

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH**

SUMMARY OF TOXICOLOGY DATA

Sodium Chlorite, Chlorine Dioxide

Chemical Code # 2148, 2053, Document Processing Number (DPN) 50288, 50037

SB 950 # 318, 566

1/25/01

9/10/01, 4/18/17

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect indicated
Chronic toxicity, dog:	No study on file*
Oncogenicity, rat:	No data gap, no adverse effect indicated
Oncogenicity, mouse:	No data gap, possible adverse effect indicated
Reproduction, rat:	No data gap, possible adverse effect indicated
Developmental toxicity, rat:	No data gap, possible adverse effect indicated
Developmental toxicity, rabbit:	No data gap, possible adverse effect indicated
Gene mutation:	No data gap, possible adverse effect indicated
Chromosome effects:	No data gap, possible adverse effect indicated
DNA damage:	No data gap, possible adverse effect indicated
Neurotoxicity:	No data gap, no adverse effect indicate**

Toxicology one-liners are attached.

All record numbers for the above study types through 297615 (Document No. 50288-0268) were examined. This includes all relevant studies indexed by DPR as of 4/18/17.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T170418

Revised by [REDACTED] 4/18/17

* This study is not required at this time. A monkey subchronic toxicity study has been reviewed to fulfill the non-rodent toxicity study data requirement.

** A rat developmental toxicity study was reviewed which also fulfilled the toxicity data requirements for the acute and subchronic neurotoxicity studies.

NOTE: The following symbols may be used in the Table of Contents which follows:

- * = data adequately address FIFRA requirement
- † = study(ies) flagged as “possible adverse effect”
- N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

Rat Metabolism

Sodium Chlorite

50288-266; 296385; “The Kinetics of Chlorite and Chlorate in Rats”; (M.S Abdel-Rahman, D. Couri, R.J. Bull; Department of Pharmacology CMDNJ-New Jersey Medical School, Newark, NJ; Journal of Environmental Pathology and Toxicology 6: 97-103 (1981)); Male Sprague-Dawley rats were dosed orally by gavage with ³⁶ClO₂⁻ and pharmacokinetic parameters were evaluated. In the 1st phase, 4 male rats were dosed with a dose which ranged from 0.12 to 0.14 mg/kg of the test material. Blood samples were collected at 5, 10, 20, 30 and 60 minutes and 2, 4, 8, 24, 48 and 72 hours post-dose. The animals were euthanized at 72 hours and selected tissues/organs were assayed for radiolabel content. In the 2nd phase the rats were treated in the same manner with 0.06 to 0.07 mg/kg of the test material. Urine, feces and expired air were collected over a 72-hour interval. The peak concentration of radiolabel in the plasma was 470 ng/ml at 2 hours post-dose with a T_{1/2} value for elimination of 35 hours. At 72 hours post-dose, the blood was the primary site of recovery. Other sites were the stomach, testes, skin and lungs. The radiolabel was less concentrated in the kidneys and duodenum. The liver and bone marrow were the two sites with the least concentration of the radiolabel. Fourteen and 0.9% of the administered dose was recovered in the urine and feces at 24 hours post-dose, increasing to approximately 35 and 5% of the administered dose, respectively, at 72-hours post-dose. No radiolabel was recovered in the expired air. The Cl⁻ and ClO₂⁻ ions were the two constituents which were recovered in the urine and represented 32 and 6%, respectively, of the administered dose at 72 hours post-dose. **Summary report.** (██████████, 1/13/17)

Chlorine Dioxide

50288-0266; 296387; “Chlorine Dioxide Metabolism in Rat”; (M.S. Abdel-Rahman, D. Couri, J.D. Jones; The Ohio State University College of Medicine, Department of Pharmacology, Toxicology Division, Columbus, OH; Journal of Environmental Pathology and Toxicology 3: 421-430 (1980)); This study included two phases. In the 1st phase male Wistar rats were dosed orally by gavage with 100 mg/l of ³⁶ClO₂ (volume administered was not reported). Urine was collected up to 72 hours post-dose. Blood was collected at that time. Radiolabel moieties were quantified. In the second phase 4 rats/group were dosed orally with 10 or 100 mg/l of ³⁶ClO₂ (volume administered was not reported). The animals were euthanized at 30 minutes post dose and the blood was collected. In the first phase the two predominant analytes recovered in the urine were Cl⁻ and ClO₂⁻ which totaled 26.9 and 3.5% of the administered dose, respectively by 72 hours post-dose. ClO₃⁻ was recovered only at 12 to 24 hours post-dose and totaled 0.7% of the administered dose. Approximately 1.1% of the administered dose was recovered in the plasma at 72 hours post-dose. In the 2nd phase at 30 minutes post-dose, 2.22 and 1.42% of the administered dose was recovered in the plasma of the 10 and 100 mg/l treatment groups,

respectively. Cl^- and ClO_2^- constituted 82 to 86% of the radiolabel which was recovered.

Summary report. (██████████), 2/13/17)

Sodium Chlorite and Chlorine Dioxide

50288-0265; 296192; "Metabolism and Pharmacokinetics of Alternate Drinking Water Disinfectants"; (M.S. Abdel-Rahman, D. Couri, R.J. Bull; Department of Pharmacology, UMDNJ-New Jersey Medical School, Newark, NJ, Department of Pharmacology, College of Medicine, Ohio State University, Columbus, OH, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH; Environmental Health Perspectives 46: 19-23 (1982)); Four male Sprague-Dawley rats/group were dosed with 1) 1.5 mg/kg of $^{36}\text{ClO}_2$ (0.7 μCi), 2) 0.15 mg/kg of $^{36}\text{ClO}_2^-$ (0.17 μCi), 3) 0.065 mg/kg of $^{36}\text{ClO}_3^-$ (0.85 μCi), or 4) 3.26 mg/kg of HO^{36}Cl (0.45 μCi) by gavage. Blood samples were collected from 5 minutes through 48 hours post-dose. Expired air, urine and fecal samples were collected over that time period. The animals were euthanized at 72 hours post-dose and the tissue distribution of radiolabeling was assessed. The absorption rate constants for $^{36}\text{ClO}_2$ and $^{36}\text{ClO}_2^-$ were 3.77 and 0.198/hr, respectively. The $T_{1/2}$ values were 0.18 and 3.50 hours, respectively. Only approximately 40% of the administered dose was recovered in the urine and feces of the $^{36}\text{ClO}_2$ and $^{36}\text{ClO}_2^-$ groups by 72 hours post-dose (30 to 35% in the urine, 5 to 10% in the feces). No radiolabel was trapped in the exhaled air. Eighty four to 87% of the radiolabel which was recovered in the urine was as the Cl^- ion for both treatment groups. In the tissue distribution assessment, approximately 4 to 4.5% of the administered radiolabel was recovered in the tissues at 72 hours post-dose. The plasma, kidneys, lungs and stomach were the primary sites at which the radiolabel was recovered in the $^{36}\text{ClO}_2$ group. For the $^{36}\text{ClO}_2^-$ group, the radiolabel was dispersed throughout the tissues with the highest level being in the blood. In this study approximately 55% of the radiolabel was unaccounted for over the 72-hour sample collection period. **Summary Report.** (██████████), 12/30/16)

