

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

SILVER SODIUM HYDROGEN ZIRCONIUM PHOSPHATE

Chemical Code # 5765, Tolerance # 52857

5/22/01

Revised: 8/17/01

I. DATA GAP STATUS

| | |
|------------------------|--|
| Combined, rat: | No study on file ¹ |
| Chronic toxicity, dog: | No study on file ¹ |
| Oncogenicity, mouse: | No study on file ¹ |
| Reproduction, rat: | No study on file ¹ |
| Teratology, rat: | No data gap; no adverse effect indicated |
| Teratology, rabbit: | No study on file ¹ |
| Gene mutation: | No data gap |
| Chromosome effects: | No data gap; possible adverse effect indicated |
| DNA damage: | No data gap |
| Neurotoxicity: | Not required at this time |

¹Toxicology one-liners are attached.

All record numbers through # 182215 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T184876A.doc

T. Moore, 8/17/01

¹ This new active ingredient was submitted as antimicrobial and these studies are not required at this time.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

No study on file.

CHRONIC TOXICITY, RAT

No study on file.

CHRONIC TOXICITY, DOG

No study on file.

ONCOGENICITY, MOUSE

No study on file.

REPRODUCTION, RAT

No study on file.

TERATOLOGY, RAT

** 006, 012; 176983, 182215; "Supplementary Submission of Data, Requested for a Pending Application" (Wood, E., and Doleman, N.; Keller and Heckman LLP, Washington D.C.; SPL Project No.: 656/017). Twenty-five Sprague-Dawley CD mated female rats/group were treated by oral gavage with 0, 100, 300, or 1000 mg/kg of Experimental Additive Number 9823-37 (Lot # 7170706, % a.i. >99.9%) from days 6-15 of gestation inclusive. Clinical signs of toxicity and effects on bodyweight gain and food consumption during gestation were not observed during the test. There were no significant effects seen at caesarian necropsy. Uterine implantation data showed no significant differences between dose groups and control. Fetal visceral and skeletal evaluation showed no significant differences between the treated and control groups in the proportion of fetuses with anomalies/variances in development, and in the incidence and type of anomalies/variances found. Females dosed with the test material from day 6-15 of gestation at dose levels up to 1000 mg/kg showed no evidence of maternal toxicity and no significant effects on the growth and development of their offspring. **No adverse effects. Maternal NOEL: \geq 1000 mg/kg/day; Developmental NOEL: \geq 1000 mg/kg/day. Study previously unacceptable but possibly upgradeable** with submission of individual female clinical signs and necropsy finding for each animal, and analysis of silver content and purity data of the test material (Lot #: 7170706); data submitted in volume 52857-012, rec #182215 provided this information; **Study acceptable.** (Eya, 04/02/01, upgraded Moore, 8/17/01).

006; 176982; "Supplementary Submission of Data, Preliminary Oral Gavage Teratology Study in the Rat" (Wood, E.; Keller and Heckman LLP, Washington D.C.; SPL Project No.: 656/016). **Eight** Sprague-Dawley CD mated female rats/group were treated by oral gavage with 0, 100, 300, or 1000 mg/kg of Novaron AG 1100 (Lot # 7170706, % a.i. not described in text) from day 6-15 of gestation inclusive. There were no significant treatment-related differences in clinical findings observed during the in-life phase of the study for the adults. Also, no significant treatment-related differences were observed in the uterine implantation and fetal parameters examined during the necropsy of adults and offsprings. No evidence of maternal or fetal toxicity was observed up to 1000 mg/kg/day. The results from this study suggest that 1000 mg/kg/day (limit dose) should be used as the highest dose for the main study. **No adverse effects. Nominal Maternal NOEL: \geq 1000 mg/kg/day; Developmental NOEL: can not be determined. Supplemental Study.** (Eya, 03/23/01)

TERATOLOGY, RABBIT

No study on file.

GENE MUTATION

007; 176984; "Novaron Bacterial Mutation Assay" (Jones, E., and Gant, R.A., Huntingdon Life Sciences, Ltd., Cambridgeshire, England., HRC Study Report No.: TSI 72/941424, 05/18/94). Novaron AG 300, (Batch No: 7130519; \geq 99% purity) was tested in the bacterial reverse mutation assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 in the presence and absence of Aroclor-induced rat liver S-9. The tester strains were treated with 6-dose levels of test material ranging from 1.5 to 500 ug/plate with and w/o activation (72 hours incubation at 37 °C). Each treatment level was plated in triplicate. The assay was conducted twice to confirm the results. No evidence of mutagenic activity was observed at any dose level of Novaron in either mutation assay. Novaron AG 300 in dimethyl sulfoxide was not mutagenic in the tester strains of *S. typhimurium* up to 500 ug/plate concentration. **No adverse effect indicated. Study Acceptable. (Eya, 04/04/01).

