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:

Tris(2-methoxyethoxy)vinylsilane

EC Number: **213-934-0**

CAS Number: **1067-53-4**

Index Number: **-**

Contact details for dossier submitter:

Environment Agency Austria, Spittelauer Laende 5, A-1090 Vienna

on behalf of the Austrian Competent Authority (Austrian Federal Ministry of Agriculture, Forestry, Environment and Water Management, Stubenring 1, 1010 Vienna, Austria)

Version number: 02 **Date: May 3rd 2017**

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Evaluation not performed for this substance

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Evaluation not performed for this substance

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Data conclusive but not sufficient for classification

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Data lacking

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3.10.1.1 [Study 1]

Study reference:

2005, unpublished study report, combined 28-day repeated dose oral (gavage) toxicity study with the reproduction/developmental toxicity screening test

Note on documentation procedure: *All data (below) are cited from disseminated database-file (ECHA, 2016) The original study report was not available for this documentation. Therefore, some relevant details on the study and results (e.g., significance of findings) are not documented. Results interpretation is taken from the registrants, if not indicated otherwise.*

Detailed study summary and results:

Test type

OECD Guideline 422

(Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test).

Test substance

- The test material used in the study is equivalent to the substance identified in the CLH dossier
- EC number: not different from the substance identified in the CLH dossier
- CAS number: not different from the substance identified in the CLH dossier
- Purity information: confidential information
- Impurities do not affect the classification
- Batch no: confidential information

Test animals

- Species/strain/sex: Rat, Crl:CD®(SD)IGS BR male, female
- Number of animals: 10/sex/group
- Age and weight at the study initiation: 57 days old upon receipt,.; about 12 weeks old, when paired for maiting. *No information on body weight provided*.

Administration/exposure

- Route of administration: oral gavage
- Duration and frequency:
  frequency: daily
  duration:
  a) 28 days 4 groups of males were treated 14 days prior to mating and continuing throughout mating (mating period 14 days)*;* 4 groups of females were treated 28 days (= toxicity phase females).
  b) 4 additional groups of female rats were mated with the treated males and were also administered the test article by oral gavage daily for a minimum of 14 days prior to mating, throughout mating and gestation and continuing through lactation day 3 (= reproductive phase females).
- Dose levels were 0, 25, 75 and 250 mg/kg bw/day for the males, unmated females (toxicity phase) and mated females (reproductive phase).
- Dose selection: based on the results of a 7 day dose-range finding test using 0, 100, 300, and 1000 mg/kg bw/day: one male of high dose died, males of mid and high dose showed, inter alia, reduced food consumption throughout the study and reduced absolute and relative organ weights (testes, epididymides and prostate), females of the mid and high dose showed reduced food consumption and mean body weights of females of the high dose was slightly reduced.
- Control group: yes, concurrent vehicle
- Historical control data: *not provided*
- Vehicle: dehydrated, deacidified corn oil*;* concentration and volume used, justification of choice of vehicle *not provided*.
- Test substance formulation/ stability and homogeneity of the preparation:
  Prior to the initiation of dosing (May 5, 2004), representative control and test article formulations were prepared. Duplicate samples (1 mL each) for homogeneity determination were collected from the top, middle and bottom strata of the 25, 75 and 250 mg/kg bw/day dosing formulations and from the middle stratum of the control group preparation. The aliquots dispensed for homogeneity were representative of the size of aliquots dispensed for daily dosing procedures and included resuspension analysis over the longest period of aliquot storage. Samples from the control formulation and samples from the top and bottom strata were withdrawn from the aliquots after 6 and 12 days of refrigerated storage to confirm resuspension homogeneity and stability of the test article in the formulations. Fourteen-day refrigerated stability was assessed by comparison of the test

article concentrations from samples collected from the middle stratum of each formulation on the day of preparation and following 14 days of storage. Duplicate samples (1 mL each) were collected from the middle stratum of each formulation, including the control group, for study weeks 0, 1, 2, 4 and 6 for confirmation of concentration. Characterization of the test article structure was performed by gas chromatography (GC) with mass selective detection (MSD). The determination of vinyl-tris(2-methoxyethoxy)silane in dried/deacidified corn oil formulations was performed by gas chromatography (GC) with mass selective detection (MSD).