50288-0265; 296200; "Pharmacodynamics of Alcide, a New Antimicrobial Compound, in Rat and Rabbit"; (J. Scatina, M.S. Abdel-Rahman, S.E. Gerges, M.Y. Khan, O. Gona; Toxicology Laboratory, Department of Pharmacology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ; Fundamental Applied Toxicology 4: 479-484 (1984)); Alcide gel is an antimicrobial preparation which is supplied as Part A (sodium chlorite) and Part B (lactic acid). Equal weights of these two formulations were mixed immediately prior to application with the evolution of chlorine dioxide. In the first part of this study, the skin of female Sprague-Dawley rats was treated with 2 g/kg of the Alcide preparation for 10 days followed by an application of 2 g/kg of Alcide ($\text{Na}^{36}\text{ClO}_2$ in Part A:Part B (1:1 (w/w))) on day 11. In the 1st phase, blood was collected by cardiac puncture from 0.5 to 168 hr post-final dose. In the 2nd phase, the skin of the animals was treated in the same manner. At 96 hours post-final dose, selected tissues/organs were dissected and the retention of radiolabel was assayed. In the 3rd phase, the skin of the animals were treated as above. The feces and expired air were collected up to 96 hours post-final dose and the urine was recovered up to 168 hours post-final dose. In the second part of the study, the skin of 5 New Zealand white rabbits/sex/group was exposed to 0 (Alcide gel minus sodium chlorite), 0.5, 1.0 or 2.0 g/kg of Alcide gel (Part A: Part B (1:1 (w/w))) 5 days/week for 3 months. At the termination of the study, hematological and clinical chemical parameters were evaluated. The animals were euthanized and selected tissues/organs were examined histologically. When Part A (sodium chlorite) preparation was mixed with Part B (lactic acid), a concentration of 0.4% sodium chlorite resulted in the evolution of 0.025% solution of chlorine dioxide initially. The concentrations of sodium chlorite and chlorine dioxide gradually diminished to 0.28% and 0.02%, respectively, at 60 minutes post-preparation. In the pharmacokinetic assessment of the 1st phase, $T_{1/2}$ values for absorption and excretion of the radiolabel were 22.1 and 64.0 hours, respectively. In the tissue distribution of the 2nd phase, at

96 hours post-dose, whole blood was the highest site of recovery, followed by the kidneys and untreated skin. As a consequence of the route of exposure, recovery in the liver and gastrointestinal tract was limited. Radiolabeled chloride and chlorite ions were identified in rat urine for the first 96-hours post-dose. Radiolabel was recovered in the rat urine up to 168 hours post-dose. Radiolabel was not recovered in the feces or expired air at any time during the sample collection period. Repeated dermal exposure of rabbits for 3 months at a treatment level of 2 g/kg of Alcide did not result in any apparent treatment-related effects on the hematology, clinical chemistry or histological evaluations. **Summary Report.** (██████████, 1/10/17)

50288-0266; 296386; "The Kinetics of ClO₂ and Effects of ClO₂, ClO₂⁻, and ClO₃⁻ in Drinking Water on Blood Glutathione and Hemolysis in Rat and Chicken"; (M.S. Adelman, D. Couri, R.J. Bull; The Ohio State University of Medicine, Department of Pharmacology, Toxicology Division, Columbus, OH; Journal of Environmental Pathology and Toxicology 3: 431-449 (1980)); Male Sprague-Dawley rats were treated by gavage with ³⁶ClO₂ and the absorption, distribution and excretion of the test material was assessed. In addition, male rats received either ClO₂ or ClO₂⁻ in the drinking water for 4 months. In the 1st phase, 4 male Sprague-Dawley rats were dosed orally by gavage with ³⁶ClO₂ (specific activity: 420 dpm/μg) at a dose ranging from 1.36 to 1.5 mg/kg or 4 male rats received ClO₂ (100 mg/l) in the drinking water for 2 weeks, followed by a single treatment with ³⁶ClO₂ (specific activity: 1800 dpm/μg) (300 mg/l) orally, by gavage (actual dose cannot be determined due to the limited data reported). In both instances, blood was collected at specified intervals up to 72 hours post-dose. A third group of 4 male rats were dosed orally with ³⁶ClO₂ at a dose range of 1.36 to 1.50 mg/kg and urine, feces and expired air were collected up to 72 hours post-dose. When the rats received a single dose of approximately 1.5 mg/kg of chlorine dioxide, a peak concentration of 7 μg/ml was observed at 1 hour post-dose with a T_{1/2} value for elimination of 43.9 hours. When the rats were pretreated with chlorine dioxide for 2 weeks, the reported peak concentration was at 2 hours and the T_{1/2} value for elimination was 31.0 hours. In both dosing scenarios, plasma was the primary site of radiolabel recovery at 72 hours post-dose. The kidneys, lungs, testes and stomach were also prominent in sequestering the radiolabel. Eighteen and 4.5% of the administered dose was excreted in the urine and feces, respectively, by 24 hours post-dose. By 72 hours post-dose, 30 and 10% of the administered dose was recovered in the urine and feces, respectively. Treatment of the ClO₂-treatment groups for 4 months, up to the 100 mg/l treatment level, resulted in a decreased hemolysis of the red blood cell in a treatment-related manner. At the same treatment levels, the blood glutathione levels did not correlate well with the degree of hemolysis. However treatment with 10 or 100 mg/l of ClO₂⁻ for 4 months resulted in a dose-related decrease in the serum levels of blood glutathione and a reciprocal increase in hemolysis. **Summary report.** (██████████, 1/17/17)

