**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY**
**DEPARTMENT OF PESTICIDE REGULATION**
**MEDICAL TOXICOLOGY BRANCH**

# SUMMARY OF TOXICOLOGY DATA

**ACTIVE INGREDIENT:** N,N-Dimethyl-N-[3-(Trimethoxysilyl)-Propyl]-1-Tetradecanaminium Chloride

**Chemical Code** # 6006, **Document Processing Number (DPN)** # 53089
**SB 950** # Not applicable
**Original date:** 1/3/12

## I. DATA GAP STATUS

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|---|---|
| **Chronic toxicity, rat:** | Not required at this time* |
| **Chronic toxicity, dog:** | Not required at this time* |
| **Oncogenicity, rat:** | Not required at this time* |
| **Oncogenicity, mouse:** | Not required at this time* |
| **Reproduction, rat:** | Not required at this time* |
| **Developmental toxicity, rat:** | Not required at this time* |
| **Developmental toxicity, rabbit:** | No data gap, no adverse effect |
| **Gene mutation:** | No data gap, no adverse effect |
| **Chromosome effects:** | No data gap, no adverse effect |
| **DNA damage:** | No data gap, no adverse effect |
| **Neurotoxicity:** | Not required at this time* |

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Toxicology one-liners are attached.

* N,N-Dimethyl-N-[3-(Trimethoxysilyl)-Propyl]-1-Tetradecanaminium Chloride has been submitted and classified as an “antimicrobial” for purpose of toxicological data requirements by U.S. EPA. No further studies are required at this time for study types marked with (*).

All record numbers for the above study types through 262524 (Document No. 53089-0013) were examined.

In the 1-liners below:
** indicates an acceptable study. **Bold face** indicates a possible adverse effect.
File name: T120103
Revised by Name, Date: Moore, 1/3/12.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

### COMBINED, RAT

(Study type not required at this time)

### CHRONIC TOXICITY, RAT

(Study type not required at this time)

### CHRONIC TOXICITY, DOG

(Study type not required at this time)

### ONCOGENICITY, RAT

(Study type not required at this time)

### ONCOGENICITY, MOUSE

(Study type not required at this time)

### REPRODUCTION, RAT

(Study type not required at this time)

### DEVELOPMENTAL TOXICITY, RAT

(Study type not required at this time. DPR report 53089-0004 245154 is a waiver request, noting that U.S. EPA accepted the waiver petition in a 1/29/88 memo).

### DEVELOPMENTAL TOXICITY, RABBIT

** 53089-0010; 249230; "Sanitized® T99-19 TGAI (80%): Prenatal Developmental Toxicity Study in the Himalayan Rabbit"; (C. Senn, D. Flade; RCC Ltd., Wölferstrasse 4, 4414 Füllinsdorf/Switzerland; Study No. A92496; 6/6/08). Thirty, 20, 20, 20 and 23 mated female rabbits were administered by gavage to 0 (corn oil), 10, 30, 90 and 180 mg/kg/day Sanitized® T99-19 TGAI (80%), respectively, from day 6-27 post coitum. Three females in 180 mg/kg/day group were killed in extremis due to rales and/or gasping. Two females in the control group were killed *in extremis*, one after abortion and one due to back injury. **Maternal NOEL** = 90 mg/kg/day due to decreased body weight gain, body weight, food consumption, clinical signs and observations at necropsy. **Developmental NOEL =** 90 mg/kg/day due to increased number of resorption, decreased number of implantation, live fetus, increased percentages of fetuses and litters with sternebra fused and/or wide. **Study acceptable, with no adverse effects.** (Pan, 3/23/10).

### GENE MUTATION

** 53089-0005; 245155; "Reverse Mutation Assay "Ames Test" Using *Salmonella typhimurium* and *Escherichia coli* with T99-19 (40%)"; (P. W. Thompson; Safepharm Laboratories Limited, Derby DE1 2BT, United Kingdom; Project No. 502/021; 7/13/00); *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and *E. coli* strain WP2 *uvrA*$^-$ were treated for 48 hours at 37$^o$ C with Sanitized T99-19 (40%) (batch no. 232; a.i.: 40%) at concentrations ranging from 5 to 5000 µg/plate under conditions of non-activation and from 15 to 5000 µg/plate under conditions of activation. Two trials were performed with each treatment level plated in triplicate. An S9 fraction derived from the livers of rats pretreated with phenobarbitone/β-naphthoflavone was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect was indicated.** Positive controls were functional. **Study acceptable.** (Moore, 6/5/09).