Stability and homogeneity of the preparation: *no further details provided*

- Diet preparation: Reported, *but no relevant information for this gavage study*.
- Doses: 0, 25, 75 and 250 mg/kg bw/day (nominal concentration)

Description of test design

- Details on mating procedure:
  - M/F ratio per cage: 1:1
  - Length of cohabitation: up to 14 day
  - Proof of pregnancy: vaginal plug referred to as day 0 of pregnancy
  - After successful mating each pregnant female was caged individually in plastic maternity cages containing nesting material. Females that had not shown evidence of mating in 14 days were also placed in plastic maternity cages with nesting material.
- Premating exposure period for males and females: 14 days
- Pre and post dosing observation periods (parental):

  During the acclimation period and thereafter the rats were observed twice daily for general changes in appearance or behavior. Clinical observations, bodyweights and food consumption were recorded at appropriate intervals. In addition, detailed clinical observations were evaluated for all adult male and toxicity phase females once prior to the start of test article administration (baseline evaluations) and again during the last week of the test article administration. No post-exposure observation period.
- Litter observation periods:

  All reproductive phase females were allowed to deliver and rear their offspring to lactation day 4; surviving dams and pups were euthanized and examined on lactation day 4. On the day parturition was initiated (PND 0), the pups were sexed and examined. The dam and litter remained together until PND 4.
- Standardisation of litters: not applicable
- Parameters assessed for P:

  Clinical observations, bodyweights and food consumption were recorded at appropriate intervals. In addition, detailed clinical observations (functional observational battery [FOB] conducted out of the

home cage) and locomotor activity were evaluated for all adult males and toxicity phase females. Individual gestation length was calculated using the date delivery started.
Clinical pathology assessments (hematology and serum chemistry) and macroscopic and microscopic examinations (including organ weights) were also performed on the appropriate groups of adult males and toxicity phase females.
Mean body weights and body weight changes, maternal food consumption, gestation lengths, implantation sites, unaccounted for sites, pre-coital intervals, numbers of pups born, live litter sizes, ambulatory counts measured in locomotor activity assessment, functional observational battery, clinical pathology values (excluding differential white cell counts other than lymphocytes and neutrophils) and organ weight data (absolute and relative) subjected to a parametric one-way analysis of variance (ANOVA) to determine intergroup differences.
For females that delivered or had macroscopic evidence of implantation, the numbers of former implantation sites and corpora lutea were recorded. Recognizable fetuses for the females euthanized in extremis were examined externally and preserved in 10% neutral-buffered formalin. For females that failed to deliver, a pregnancy status was determined. Uteri with no macroscopic evidence of implantation were opened and subsequently placed in a 10% ammonium sulfide solution for detection of early implantation loss.

- Parameters assessed for F1:
  On the day parturition was initiated (PND 0), the pups were sexed and examined for gross malformations, and the numbers of still born and live pups were recorded. Abnormal behavior of the offspring was recorded. Intact offspring dying from PND 0 to 4 were necropsied. Cannibalized pups were discarded without necropsy. Tissues were preserved in 10% neutral-buffered formalin for possible future histopathologic examination only as deemed necessary by gross findings. The carcass of each pup was then discarded.
- Reproductive parameters assessed were male (female) Mating Index (%), male Fertility Index (%), male Copulation Index (%), female Fertility Index (%), and female Conception Index (%).
  Mating, fertility, copulation and conception indices were analyzed using the Chi-square test with Yates' correction factor. Mean litter proportions (percent per litter) of pup viability and percent males at birth were subjected to the Kruskal-Wallis nonparametric ANOVA test to determine intergroup differences. If the ANOVA revealed statistically significant ($p<0.05$) intergroup variance, the Mann-Whitney U-test was used to compare the test article-treated groups to the control group.
  No details on sperm analysis are available. No information is provided on estrus cycle analysis.

Results and discussion:

- General toxicity to exposed males/ females (P0, "toxicity phase"):