50288-0266; 296408; "Pharmacokinetics of Alcide, a Germicidal Compound in Rat"; (J. Scatina, M.S. Abdel-Rahman, S.E. Gerges, H. Alliger; UMDNJ-New Jersey Medical School, Pharmacology Department, Toxicology Laboratory, Newark, NJ; Journal of Applied Toxicology 3: 150-153 (1983)); Alcide is an antimicrobial preparation which is supplied as Part A (sodium chlorite) and Part B (lactic acid). Equal weights of these two formulations were mixed immediately prior to application with the evolution of chlorine dioxide. When Part A (sodium chlorite) preparation was mixed with Part B (lactic acid), a concentration of 0.4% sodium chlorite resulted in the evolution of 0.025% solution of chlorine dioxide initially. The concentrations of sodium chlorite and chlorine dioxide gradually diminished to 0.28% and 0.02%, respectively, at 60 minutes post-preparation (vol no. 50288-0265, rec. no. 296200). In the pharmacokinetic phase 5 female Sprague-Dawley rats were dosed orally by gavage with 19.05 mg of ³⁶ClO₂⁻/animal (approximate dose: 70 mg/kg). Blood was drawn periodically up to 144 hours post-dose. The animals were euthanized and particular tissues/organs were dissected and analyzed for the presence of radiolabel. In the excretion phase 4 female Sprague-Dawley rats were

dosed orally by gavage with 19.05 mg of $^{36}\text{ClO}_2^-$ /animal (approximate dose: 85 mg/kg). Urine, feces and expired air were collected periodically up to 144 hours post-dose. Metabolites were identified in the urine. In the pharmacokinetic analysis, the maximal concentration of 341.5 $\mu\text{g/ml}$ of ^{36}Cl was achieved at 8 hours post-dose in the serum. The T1/2 for radiolabel elimination was 48 hours. At 144 hours post-dose whole blood, lungs, kidneys and skin were the primary sites in which the radiolabel was isolated. The radiolabel was distributed extensively at a lower concentration throughout the other tissues/organs. Excretion of the radiolabel was primarily in the urine (% of administered dose: 45.3% in the urine vs. 10.2% in the feces). None of the radiolabel was recovered in the expired air. Seventeen percent of the radiolabel was excreted within the 1st 24 hours post-dose. The two primary metabolites were Cl^- and ClO_2^- .

Summary report. (██████████, 2/7/17)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT (Sodium Chlorite)

Acute oral toxicity, rat

50288-100; 174504; Acute Oral LD50; 811; rat; HAZLETON LABORATORIES AMERICA, INC., Vienna, VA; Project No. 2044-103; 10/16/84; Sodium Chlorite, (Technical 80% purity) a white powder; oral dose- 20, 63, 200, 630 and 2000 mg/kg; 5/sex/dose; mortalities- (M) 0/5, 0/5, 2/5, 5/5, 5/5 and (F) 0/5, 0/5, 1/5, 5/5, 5/5; clinical observations- depression, soft feces, rough haircoat, ataxia, hunched and cyanotic appearance; body weight gain- all test animals that survived the observation period gained weight; necropsy- blanched stomach lining, intestines contained colored fluids, stomach and intestines contained compound like material, black liver and black kidney; LD50 (95% confidence limits) (M) 242 (101-582) mg/kg, (F) 308 (168-564) mg/kg and (C) 278 (157-491) mg/kg; Toxicity Category II; study acceptable (██████████ 5/25/00)

Acute dermal toxicity

50288-100; 174505; Acute Dermal LD50; 812; rabbit; HAZLETON LABORATORIES AMERICA, INC., Vienna, VA; Project No. 2044-104; 11/21/84; Sodium Chlorite, (Technical 80% purity) a clear colorless powder; dermal dose- 50, 100, 150 and 300 mg/kg; 5/sex/dose; exposure period of 24 hours; mortalities- (M) 0/5, 0/5, 3/5, 5/5 and (F) 0/5, 0/5, 4/5, 5/5; clinical observations- depression, cyanotic appearance and skin irritation at the dose site; body weight gain- body weights of deceased test animals showed decrease from initial weight; test animals that survived the observation period gained weight; necropsy- kidneys dark red, adrenals reddened, urinary bladder distended or filled with red fluid and abdominal cavity contained red fluid; LD50 (95% confidence limits) (M) 140 (93-211) mg/kg, (F) 129 (96-173) mg/kg and (C) 134 (104-172) mg/kg; Toxicity Category I; study acceptable (██████████ 5/25/00)

Acute inhalation toxicity, rat

50288-070; 132278; Acute Inhalation Toxicity; 813; Rat; International Research and Development Corporation, Mattawan, MI, Laboratory Project Identification 632-001, 8/14/92; Technical Sodium Chlorite (administered as an aerosol atmosphere, 35% (w/v) in distilled water for the 0.29 mg/l group and 40% for the other 4 groups); 5/sex/dose; doses (mean gravimetric concentrations) of 0.29, 0.3, 0.35, 0.7, 1.6 mg/l with MMAD determinations of 2.4, 1.2, 2.7, 2.7, and 3.4 μm , respectively, and GSD of 2.08, 1.77, 2.04, 1.89, and 1.80, respectively; 4 hr exposure; mortalities- males: 4/5, 0/5, 5/5, 5/5, 5/5, respectively; females: 1/5, 0/5, 2/5, 5/5, 5/5, respectively; observations- lethargy, ataxia, gasping, decreased respiratory rate, increased respiratory rate, anogenital staining, increased salivation, red or brown, dry material around nose, mouth and/or eye, hypersensitivity to touch, cold to touch, and stained body surface; necropsy- mortalities: discolored or congested lungs; survivors: no treatment-related lesions; Reported LC50 (M/F)=0.29 mg/l; Category not assigned; Unacceptable and not upgradeable (did not adequately establish dose-response for males). (██████████ 10/25/94)

Primary eye irritation, rabbit

No study on file at DPR nor required at this time.