** 53089-0005; 245156; "Cell Mutation Assay at the Thymidine Kinase Locus ($TK^{+/-}$) in Mouse Lymphoma L5178Y Cells with T99-19 (80%)"; (H.E. Wollny; RCC Ltd., Toxicology Division, CH-4452 Itingen, Switzerland; Study No. 841110; 3/11/02); ); Mouse lymphoma L5178Y cells were treated with Sanitized T99-19 (batch no. KV 01/11, purity: 80%) at concentrations ranging from 0.8 to 50 µg/ml under conditions of both non-activation and activation for 4 hours at 37° C in the first trial. In the second trial, the cells were exposed to concentrations ranging from 0.3 to 20 µg/ml for 24 hours under conditions of non-activation. Duplicate cultures/treatment level were included in the study. A phenobarbital/β-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. Cell survival and viability and mutation frequency for each treatment level were determined and compared to those of the solvent control. There was no increase in the mutation frequency with or w/o activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 6/10/09).

## CHROMOSOME EFFECTS

** 53089-0005; 245157; "*In Vitro* Chromosome Aberration Test in Chinese Hamster V79 Cells with T99-19 (80%)"; (M. Schulz; RCC Ltd., Toxicology Division, CH-4452 Itingen, Switzerland; Study No. 841109; 3/14/02); V79 Chinese hamster lung cells were treated with concentrations of Sanitized T99-19 (batch no. KV 01/11, purity: 80%) ranging from 0.3 to 25 µg/ml for the 4-hour non-activation and activation exposures in trial no. 1. In the 2nd trial, the concentrations ranged from 1.3 to 25 µg/ml for the 18-hour non-activation exposure, from 2.5 to 15.0 µg/ml for the 28-hour non-activation exposure and from 5.0 to 50 µg/ml for the 4-hour activation exposure. The S9 fraction used to metabolize the test material was derived from the livers of male Sprague-Dawley rats which had been pretreated for 3 consecutive days by oral dosing with phenobarbital/β-naphthoflavone (80/80 mg/kg/day). Duplicate cultures were performed at each treatment level. Two hundred metaphases per treatment level were evaluated. There was no treatment-related increase in chromosomal cell aberrations. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 6/10/09)

## DNA DAMAGE

53089-0012 255613 Vogel, J., "*In vitro* single cell gel electrophoresis (comet assay) in Chinese hamster V79 cells with Sanitized ® T 99-19," Harlan Cytotest Cell Research GmbH, Rossdorf, Germany, 9/21/10. Laboratory Study # 1299900. Cells were incubated for 3 hrs with treatment medium, then trypsinized, lysed, treated with alkaline solution, and subjected to electrophoresis to form the "comet" patterns (visualized by a fluorescence dye for DNA). An initial cytotoxicity assay found excessive cytotoxicity at 39 µg/ml without S-9 and at 78 µg/ml with S-9. Appropriate choices of dose ranges were selected for the primary study: 10-20 µg/ml without S-9 and 5-39 µg/ml with S-9. Cytotoxicity in the primary assay without S-9 was excessive at 20 µg/ml, hence only 10.0, 13.3, and 16.6 µg/ml were evaluated without S-9. The planned range for evaluation with S-9 was not limited by cytotoxicity. The percent tail intensity of the 13.3 µg/ml group without S-9 was elevated 4-fold compared to concurrent negative control value or other treated group values (but well below positive control: MMS). This elevation was considered by investigators as not biologically relevant, since the intensity at13.3 µg/ml was at the lower end of historical control values. All results obtained in the presence of S-9 were close to the concurrent negative control, and clearly below the positive control (benzo[a]pyrene). Concurrent control and treated group values were more than 20 x lower than historical means without S-9, and about 6 x lower than historical means with S-9. Results indicate atypical test conditions for the test facility, and should be considered uninterpretable. Study is **unacceptable**, with no adverse effects. Aldous, 11/15/10. [see re-examination, below]

