (inflated to approximately normal inspiratory volume with buffered 10% formalin before immersion in fixative), Lymph nodes (mandibular and mesenteric), Mammary gland, Muscle (skeletal), Ovaries, Pancreas, Pituitary, Prostate, Rectum, Salivary glands (submaxillary), Sciatic nerve, Seminal vesicles, Skin (hind limb), Spinal cord (cervical, mid thoracic and lumbar), Spleen, Stomach, Testes (preserved in Modified Davidsons fluid), Thyroid/Parathyroid, Trachea, Thymus, Urinary bladder, Uterus & Cervix, Vagina

The tissues from five selected control and 600 mg/kg bw/day dose group animals and any animals dying during the study were prepared as paraffin blocks, sectioned at a nominal thickness of 5 µm and stained with hematoxylin and eosin for subsequent microscopic examination. The tissues from the remaining control and 600 mg/kg bw/day animals and animals which did not achieve a pregnancy were also processed. In addition, sections of testes from all control and 600 mg/kg bw/day males were also stained with Periodic Acid-Schiff (PAS) stain and examined.

Detailed qualitative examination of the testes was undertaken, taking into account the tubular stages of the spermatogenic cycle. The examination was conducted in order to identify treatment-related effects such as missing germ cell layers or types, retained spermatids, multinucleated or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell-or stage-specificity of testicular findings was noted.

Since there were indications of treatment-related stomach changes, examination was subsequently extended to include similarly prepared sections of the stomach from animals in the low and intermediate groups.

Postmortem examinations (offspring):

SACRIFICE

- The F1 offspring were sacrificed at 5 days of age.

- These animals were subjected to postmortem examinations (macroscopic and/or microscopic examination) as follows:

GROSS NECROPSY

All adult animals and offspring, including those dying during the study, were subjected to a full external and internal examination, and any macroscopic abnormalities were recorded.

Reproductive indices: Pre-coital Interval, Fertility Indices (Mating Index), Gestation Length, Parturition Index, Offspring viability indices: Implantation Losses (Pre-implantation loss, Post-implantation loss), Live Birth and Viability Indices (Live Birth Index, Viability Index), Sex Ratio (% males)

Results and discussion

Results: P0 (first parental generation)

General toxicity (P0)

Clinical signs: Animals of either sex treated with 600 mg/kg bw/day showed incidences of increased salivation between Days 18 and 25. No such effects were evident in animals of either sex treated with 300 or 100 mg/kg bw/day.

Mortality: There were no unscheduled deaths considered to be associated with treatment. One female treated with 300 mg/kg bw/day was killed in extremis on Day 4. This female had hunched posture, pilo-erection, a decreased respiratory rate and was lethargic. At necropsy, enlarged adrenals, enlarged and fluid filled kidneys with increased pelvic space and reddened lungs was evident. Histopathological examination of this animal revealed pyelonephritis (both kidneys) which was considered likely to have caused the poor condition of the animal and its subsequent early termination.

Body weight and weight changes: Males treated with 600 mg/kg bw/day showed a statistically significant reduction ($p<0.01$) in body weight gain during the first week of treatment. Recovery was evident thereafter however, a slight reduction in body weight gain was evident in these males during the final week of treatment. Consequently, a 10% reduction in overall body weight gain was evident in these males. No such effects were detected in males treated with 300 or 100 mg/kg bw/day. No adverse effects were detected in treated females during maturation. Body weight gain during the first week of gestation for females treated with 100 mg/kg bw/day was comparable to controls however a reduction in body weight gain was evident in these females during the final two weeks of gestation. Consequently, cumulative body weight gain between Days 0 and 20 of gestation was lower in these females. A statistically significant reduction ($p<0.01$) in body weight gain was also evident in females treated with 100 mg/kg bw/day during lactation.

Although females treated with 600 and 300 mg/kg bw/day were all non-pregnant, body weight gain during the first week post coitum was comparable to control females. Body weight gain for these females during the remaining treatment period was reduced; with the majority of females showing actual body weight losses.