Primary dermal irritation

50288-100; 174506; Dermal Irritation; 815; rabbit; HAZLETON LABORATORIES AMERICA, INC., Vienna, VA; Project No. 2044-105; 11/6/84; Sodium Chlorite, (Technical 80% purity) a white powder; dermal dose- 0.5 g/test site; 6 rabbits were treated; exposure period of 4 hours (occluded); one female was found dead on Day 20 post-dose; clinical observations- at Day 7 post patch removal -Necrosis and blanching (2/6), at Day 21 post patch removal -Necrosis and blanching (1/6); Toxicity Category not determined; study unacceptable; test material not moistened just prior to application; study unacceptable. (██████, 6/1/00)

Dermal sensitization

50288-0186; 208294; Skin Sensitization; 816; guinea pig; Product Safety Laboratories, Dayton, NJ; Study #: 14126; 11/12/03; 2L500 (composition: a. i., 13.45% sodium chlorite); 34 subjects (33 M & 1 F with 20 test article, 10 naïve control, and 4 preliminary irritation test subjects); Method of Ritz and Buehler (1980); the Induction phase consisted of 3 applications of 0.4 mL of undiluted test article applied to each test subject, using an occlusive, 25-mm, Hilltop Chamber at the same site (left side) for at least 6 hours per exposure (7 days between each exposure); the Challenge phase initiated 14 days after 3rd induction treatment consisted of a single, 0.4 mL aliquot of undiluted test article applied for 6 hours to the skin on right side in the manner described above; mortality: 1/20; probably not treatment related after 1st induction treatment; clinical signs: (treatment group) challenge, erythema - score 0.5 in 6/19 at 24 hours post-treatment, decreasing to score 0.5 in 1/19 by 48 hours; Toxicity Category: **Not a Contact Sensitizer; Acceptable.** (██████, 01/12/04)

SUBCHRONIC STUDIES

Rat Subchronic Oral Toxicity

Sodium Chlorite

**50288-0058 115605 Ridgway, P., "Sodium chlorite: 13 week oral (gavage) toxicity study in the rat", Toxicol Laboratories Ltd., Herefordshire, 4/24/92. Laboratory Project ID # CMA/13/R. Fifteen CrI:CD@(SD)BR rats/sex/group were dosed by gavage with sodium chlorite (adjusted for 80.9% purity) at 0, 10, 25, or 80 mg/kg/day, 7 days/week in a standard subchronic study design. Subchronic NOEL = 10 mg/kg/day (primarily based on ulceration, hyperkeratosis, and/or chronic inflammation of the non-glandular stomach epithelium in 2 males at 25 mg/kg). Similar histopathology was found in both sexes at 80 mg/kg/day, along with reduced RBC counts, Hb, HCT, and elevated reticulocyte counts (some findings only in males). This dose presented some enlarged spleens, and low incidences of splenic extramedullary hematopoiesis, considered to be treatment-related. Clinical observations of "salivation" were reported in all 80 mg/kg/day rats. Four high dose rats died prematurely due to treatment: two of them having severe anemia. Study is acceptable, with no adverse effects (since findings were primarily limited to a comparatively high dose level of a compound expected to be irritating to exposed mucosae because it is an oxidant at a comparatively high pH). (██████, 12/11/00.

50288-0267; 296808; "Subchronic Toxicity of Sodium Chlorite in the Rat"; (R.M. Harrington, R.R. Romano, D. Gates, P. Ridgeway; Toxicol Laboratories, Ltd., Ledbury, Herefordshire, England; Journal of the American College of Toxicology 14: 21-33 (1995); There were two phases in this study. In the first phase 5 CrI: CD (SD) rats/sex/group were dosed orally by gavage with 0 (purified water), 25, 50, 100 or 200 mg/kg/day of NaClO₂ for 14 days. Blood and urine were collected during the 2nd week of dosing. At the termination

of the dosing, the animals were euthanized and examined grossly for lesions. In the 2nd phase 15 animals/sex/group were dosed orally by gavage with 0, 10, 25 or 80 mg/kg/day of NaClO₂ for 13 weeks. Body weight gain and food consumption were monitored over the course of the study. The eyes of each study animal were examined ophthalmologically prior to the initiation of the study. During the 12th week, the eyes of the control and high dose groups were reexamined. Blood and urine samples were collected during the 13th week. Hematological and clinical chemical parameters were evaluated and urinalysis was performed. The animals were euthanized and grossly examined. The appropriate tissues/organs were dissected, processed and examined microscopically. In the 1st phase two females and one male in the 200 mg/kg group died by day 3 of the dosing. At that point this treatment group was terminated. The mean body weight gains of both sexes in the 100 mg/kg group and the males in the 50 mg/kg group were less than that of the control group ($p < 0.05$, NS). In the hematological examination the red blood cell count, hemoglobin concentration and hematocrit of both sexes were reduced in the 100 mg/kg groups. The methemoglobin level of both sexes was increased in this treatment group. In phase two three males and one female in the 80 mg/kg group died during the study. These deaths were deemed to be treatment-related. Salivation was observed in the 80 mg/kg group from the 3rd week onward. The red blood cell count for both sexes in the 80 mg/kg was less than the control group. The hematocrit and hemoglobin concentration of the males in the 80 mg/kg group were less than the control values ($p < 0.05$). The methemoglobin concentration and reticulocyte percentage of these males were greater than the control level ($p < 0.05$, NS). The clinical chemical evaluation and the urinalysis did not reveal any apparent treatment-related effect. The ophthalmological examination did not reveal any treatment-related ocular lesions. The mean relative adrenal and spleen weights of both sexes in the 80 mg/kg group and the females in the 25 mg/kg group were greater than the control group values ($p < 0.05$). In the histologically examination squamous epithelial hyperplasia with hyperkeratosis, ulceration, chronic inflammation and edema were noted in the stomach of both sexes of the 80 mg/kg group. Ulceration, chronic inflammation and edema were noted in the stomach of two males in the 25 mg/kg group. Extramedullary hematopoiesis was noted in the spleens of two males and two females of the 80 mg/kg group. **No adverse effect indicated. Rat Subchronic Oral Toxicity NOEL:** (M/F) 10 mg/kg/day (based on the histological lesions in the stomachs of the males and the increased relative spleen and adrenal weights of the females in the 25 mg/kg treatment group); **Summary report.** (2/15/17)