007; 176988; "Bacterial Mutation Assay" (Jones, E., and Scammell, R., Huntingdon Research Centre, Ltd., Cambridgeshire, England., HRC Study Report No.: TSI 80B/941609, 01/10/95). Novaron AG 1100, (Batch No: D-1-3; \geq 99% purity) was tested in the bacterial reverse mutation assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strain WP2 *uvrA* in the presence and absence of Aroclor-induced rat liver S-9. The tester strains were treated with 7-dose levels of test material ranging from 0.78125 to 50 ug/plate w/o activation, and 9-dose levels ranging from 7.81 to 2000 ug/plate with activation (72 hours incubation at 37 °C). Each treatment level was plated in triplicate. The assay was conducted twice in absence of S-9 and thrice in presence of S-9 to confirm the results. No evidence of mutagenic activity was observed at any dose level of Novaron in either mutation assays. Novaron AG 1100 in dimethyl sulfoxide was not mutagenic in the tester strains of *S. typhimurium* and *E. coli*. **No adverse effect indicated. Study Acceptable. (Eya, 04/011/01).

007; 176985; "Novaron Mammalian Cell Mutation Assay" (Adams, K.; Huntingdon Research Centre, Ltd., Cambridgeshire, England, I.D. No.: TSI 73/941431, 06/16/94). Novaron AG 300 was assayed for its ability to induce mutation at the *tk* locus (5-trifluorothymidine resistance) in mouse lymphoma cells. Cultures without S9 at Novaron concentrations of 1-25 ug/mL, and with S9 at Novaron concentrations of 10-100 ug/mL, were selected for test for the mutation assay. Novaron was cytotoxic to the mouse lymphoma cell both in presence and absence of S-9. Small but statistically significant increases in mutant frequencies were observed at dose ranging from 15-25 ug/mL in the absence of S-9 in one of the two tests conducted. Similarly, a statistically significant increase in mutant frequency was observed at 100 ug/mL in one of the two test conducted in presence of S-9. These increases were not considered to be biologically significant since dose-response was not observed in one of the two duplicate tests. Increases in mutant frequency indicative of a mutagenic response were not observed in this *in vitro* gene mutation assay. **No adverse effect indicated. Study Acceptable (consistent increase in mutation was not observed at dose levels which were not toxic to the lymphoma cells with or without S9 activation) (Eya, 04/04/01).

CHROMOSOME EFFECTS

** 007, 012; 176987, 182215; "Experimental Additive 9823-37: L5178Y TK +/- Mouse Lymphoma Assay" (Durward, R.; Safepharm Laboratories, Ltd., Derby UK, SPL Project No.: 656/046, 04/25/00). Experimental Additive 9823-37 (lot no. 7170707, purity: >99.9%) was assayed for its ability to induce mutation at the *tk* locus (5-trifluorothymidine resistance) in mouse lymphoma cells. Cultures without S9 at Novaron concentrations of 2.5-80 ug/mL (3h exposure), and at 1.25-15 ug/mL (24 h exposure), and with S9 at test material concentrations of 5-80 ug/mL, were tested for their mutagenicity. Novaron was cytotoxic to the mouse lymphoma cell both in absence of S-9 at \geq 30 ug/mL (3 h exposure), and at \geq 15 ug/mL (24 h exposure), and in presence of S-9 at \geq 80 ug/mL (3 h exposure). The test material induced modest but statistically significant and dose-related increase in mutation frequency, particularly in the absence of metabolic activation

following a 3 h exposure. Experimental Additive 9823-37 was considered to be mutagenic under the test conditions. **Possible adverse effect indicated** (test material induced small but reproducible increases in the mutant frequency at the TK +/- locus in L5178Y cells in the absence of S-9, the increase in mutant frequency was due to small colony formation suggesting clastrogenic activity). **Study previously unacceptable but possibly upgradeable** with submission of purity of Experimental Additive 9823-37 (Lot # 7170707) and stability of test material in vehicle; submitted information was sufficient to upgrade the study; **Study acceptable.** (Eya, 04/04/01, upgraded, Moore, 8/17/01)