**DPR's Response to the Registrant's Rebuttal**

53089-0012 255613 Vogel, J., "*In vitro* single cell gel electrophoresis (comet assay) in Chinese hamster V79 cells with Sanitized ® T 99-19," Harlan Cytotest Cell Research GmbH, Rossdorf, Germany, 9/21/10. Laboratory Study # 1299900. Response by Harlan investigators (A. Poth and J. Vogel) clarified existing results and offered to provide additional data. (1) They noted

that historical control ranges in their laboratory bracketed the control value of the Sanitized ® T 99-19 study with S9, whereas the control without S9 fell only slightly below the facility's historical range. (2) Data in the original submission show that exposures encompassed a range to the limits of cytotoxicity, and investigators are willing to send cytotoxicity data from a range-finding study not previously submitted. (3) Investigators would include in an additional submission an independent experiment to fulfill the recommendations of Tice et al. (2000) for a confirmatory study in the event of a negative primary study. (4) The proposed new submission will also include a re-evaluation of slides from the existing study to assess cytotoxicity parameters such as apoptosis and cellular necrosis. DPR conclusion: it does not appear that U.S. EPA has validated this study type. If the study type is indeed not validated, then any additional data will be evaluated as supplementary information, but will not fill a data requirement. It is recommended that investigators provide a DNA damage study of a validated study type. Aldous, 3/14/11.

** 53089-0013; 262524; "Unscheduled DNA Synthesis in Primary Hepatocytes of Male Rats *in Vitro* with Sanitized T99-19"; (C. Hall; Harlan Cytotest Cell Research GmbH, 64380 Rossdorf, Germany; Study No. 14134400; 11/3/11); Primary rat hepatocyte cultures were exposed to Sanitized T99-19 (batch no. 5263; a.i.: 40-55%) at concentrations ranging from 2.5 to 20 ug/ml for approximately 18 hours at 37° C. Vehicle and positive (2-AAF, 2.23 ug/ml) controls were included in the assay. There were 2 trials with 2 cultures/treatment level. Fifty cells per coverslip were scored per concentration per trial. There was no treatment-related increase in unscheduled DNA synthesis. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 12/29/11)

## NEUROTOXICITY

(Study type not required at this time)

## SUBCHRONIC AND SUBACUTE STUDIES

** 53089-0003; 245153; "13-Week Oral Toxicity (Gavage) Study in the Wistar Rat with T99-19: TGAI (80%)"; (W. H. Braun, H.-J. Chevalier; RCC Ltd., Toxicology Division, CH-4452 Itingen, Switzerland, Histotox, F-17000 La Rochelle, France and EPS, Experimental Pathology Services AG, CH-4132 Muttenz, Switzerland; Study No. 841107; 12/13/02); Ten Wistar rats/sex/group were dosed orally by gavage with 0 (vehicle: polyethylene glycol 300), 15, 60 or 240 mg/kg/day of Sanitized T99-19 (batch no. KV 01/11, purity: 80%) for 13 weeks. One female and one male in the 240 mg/kg group were found dead on study days 43 and 73, respectively. These deaths were likely due to a dosing error. There was no treatment-related effect on the mean body weights or food consumption. In the functional observational battery, the hindlimb grip strength of both sexes in the 240 mg/kg group was less than that of the control animals (NS, $p<0.05$). There was no apparent treatment-related effect on the hematology or ophthalmological parameters. In the clinical chemistry, the mean alanine aminotransferase activity in the serum was elevated in comparison to the control values ($p<0.01$). Although the sodium, potassium and chloride ion levels in the serum increased for either the males and/or females in the 240 mg/kg group, no consistent dose-response pattern was evident for both sexes. The profile for the different species of globulin proteins was affected in a dose-related manner for the females. However, there was no treatment-related effect on the albumin to globulin ratio and therefore the altered profile was not deemed to be of toxicological relevance. In the urinalysis, the relative density and osmolality of the urine recovered from both sexes in the 240 mg/kg group were greater than the control values. ($p<0.05$ or 0.01). The mean absolute and relative kidney weights and relative liver weight of the 240 mg/kg males were greater than those of the control group ($p<0.05$ or 0.01). No treatment-related lesions were noted in the histopathological examination. **No adverse effect indicated. Rat Subchronic Oral Toxicity NOEL:** (M/F) 60 mg/kg/day) (based upon effects noted in the FOB, clinical chemistry and urinalysis for both sexes in the 240 mg/kg treatment group); **Study acceptable.** (Moore, 6/5/09).