Chlorine Dioxide

50288-0267; 296809; "Comparative Subchronic Toxicity Studies of Three Disinfectants"; (F. B. Daniel, L.W. Condie, M. Robinson, J.A. Stober, R.G. York, G.R. Olson, S-R. Wang; Health Effects Research Laboratory, USEPA, Cincinnati, OH, Biotechnology Branch, Life Sciences Division, US Army Dugway Proving Ground, UT, Reproductive & Developmental Toxicology, International Research and Development Corporation, Mattawan, MI, Pathology Associates, Inc., West Chester, PA, Computer Sciences Corporation, Cincinnati, OH; Journal of American Water Works Association 82: 61-69 (1990)); Ten Sprague-Dawley rats/sex/group received 0 (distilled water), 25, 50, 100 or 200 mg/l of chlorine dioxide in the drinking water for 90 days ((M) 0, 1.9, 3.6, 6.2, 11.5 mg/kg/day, (F) 0, 2.4, 4.6, 8.2, 14.9 mg/kg/day). No deaths resulted from the treatment. Water consumption declined in a dose-related manner. Mean body weight gain was reduced for both sexes in the 200 mg/l group ($p < 0.05$). There was no treatment-related effect on the hematological parameters. In the clinical chemistry, although the values for the treated animals were statistically different from those of the control group for some of these parameters, there were no physiologically relevant effects. In the histological examination there was a treatment-related increase in the incidence of goblet cell hyperplasia and subacute

inflammation of the nasal cavity at 25 mg/l and above. Squamous metaplasia was also noted in some of these animals. **Possible adverse effect:** significant inflammation in the nasal cavity. **Rat Subchronic Oral Toxicity NOEL::** (M/F) < 25 mg/l ((M) <1.9 mg/kg/day, (F) <2.4 mg/kg/day) (based upon the incidence of inflammation in the nasal cavity of both sexes in the 25 mg/l treatment group). **Summary report.** (██████████, 2/16/17)

Mouse Subchronic Dietary Toxicity

Sodium Chlorite

50288-0266; 296394; "The Renal Effects of Sodium Chlorite in the Drinking Water of C57L/J Male Mice"; (P.M. Connor, G.S. Moore, E.J. Calabrese, G.R. Howe; Division of Public Health, School of Health Sciences, University of Massachusetts, Amherst, MA; J. Environ. Pathol. Toxicol. Oncol. 6: 253-260 (1985)); Eleven or 12 male C57L/J mice/group received sodium chlorite in the drinking water at concentrations of 0, 4.0, 20.0, or 100 ppm for 30, 90 or 180 days (30: 0, 0.98, 4.73, 22.8 mg/kg/day, 90: 0, 0.85, 4.17, 21.4 mg/kg/day, 180: 0, 0.91, 4.91, 22.67 mg/kg/day). There was no treatment-related effect on survival, body weight gain or water consumption. Potential nephrotoxicity was evaluated by excising the kidneys at the time of necropsy. The absolute and relative kidney weights of the treated animals were not affected. Histological examination did not reveal any treatment-related lesions. **No adverse effect indicated. Summary report.** (██████████, 1/23/17)

Dog Subchronic Oral Toxicity Study

No study has been submitted nor is required at this time.

Monkey 8-Week Oral Toxicity Study

See Record No. 296399 under Mechanism Section.

Rabbit Repeated Dosing 4-Week Dermal Toxicity

Sodium Chlorite and Chlorine Dioxide

50288-0266; 296391; "Subchronic Dermal Toxicity Studies of Alcide Allay Gel and Liquid in Rabbits"; (M.S. Abdel-Rahman, G.A. Skowronski, R.M. Turkall, S.E. Gerges, A.R. Kadry, A.H. Abu-Hadeed; University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Department of Pharmacology, Toxicology Laboratory, Newark, NJ; Journal of Applied Toxicology 7: 327-333 (1987)); Allay in gel and liquid form is a germicidal agent which consists of two parts. Part A consists of sodium chlorite and Part B is lactic acid. When the two components are mixed, chlorine dioxide is produced. The skin of twelve New Zealand White rabbits/sex/group were treated in the following manner: Allay Gel, Group 1 (high dose) 2 g/kg (Part A:Part B (1:1) 4x low dose concentration of sodium chlorite and lactic acid; Group 2 (low dose) 2 g/kg (Part A:Part B (1:1)), Group 3 (placebo) 2 g/kg (Part A:Part B (1:1)), (no active ingredients were in the materials which were applied); Allay Liquid, Group 4 (high dose) 2 g/kg (Part A:Part B (1:1) 1.67x low dose concentration of sodium chlorite and lactic acid; Group 5 (low dose) 2 g/kg (Part A:Part B (1:1)), Group 6 (placebo) 2 g/kg (Part A:Part B (1:1)), (no active ingredients were in the materials which were applied); Groups 7 and 8 were untreated control groups for both of the treatment cohorts. For the Allay Gel cohort the test material was applied immediately after mixing and covered with a wrapping for 6 hours, 5 days/week for 30 days. For the Liquid cohort the test material was mixed and applied immediately after mixing for a 5-minute exposure, 3 times per day, 5 days per week for 30 days. Although dermal exposure to sodium chlorite and chlorine dioxide was not assessed in this study, in another study by this laboratory (rec. no. 296200) in which the gel product was used as the test material, the initial concentrations of the two components were 0.4 and 0.025%, respectively, at the time of mixing. The skin of the high dose gel group demonstrated irritation from day 3 through the 3rd week of

treatment that achieved a maximal degree of moderate to severe erythema. Ultimately the skin appeared to be normal by the end of the treatment period. Treatment with the liquid material resulted in some signs of irritation for both treatment groups which resolved by the end of the 2nd week. Histological examination of treated skin sections from both gel treatment groups revealed slight to severe inflammatory changes. Treatment with the liquid resulted in minimal histological effects in the treated skin. Although some of the hematological and clinical chemical parameters demonstrated statistically significant differences between the control and treated groups, these differences did not indicate any toxicologically relevant effects. Likewise, in the necropsy examination some of the mean relative organ weights of the treated group animals were reported to be statistically significantly different from those of the control group. However, histological evaluation of these organs did not indicate any treatment-related lesions. **No adverse effect indicated.** Exposure to chlorine dioxide and/or sodium chlorite was not well documented in this report. **Summary report.** (██████████, 1/18/17)