Food consumption and compound intake (if feeding study): No adverse effects were detected in male food consumption. Males treated with 600 mg/kg bw/day showed a reduction in food conversion efficiency during the first week of treatment.

No adverse effects were detected in food consumption for treated females during maturation. Food consumption for 100 mg/kg bw/day females was comparable to controls throughout gestation however it was statistically significantly reduced ($p<0.05$) during lactation. This lower food consumption was consistent with lower body weight gain compared to control during this phase of the study.

Although females treated with 600 and 300 mg/kg bw/day were all non-pregnant, food consumption during the first week post coitum was comparable to control females and remained fairly consistent throughout the remainder of the treatment period.

Food efficiency: Males treated with 600 mg/kg bw/day showed a reduction in food conversion efficiency during the first week of treatment.

Water consumption and compound intake (if drinking water study): No adverse effects were detected in water consumption.

Haematological findings: There were no toxicologically significant effects detected in the hematological parameters measured for males treated with 600 and 300 mg/kg bw/day or both sexes at 100 mg/kg bw/day.

Males treated with 600 and 300 mg/kg bw/day showed statistically significant reductions ($p<0.05$-0.01) in hemoglobin (600 mg/kg bw/day only), mean corpuscular hemoglobin concentration, total leucocyte count and lymphocytes. All of the individual values were within historical control ranges and in the absence of any associated histopathological correlates or true dose related responses the intergroup differences were

considered of no toxicological significance. Females treated with 100 mg/kg bw/day showed a statistically significant reduction ($p<0.01$) in platelet count. All of the individual values were within the historical control range and in the absence of any associated histopathological correlates the intergroup difference was considered of no toxicological significance.

Assessment of hematology parameters for females at 600 and 300 mg/kg bw/day has to be treated with caution as no females at these dosages were maintaining a litter at the time of blood sampling and all of theses females were non-pregnant. The female animals at these dosages were therefore in a different physiological state in comparison to the other females on the study and also those females contributing to the historical control data.

At 600 and 300 mg/kg bw/day, higher hemoglobin, erythrocyte count and hematocrit and lower neutrophils and platelet count for females attained statistical significance ($p<0.05$-0.01) when compared with control. Excluding one female treated with 300 mg/kg bw/day for platelet count, all of the remaining individual values for these parameters were within the historical control range. A true dose related response was also not evident in platelet count.

Clinical biochemistry findings: There were no toxicologically significant effects detected in the blood chemical parameters measured for males treated with 600 or 300 mg/kg bw/day or both sexes at 100 mg/kg bw/day.

Males treated with 600 mg/kg bw/day showed a statistically significant increase in bile acids ($p<0.01$) and alanine aminotransferase ($p<0.05$). Males from all treatment groups and females treated with 100 mg/kg bw/day showed a statistically significant increase ($p<0.05$) in albumin/globulin ratio. All individual values (excluding one alanine aminotransferase value) were within historical control ranges and a true dose related response was not evident for albumin/globulin ratio. In the absence of any associated histopathological correlates the intergroup differences were considered not to be of toxicological significance.

Assessment of blood chemistry parameters for females at 600 and 300 mg/kg bw/day has to be treated with caution as no females at these dosages were maintaining a litter at the time of blood sampling and all of theses females were non-pregnant. The female animals at these dosages were therefore in a different physiological state in comparison to the other females on the study and also those females contributing to the historical control data.

For females at 600 and 300 mg/kg bw/day, higher bile acids, inorganic phosphorus and albumin/globulin ratio attained statistical significance ($p<0.05$) compared to control. For inorganic phosphorus and albumin/globulin ratio, all individual values were within the historical control ranges however for bile acids the majority of individual values were outside of the historical control range. Additionally higher bilirubin and lower creatinine and urea levels for females treated with 600 mg/kg bw/day attained statistical significance ($p<0.05$-0.01) compared to control but all individual values were within the historical control ranges.

Behaviour (functional findings): Behavioral Assessments: There were no treatment-related changes in the behavioural parameters for either sex at 100, 300 or 600 mg/kg bw/day.