DNA DAMAGE

007; 176986; "Novaron Mouse Micronucleus Test" (Proudlock, R.J., and Taylor, K.; Huntingdon Research Centre, Ltd., Cambridgeshire, England, HRC Study Report No.: TSI 74/941459, 09/15/94). Five mice/sex/group were dosed with a single acute oral administration via intragastric gavage with (M/F): 0, 1250, 2500 and 5000 mg/kg of Novaron (Lot # 7130519, $\geq 99\%$ purity). The mice were sacrificed 24, 48 or 72 h after the administration. The test material at dose volume of 20 mL/kg was prepared in 1 % methylcellulose. Mortality was not observed during the test. At all sampling times, mice treated with Novaron did not show any significant increases in the frequency of micronucleated polychromatic erythrocytes. A slight but statistically significant dose related decrease in the ratio of polychromatic to normochromatic erythrocytes was obtained at the 48 h sampling time after treatment of animals. This decrease may be indicative of a slight transient bone marrow depression induced by the test substance. Novaron did not show any evidence of chromosome-damage in this *in vivo* test. **No adverse effect indicated. Study Acceptable. (Eya, 04/09/01).

007, 012; 176989, 182215; "Experimental Additive 9823-37: Micronucleus Test in the Mouse" (Durward, R. and Nolan, S.; Safepharm Laboratories, Ltd., Derby UK, SPL Project No.: 656/047, 04/25/00). Seven male mice/group were dosed with a single acute intraperitoneal administration with 0, 500, 1000 and 2000 mg/kg of Experimental Additive 9823-37 (Lot # 7170707, purity: >99.9%). The mice were sacrificed 24, or 48 h after the administration. A preliminary study indicated no sex difference, therefore only males were used. The test material at dose volume of 10 mL/kg was prepared in Arachis oil. Mortality was not observed during the test. There were no evidence of a significant increase in the incidence of micronucleated polychromatic erythrocytes in animals dosed with Novaron when compared to the concurrent vehicle control groups. A statistically significant decrease in the PCE/NCE ratio was observed in the 24 h 500 mg/kg dose level when compared to the control groups. However, this was part of an inverse dose-related response and was not considered to be treatment-related. Novaron was considered to be non-genotoxic under the condition tested. **No adverse effect indicated. Study previously unacceptable but possibly upgradeable** with submission of purity of the test material and stability of test material in vehicle; stability of the test material in arachis oil was not determined; **Study unacceptable.** (Eya, 04/12/01, updated, Moore, 8/17/01)

NEUROTOXICITY

Not required at this time.

SUBCHRONIC STUDIES

52857-005; 176981; "13-week dietary toxicity study in the rat with NOVARON" (Allan, S.A., and Hawkins, A., Huntingdon Life Sciences, Ltd., Cambridgeshire, England., Study Report No.: TSI 76/950471, 11/29/95). Novaron AG 300 (Lot # 7130519; $\geq 99\%$ a.i) was administered in diet to 4 groups of rats (M/F: 10/sex/dose) for 13 weeks at dietary doses of 0 (control), 30, 300, and 1000 mg/kg/day. Cholesterol levels were higher than controls in both sexes treated at 1000 mg/kg/day, and in males treated at 300 mg/kg/day. Alkaline phosphatase levels were higher than control in both sexes treated at 1000 mg/kg/day, and in females at 300 mg/kg/day. Since these findings were not accompanied by any related physiological or histological changes, it was not considered to be toxicologically significant. There were no other significant findings in the treated animals, i.e., in clinical signs, bodyweight gains, food consumption, ophthalmology,

hematology, urinalysis, organ weights, macroscopic and microscopic pathology. NOEL (M/F) = 30 mg/kg/day (based on coarse fur and histological changes of the harderian glands in females). **No adverse effects. Acceptable** (Eya, 03/20/01).

52857-005; 176980; "Two-week palatability study in the rat with Novaron" (Allan, S.A., and Hawkins, A., Huntingdon Research Centre, Ltd., Cambridgeshire, England, HRC Study Report No.: TSI 75/942358, 09/13/94). Novaron AG 300 (Batch #: 7130519; $\geq 99\%$ a.i) was administered in the diet to 4 groups of Sprague-Dawley rats (M/F: 5/sex/dose) for 2 weeks at dietary doses of 0 (control), 250, 500, and 1000 mg/kg/day. This study was designed to assess the palatability of Novaron to the rat, and to determine a suitable high dosage for use in a subsequent 13-week study. The inclusion of Novaron in the diet at the concentrations used for this study had no effect on food consumption and was therefore considered palatable at these levels. **No adverse effects.** (Eya, 03/19/01).