CHRONIC STUDIES

Chronic, rat

Sodium Chlorite and Chlorine Dioxide

50288-0266; 296388; "Toxicity of Chlorine Dioxide in Drinking Water"; (M.S. Abdel-Rahman, D. Couri, R.J. Bull; Department of Pharmacology, CMDNJ-New Jersey Medical School, Newark, NJ, Ohio State University, College of Medicine, Department of Pharmacology, Columbus, OH, U.S.E.P.A., Health Effects Research Laboratory, Cincinnati, OH; Journal of Environmental Pathology, Toxicology and Oncology 6: 105-113 (1985)); Male Sprague-Dawley rats received 0, 1, 10, 100 or 1000 mg/l of ClO₂ or 10 or 100 mg/l of ClO₂⁻ in the drinking water for 1 year. At 2, 4, 7 and 9 months of treatment, blood was drawn and red blood cell parameters, red blood cell fragility and blood glutathione levels were assessed. At 3 months of treatment, ³H-thymidine, 0.5 mCi/kg bw was administered intraperitoneally. Incorporation of radiolabel into the DNA of the liver, kidneys, testes, and small intestine was assayed. For the ClO₂-treatment groups, up to the 100 mg/l treatment level, the stability of the red blood cells was increased in a treatment-related manner. The blood glutathione levels were lower in the treated groups in comparison to the controls but not necessarily in a treatment-related manner. Treatment with ClO₂⁻ resulted in decreased levels of blood glutathione. The red blood cells were more stable but not necessarily in a dose-related manner. Red blood cell parameters were not physiologically affected over the treatment period. Incorporation of thymidine into DNA was reduced in the livers, kidneys and testes in a treatment-related manner after 3 months with either ClO₂ or ClO₂⁻. In contrast treatment with ClO₂ resulted in an increase in incorporation of thymidine in the small intestine. This effect was not so apparent for the animals which were treated with ClO₂⁻. **Summary report.** (██████████ 1/17/17)

Chronic, dog

No study on file with DPR nor required at this time.

Oncogenicity, rat

Sodium Chlorite

50288-0265; 296198; "Long Term *In Vivo* Carcinogenicity Tests of Potassium Bromate, Sodium Hypochlorite, and Sodium Chlorite Conducted in Japan"; (Y. Kurokawa, S. Takayama, Y. Konishi, Y. Hiasa, S. Asahina, M. Takahashi, A. Maekawa, Y. Hayashi; Department of Pathology, National Institute of Hygienic Sciences, Setagayaku, Tokyo 158, Japan, National Cancer Center, Chuoku 104, Tokyo, Japan, Department of Oncological Pathology, Cancer Center, Nara Medical College, Kashihara, Nara 634, Japan, Department of Pathology, Cancer Center, Nara Medical College, Kashihara, Nara 634, Japan Department of Pathology,

Fukushima Medical College, Fukushima, Japan; Environmental Health Perspectives 69, 221-235 (1986)); In this report B6C3F1 mice and F344 rats received sodium chlorite in the drinking water. The mice study data were previously reported in rec. no. 296188. Fifty rats/sex/group received 0, 300 or 600 ppm of sodium chlorite (purity: 99.4%) in the drinking water for 85 weeks ((M) 0, 18.0, 32.1 mg/kg/day, (F) 0, 28.3, 40.9 mg/kg/day). This study was compromised by the presence of a Sendai virus infection in all of the study animals which necessitated terminating the study after 85 weeks of treatment. There was no treatment-related effect reported for the hematology, clinical chemistry or urinalysis. No increase in incidence of oncogenic lesions was noted. No adverse effect was evident. Summary report. (██████████, 3/15/17)

Oncogenicity, mouse

Sodium Chlorite

50288-0265; 296188; “Studies of Carcinogenicity of Sodium Chlorite in B6C3F1 Mice”; (Y. Yokose, K. Uchida, D. Nakae, K. Shiraiwa, K. Yamamoto, Y. Konishi; Department of Oncological Pathology, Cancer Center, Nara Medical College, Kashihara, Nara 634, Japan; Environmental Health Perspectives 76: 205-210 (1987)); Fifty B6C3F1 mice/sex/group received sodium chlorite technical (purity: 82-87%) in the drinking water at concentrations of 0, 0.025% or 0.05% for 80 weeks ((M) 0, 51, 76.9 mg/kg/day, (F) 0, 33.3, 63.8 mg/kg/day, calculated by reviewer). These treatment levels were selected as the result of a 13-week treatment study in which the treatment levels ranged from 0.00625 to 1% of the test material in the drinking water. At treatment levels of 0.5% and above resulted in the death of the animals. A dose of 0.1% caused a lower body weight gain. In this long term study, survivors from all of the groups received an additional 5 weeks of distilled water in their drinking water before termination of the study. There was no treatment-related effect upon the survival of the study animals. There was no apparent treatment-related effect on the mean body weights. The mean absolute and relative organ weights were not affected by the treatment. In the histopathological evaluation, there was a treatment-related incidence of pulmonary adenomas and adenocarcinomas for the males (0: 0/35, 0.025: 3/47, 0.05: 7/43). **Possible adverse effect:** incidence of pulmonary adenomas and adenocarcinomas. **Summary Review.** (██████████, 12/27/16)

GENOTOXICITY

Gene mutation

Chlorine Dioxide

****50037-018 130832** Cifone, M. A., “Mutagenicity evaluation of chlorine dioxide in the mouse lymphoma forward mutation assay,” Litton Bionetics, Inc., Kensington, MD, Oct., 1986. LBI Project No. 20989. Fischer L5178Y mouse lymphoma cells were tested with chlorine dioxide in a phosphate buffered saline solution (not otherwise described). Test cells were heterozygous for thymidine kinase expression, so that a single mutation in the functional gene could lead to a phenotype lacking thymidine kinase. Survivability in medium containing 5-trifluorothymidine (TFT) was taken as evidence of mutagenicity. Test cells were added at 3×10^6 cells/tube, with 10 ml medium/tube. Cells were exposed to test article for 4 hr, then washed twice prior to being suspended in a growth medium. After an expression period of 48 hr, aliquots were transferred to medium containing TFT. Colonies were counted after 10-14 days in this medium. Chlorine dioxide was tested at 1.3 to 24.3 $\mu\text{g/ml}$ without S9 and at 6.7 to 48.3 $\mu\text{g/ml}$ with S9 (higher levels were lethal in both cases). Mutant frequency was sufficiently elevated to constitute a positive response without S9 at treatment levels of 3.2 to 24.3 $\mu\text{g/ml}$ and in chlorine dioxide medium with S9 at 48.3 $\mu\text{g/ml}$. Positive controls (EMS and 3-MCA) were used without and with S9, respectively. This study has several acknowledged deficiencies including no repeat trial, however it presents clear positive responses, consistent with several other mutagenicity studies

of various types. This study is of sufficient quality to address the gene mutation data requirement. [REDACTED], 1/24/01.