- Clinical findings: There were no test article-related clinical findings in the males or toxicity phase females.
- Survival: All males and all toxicity phase females survived to the scheduled necropsies
- Functional Observational Battery (FOB): There were no test article-related effects observed at the FOB or locomotor activity evaluations in the males or toxicity phase females at any dose level.
- Food consumption: reduced in the 250 mg/kg bw/day group males during study days 0-7;
- Body weight: mean body weight gains were reduced in these males during study days 14-21 and 21-28. Mean body weight in the 250 mg/kg bw/day group males was 6.7 % lower than the control group value on study day 28. There were no test article-related effects on mean body weights, body weight gains or food consumption in the toxicity phase females.
- Haematology: Decreases in mean red blood cell counts, hemoglobin levels, hematocrit, mean corpuscular hemoglobin concentration, reticulocyte counts, platelet counts, basophil counts and eosinophil counts were observed in both sexes in the 250 mg/kg bw/day toxicity phase group. Examination of the bone marrow smears revealed an overall decrease in the myeloid:erythrocyte (M/E) ratio. When evaluated in combination with the blood count data and bone marrow histopathology, the decreased M:E ratio does not indicate erythroid hyperplasia, but rather a disproportionate mild supression of both myeloid and erythroid elements. However, ineffective erythropoiesis or an early regenerative response cannot be excluded. Increases in monocyte counts were also observed in these animals. These findings correlated with the microscopic finding of hypocellularity in the sternal bone marrow, in which aggregates of mature granulocytes were absent. Mean albumin, total protein and globulin levels were also reduced in the 250 mg/kg bw/day toxicity phase male and female groups, resulting in increased mean albumin/globulin ratios.
- Other mascroscopic and microscopic changes: Test article-related macroscopic changes, microscopic changes and/or reductions in organ weights were observed in the 75 mg/kg bw/day group males and the 250 mg/kg bw/day group males and females. Adhesions and/or white areas on the spleen were observed in the 75 mg/kg bw/day group males and the 250 mg/kg bw/day group males, toxicity phase females and a reproductive phase female. These findings corresponded with capsular fibrosis microscopically. Small thymus was observed in the 250 mg/kg bw/day group males and toxicity phase females. Mean absolute and relative (to final body and brain weights) thymus weights were also reduced in males and females at 250 mg/kg bw/day and correlated to the microscopic finding of lymphoid depletion. Lymphoid depletion was also observed in the mesenteric and/or mandibular lymph nodes in the 250 mg/kg bw/day group males and toxicity phase females. Mean absolute and relative adrenal gland weights were reduced in the 250 mg/kg bw/day group males and toxicity phase females; there was no microscopic correlate to this decrease.

- Maternal toxicity (reproductive phase females):

    - Body weights: There were no test article-related effects on mean body weights, body weight gains or food consumption during the pre-mating period in the reproductive phase females. However, mean gestation body weight gains and food consumption were reduced in the 250 mg/kg bw/day group females throughout gestation; mean body weight on gestation day 20 was 22.1% lower than the control group value. No test article-related effects on mean gestation or lactation body weight gains or food consumption were observed in the 25 and 75 mg/kg bw/day group reproductive phase females.
    - Clinical findings: There were no test article-related clinical findings in the reproductive phase females. In the reproductive phase, one female in the 75 mg/kg bw/day group was euthanized in extremis on gestation day 22. The cause of moribundity for this female was considered to be dystocia. All other reproductive phase females survived to the scheduled necropsy.

- Reproductive organs, reproductive function/ performance (P0):

    - Males: Small and/or soft testes and/or epididymides were observed in the 250 mg/kg bw/day group males. Mean absolute and relative (to final body and brain weights) testes and epididymides weights were also reduced in this group. Microscopically, small/soft testes correlated with seminiferous tubule degeneration observed in all males in the 250 mg/kg bw/day group. Secondary to the loss of spermatogenesis in the testes was hypospermia and luminal cellular debris in the epididymides, corresponding to macroscopic findings. Mean absolute and relative prostate weights in the 75 and 250 mg/kg bw/day group males were reduced; the reduction correlated microscopically with decreased secretion and/or atrophy. Mean absolute and relative seminal vesicle weights were also reduced in the 250 mg/kg bw/day group males; there were no correlating microscopic findings.
    - Reproductive phase females: Mean gestation body weight gains and food consumption were reduced in the 250 mg/kg bw/day group females throughout gestation; mean body weight on gestation day 20 was 22.1% lower than the control group value. Reductions in mean body weight and body weight gain late in gestation were attributed to the increased number (five of nine) of entirely resorbed litters in the 250 mg/kg bw/day group. Evaluation of lactation body weight and food consumption in the 250 mg/kg bw/day group was precluded by reduced fertility, embryonic death and total litter loss. No test article-related effects on mean gestation or lactation body weight gains or food consumption were observed in the 25 and 75 mg/kg bw/day group reproductive phase females. One female in the 250 mg/kg bw/day

group had total litter loss on lactation day 0 and one female in the 75 mg/kg bw/day group had total litter loss on lactation day 2.