Functional Performance Tests: There were no treatment related changes in functional performance considered to be related to treatment at 100, 300 or 600 mg/kg bw/day. Males treated with 600 mg/kg bw/day showed a statistically significant ($p<0.05$) increase in forelimb grip strength. The intergroup difference was confined to one out of the three tests and in the absence of any associated clinical signs to suggest a neurotoxic effect, the intergroup difference was considered not to be of toxicological importance.

Sensory Reactivity Assessments: There were no inter-group differences in sensory reactivity scores that were considered to be related to treatment at 100, 300 or 600 mg/kg bw/day.

Organ weight findings including organ / body weight ratios: effects observed, treatment-related

Histopathological findings: non-neoplastic: The following treatment-related microscopic abnormalities were detected:

Stomach: hyperplasia of the non-glandular region was present in eleven males and five females treated with 600 mg/kg bw/day.

Ovaries: the majority of females treated with 600 or 300 mg/kg bw/day and in one female treated with 100 mg/kg bw/day had the appearance of increased corpora lutea and was in metestrus or diestrus. This suggests a mild disturbance of the reproductive cycle which may account for the lack of pregnancy.

There were no test item related microscopic findings in the testes, including following the qualitative examination of the stages of spermatogenesis in the testes (no test item related abnormalities in the integrity of the various cell types present within the different stages of the sperm cycle).

Reproductive function / performance (P0)

Reproductive function: oestrous cycle: not examined

Reproductive function: sperm measures: no effects observed

There were no test item related microscopic findings in the testes, including following the qualitative examination of the stages of spermatogenesis in the testes (no test item related abnormalities in the integrity of the various cell types present within the different stages of the sperm cycle).

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

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

Results: F1 generation

General toxicity (F1)

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

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

Body weight and weight changes: As a consequence of the reduced litter size at 100 mg/kg bw/day, litter weights on Days 1 and 4 post partum were reduced when compared to controls, although statistical significance was not achieved. However, offspring body weights at birth and subsequently on Days 1 and 4 post partum and offspring body weight gain between Days 1 and 4 post partum exceeded control litters.

Food consumption and compound intake (if feeding study):not examined

Food efficiency: not examined

Water consumption and compound intake (if drinking water study): not examined

Ophthalmological findings: not examined

Haematological findings: not examined

Clinical biochemistry findings: not examined

Urinalysis findings: not examined

Sexual maturation: not examined

Organ weight findings including organ / body weight ratios: not examined

Gross pathological findings: Neither the type, incidence nor distribution of necropsy findings for offspring terminated at Day 5 of age indicated any obvious effect of maternal treatment on the offspring at 100 mg/kg bw/day.

Histopathological findings: not examined

Developmental neurotoxicity (F1)

Behaviour (functional findings):not examined

Developmental immunotoxicity:not examined

Conclusion: The oral administration of IPGE (CAS No. 4016-14-2, EC No. 223-672-9) to rats by gavage, at dose levels of 100, 300 and 600 mg/kg bw/day, resulted in reduced body weight gain and macroscopic and microscopic changes in the stomach in animals of either sex treated with 600 mg/kg bw/day and minimal disruption of the female reproductive tract (increased corpora lutea, cyclical variation) which most likely caused the complete lack of fertility at 300 mg/kg bw/day and above and the notably reduced fertility at 100 mg/kg bw/day. The reduced body weight gain and food consumption detected in 100 mg/kg bw/day females was considered not to represent an adverse effect of treatment. The 'No Observed Adverse Effect Level' (NOAEL) for systemic toxicity was therefore considered to be 300 mg/kg bw/day for males and 100 mg/kg bw/day for females. A 'No Observed Effect Level' (NOEL) could not be established for reproductive toxicity.

3.11 Specific target organ toxicity – single exposure

Not evaluated.

3.12 Specific target organ toxicity – repeated exposure

Not evaluated.

3.13 Aspiration hazard

Not evaluated.

4 ENVIRONMENTAL HAZARDS

Not evaluated in this dossier.