Chromosome effects

****50288-058 115603** Ivett, J. L., "Mutagenicity evaluation of chlorine dioxide in the mouse bone marrow cytogenetic assay," Litton Bionetics, Inc., June 1984. LBI Project No. 22202. CD-1 mice, 5/sex/group, were dosed with aqueous solutions of chlorine dioxide by ip injection, made from stock solutions of 4.25 or 3.92 mg/ml. Achieved dose levels were 0, 1.7, 5.2, or high dose of 15.4 to 16.1 mg/kg of chlorine dioxide. Positive control was triethylenemelamine (1.5 mg/kg). The latter was administered only at 24 hr before sacrifice, whereas other treatments were administered at 6 hr, 24 hr, and 48 hr before sacrifice. There were 5 mice/sex at each dose/treatment combination. Mice were administered 4 mg/kg colchicine 3 hr before sacrifice. Tibial marrow cells were collected, fixed, stained, coded, and scored (blind to treatment). Where possible, 50 spreads were read per mouse. Mitotic indices were also recorded. Various chromosome and chromatid aberrations were scored, however tables did not include chromatid gaps in summary indices. Chlorine dioxide did not elicit chromosomal aberrations. Positive control was functional. Acceptable, with no adverse effects. [REDACTED], 1/24/01.

50288-058 115604 Moore, M. R., "Evaluation of chlorine dioxide in the mouse dominant lethal assay," Litton Bionetics, Inc., Aug. 1984. LBI Project No. 22203. CD-1 mice, 12/group [15/group in the 20 mg/kg group] were dosed once intraperitoneally with chlorine dioxide (0, 2, 7, or 20 mg/kg, derived from stock solution at 2.9 mg/ml). A functional positive control group (triethylenemelamine, 0.3 mg/kg) was treated in parallel. Mice were mated weekly for 4 weeks, beginning 3 days after treatment. Mating was 1:2 M:F each week, and males were cohabited with females for 5 days, then rested for 2 days before the next mating. Females were necropsied 14 days after the midpoint of the mating week, and were examined for pregnancy and for numbers of living and dead implantations. Seven of the 15 high dose males died, and there were only 3 pregnant females during the first mating period after treatment in that group. Some mean values or indices differed from controls or other groups during that time in that group, although none were statistically significant. This sample was too small to interpret. This study is unacceptable and cannot be upgraded because (1) the protocol was limited to the last 4 weeks of the male spermatogenic cycle, and (2) there were too few females mated in all groups, and (3) there were too few pregnant females at week 1 to allow meaningful inferences, as indicated above. No adverse effect is indicated. [REDACTED], 1/24/01.

****50037-018 130833** Galloway, S. M. and J. L. Ivett, "Mutagenicity evaluation of chlorine dioxide in an *in vitro* cytogenetic assay measuring chromosomal aberration frequencies in Chinese hamster ovary (CHO) cells," Litton Bionetics, Inc., Kensington, MD, Oct., 1986. LBI Project No. 20990. The test article was variously described as concentration of 2.227 mg/ml or 4.25 mg/ml. This material was supplied in phosphate buffered saline (PBS), which was used as the vehicle for dilutions. CHO-WBI cell line cultures of 1.5×10^6 cells per flask in exponential growth phase were exposed for 10 hr without S9 or for 2 hr with S9, and mitotic cells were harvested in both cases 12.5 hr after the onset of exposure. Colcemid was added 2.5 hr before harvest in both cases. In trials both with and without S9, 200 metaphase cells per treatment level were scored [also 100 cells per untreated control group and 100 cells per solvent (PBS) control], and treated group aberration frequencies were compared against combined controls. Sufficient positive controls were tested to validate technique (cyclophosphamide with S9 and Mitomycin C without S9). Results were clearly positive without S9 at 10 to 15 $\mu\text{g/ml}$, and with S9 at the highest dose level permitting cell survival (50 $\mu\text{g/ml}$). This study has several deficiencies with respect to guidelines, however it presents clear positive responses, consistent

with several other mutagenicity studies of various types. This study is of sufficient quality to address the chromosomal aberrations data requirement. [REDACTED] 1/24/01.

Sodium Chlorite and Chlorine Dioxide

50288-0266; 296405; "Evaluation of Chemicals Used for Drinking Water Disinfection for Production of Chromosomal Damage and Sperm-Head Abnormalities in Mice"; (J.R. Meier, R.J. Bull, J.A. Stober, M.C. Cimino; Toxicology and Microbiology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH, Department of Molecular Toxicology, Litton Bionetics, Kensington, MD; Environmental Mutagenesis 7: 201-211 (1985)); In the 1st phase of the study, five CD-1 mice/sex/group were dosed orally by gavage with chlorine dioxide or sodium chlorite daily for 5 days (reported dose levels: ClO₂, 0, 3.2, 8.0, 16 mg/kg/day, NaClO₂, 0, 8, 20, 40 mg/kg/day) Six hours post-final dose the animals were euthanized and the bone marrow recovered from the tibia. The percentage of polychromatic erythrocytes (PCE) was determined. Triethylenemelamine (TEM), 0.5 mg/kg/day, was administered ip in two treatments on the last two days of the dosing regimen as the positive control. In the 2nd phase a bone marrow chromosomal aberration assay was performed in which 4 animals/sex/group were dosed in the same manner as the micronucleus assay above and in an acute dosing regimen. In the latter regimen, 4 animals/sex/group/time point were euthanized at 6, 24 and 48 hours post-dose. A positive control group was dosed ip with 1 mg/kg of TEM and euthanized 24 hours post-dose. Each animal was dosed ip with 4.0 mg/kg of colchicine 3 hours prior to being sacrificed. Bone marrow was procured from the tibia and processed. A mitotic index was assessed based on at least 500 cells. Fifty metaphase spreads from each animal were scored for structural and numerical aberrations. In the 3rd phase 30 male B6C3F1 mice/group were dosed in the same manner as in the micronucleus test. At 1, 3 and 5 weeks post-final dose, 10 animals/group/time point were euthanized. A positive control group of 30 animals was treated ip with 200 mg/kg/day of ethyl methanesulfonate for 5 days. Ten animals/time point were euthanized at 1, 3 and 5 weeks post-final dose. The caudate epididymis was dissected and sperm were recovered and processed. One thousand sperm heads/animal were assessed for abnormalities. In the micronucleus assay, there was no increase in the percentage of micronucleated PCE after treatment with chlorine dioxide or sodium chlorite. The positive control was reported to be functional. In the bone marrow chromosomal aberration assay there was no treatment related increase in the incidence of structural and/or numerical aberrations under either a single or multi-dose regimen for either chlorine dioxide or sodium chlorite. The positive control was reported to be functional. In the assessment of sperm heads, treatment with chlorine dioxide nor sodium chlorite did not result in an increase in the percentage of sperm with abnormalities. There was no reference in the text as to whether the positive control was functional or not. **No adverse effect indicated.**