- Fertility: Test article-related effects on reproductive performance (fertility indices) were observed in the 250 mg/kg bw/day group males and reproductive phase females. Male and female fertility indices were 60.0% in this group compared to 90.0% in the control group. The mean number of days between pairing and coitus was increased in the 250 mg/kg bw/day group.
- Gravidity, resorptions and implantation: Mean gestation length was increased in the 75 mg/kg bw/day group and in the single female in the 250 mg/kg bw/day group that delivered. Of the nine reproductive phase females in the 250 mg/kg bw/day group with evidence of mating, three were nongravid and five had entirely resorbed litters. In the 75 mg/kg bw/day group, the mean numbers of implantation sites were reduced while the number of unaccounted for implantation sites was increased. This effect was considered test article-related.

- Developmental effects (F1):

  - Fetal survival, litter size, other fetal effects: Only one female in the group exposed to 250 mg/kg bw/d delivered, but all pups were found dead on postnatal day (PND) 0, precluding evaluation of pup body weights. In the 75 mg/kg bw/day group, the mean numbers of pups born and live litter size on PND 0 were reduced. These effects were considered test article-related; however, only the live litter size on PND 0 was statistically significantly different ($p<0.01$) from the control group. A slight increase was observed in the number of pups found dead or missing and presumed cannibalized in the 75 mg/kg bw/day group.
  - Sex ratio of pups: *no information provided*
  - Postnatal survival in internal findings in pups: postnatal survival in the 75 mg/kg bw/day group was reduced throughout the lactation period (days 1-4), primarily due to one female with total litter loss on lactation day 2; the differences from the control group were not statistically significant but were considered test article-related. The general physical condition and mean body weights and body weight gains of pups in the 25 and 75 mg/kg bw/day groups were unaffected by maternal test article administration. No internal findings in the pups found dead or at the scheduled necropsy were attributed to maternal test article administration.

- Overall conclusion (by registrants):

- Effects on sexual function and fertility: Based on decreased fertility at 250 mg/kg bw/day, macroscopic and microscopic changes with corresponding decreases in weights for the male reproductive organs at 250 mg/kg bw/day and the reduced mean litter size in the 75 mg/kg bw/day group, the NOAEL for vinyl-tris(2-methoxyethoxy)silane for male and female reproductive toxicity was 25 mg/kg bw/day.
- Developmental: The NOAEL for fetotoxicity/developmental toxicity is 75 mg/kg bw/day. A role for developmental toxicity in the reduced postnatal survival at this dose cannot be excluded. The NOAEL for teratogenicity is ≥ 75 mg/kg bw/day.
- Reliability: Reliable without restriction

- Overall assessment results:

  - Sexual function and fertility: Clear signs of an adverse effect on sexual function and fertility were observed, e.g., by seminiferous tubule degeneration, hyprospermia and prostate atrophy (males) or reduced fertility, changes in gestation length (females) and reduced fertility index (males and females).
  - Developmental: The observed embryotoxic, fetotoxic and postpartum effects are clear signs of developmental toxicity in a broad sense, but some of these may be secondary to effects on sexual function and fertility of the parent animals.
  - Reliability of the unpublished study cannot be fully assessed, as only secondary reporting (disseminated and confidential unpublished confidential registration dossier) was available. With this restriction, however, accordance with GLP (with specifications at the time of study) can be confirmed and reliability conclusions by the registrant appear to be justified, with some uncertainties due to limited reporting.

3.11 Specific target organ toxicity – single exposure

Evaluation not performed for this substance

3.12 Specific target organ toxicity – repeated exposure

Evaluation not performed for this substance

3.13 Aspiration hazard

Evaluation not performed for this substance

4 ENVIRONMENTAL HAZARDS

4.1 Degradation

Evaluation not performed for this substance

4.2 Bioaccumulation

Evaluation not performed for this substance

4.3 Acute toxicity

Evaluation not performed for this substance

4.4 Chronic toxicity

Evaluation not performed for this substance

4.5 Acute and/or chronic toxicity to other aquatic organisms

Evaluation not performed for this substance

5 REFERENCES

ECHA, European Chemicals Agency (2016)

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OECD, Organisation for Economic Co-Operation and Development (2006)

SIDS Initial Assessment Report for SIAM 22 (Paris, France, 18-21 April 2006). Tris(2-methoxyethoxy)vinylsilane (VTMOEOS)

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