Summary report. [REDACTED], 1/31/17)

DNA damage or miscellaneous effects

Chlorine Dioxide

50037-018 130828 Rundell, J. O. "Evaluation of chlorine dioxide in the in vitro transformation of Balb/3T3 cells assay," Litton Bionetics, Inc., Kensington, MD, Oct., 1986. LBI Project No. 20992. This procedure exposed cells of a clone which usually exists in monolayer conformation, to evaluate frequency of transformation of some cells to phenotypes which form foci consisting of cells of variable shapes which often stain darkly. Chlorine dioxide liquid (test article was not further characterized) was tested at 0 (water), 1, 2, 3, 5, or 6 µg/ml starting concentration in at least 18 flasks per group. Tightly closed flasks were incubated for 72 hours with test article before cells were washed and then maintained for 4 weeks for expression of colonies of transformed cells. Chlorine dioxide concentrations spanned an effective exposure range based on cytotoxicity. The positive control (2.5 µg/ml of 3-MCA) was functional. There

was no indication of a treatment response to chlorine dioxide. This study is not acceptable as presented, and does not appear to be upgradeable, due to lack of characterization of the test article and of details of scoring of foci. Several additional concerns are also noted in this worksheet. [REDACTED], 1/24/01.

**50288-058 115602 Ivett, J. L., "Mutagenicity evaluation of chlorine dioxide in the sister chromatid exchange assay in vivo in mouse bone marrow," Litton Bionetics, Inc., July 1984. LBI Project No. 22204. Five ICR male mice/group were dosed with 0, 9, 21, 28, or 39 mg/kg chlorine dioxide (aqueous solution) intraperitoneally just after implantation with 50 mg BrdUrd. The positive control was 10 mg/kg cyclophosphamide. Colchicine was administered by subcutaneous injection 2 hr before sacrifice. Mice were killed 26 hr after treatment with test article. Marrow cells from tibiae were collected and processed for sister chromatid exchange evaluation. No increases in sister chromatid exchange occurred with chlorine dioxide. Cyclophosphamide was an effective positive control. Study was initially classified as unacceptable but upgradeable (needing justification for use of one sex only). A response letter from John DiLoreto on 8/21/01 noted that DPR Document No. 50288-017, Record No. 043602 had found males to be more sensitive than females to chlorite [the difference is negligible: oral LD50 values were 255 mg/kg (M) and 270 mg/kg (F)]. Necropsy observations were comparable between sexes in that study. The author of the response letter noted that males tend to be more sensitive than females to SCE responses. DPR has no database to confirm or refute this statement. Since test article is a simple inorganic oxidant, differential routes of metabolism between sexes would appear unlikely. The study can be upgraded to acceptable. No adverse effect. [REDACTED], 12/12/00 and 9/10/01.

Sodium Chlorite and Chlorine Dioxide

50288-0266; 296400: "Micronucleus Tests in Mice on 39 Food Additives and Eight Miscellaneous Chemicals"; (M. Hayashi, M. Kishi, T. Sofuni, M. Ishidate, Jr.; Division of Mutagenesis, Biological Safety Research Center, National Institute of Hygienic Sciences, Setagaya-ku, Tokyo, Japan, and Kanagawa Prefectural Public Health Laboratory, Asahi-ku, Yokohama-shi, Kanagawa, Japan; Food and Chemical Toxicology 26: 487-500 (1988)); The genotoxicity of chlorine dioxide and sodium chlorite was assessed in the *in vivo* mouse micronucleus test. Three studies were performed. Six male ddY mice/group were dosed in each study. In the first study, the mice received one intraperitoneal injection of 0 (vehicle: saline), 3.2, 6.3, 12.5 or 25 mg/kg of **chlorine dioxide** (4%). At 18 hours post-dose, the animals were euthanized and femoral bone marrow was recovered. One thousand polychromatic erythrocytes (PCE) per mouse were scored for the presence of micronuclei. In the 2nd study, the mice received one intraperitoneal injection of 0 (vehicle: water), 7.5, 15, 30, or 60 mg/kg of **sodium chlorite** and were euthanized at 18 hours post-dose. The PCEs were evaluated in the same manner. In the 3rd study, the mice were orally treated by gavage with 0 (vehicle: water), 37.5, 75, 150 or 300 mg/kg of sodium chlorite and were euthanized at 18 hours post-dose. The PCEs were evaluated in the same manner as the other two studies. An auxiliary study was also performed in which 6 mice were treated by intraperitoneal injection with 15 mg/kg/day once per day for 4 days. They were euthanized at 24 hours post-final dose, the bone marrow was processed and the PCEs were examined. In the first two studies in which chlorine dioxide and sodium chlorite were dosed intraperitoneally, the percentage of micronucleated PCEs (MNPCE) increased in a treatment-related manner (except at the highest treatment levels). In the 3rd study in which the animals were treated orally with sodium chlorite, there was no treatment-related increase in the percentage of MNPCEs. Likewise, when the animals were dosed ip multiple times, there was no evidence of a positive treatment effect. **Possible adverse effect:** increased treatment-related percentage of MNPCE; the positive controls were functional. **Summary report.** ([REDACTED] 1/27/17)

REPRODUCTIVE TOXICITY, RAT

Sodium Chlorite

50288-0266; 296392; "Sodium Chlorite Administration in Long-Evans Rats: Reproductive and Endocrine Effects"; (B.D. Carlton, D.L. Habash, A.H. Basaran, E.L. George, M.K. Smith; Battelle Columbus Division, Columbus, OH and HERL, USEPA, Cincinnati, OH; Environmental Research 42: 238-245 (1987)); In the 1st experiment, 24 adult female Long Evans rats/group received 0, 1, 10 or 100 ppm of sodium chlorite in the drinking water for 14 days prior to mating and during the mating, gestation, and lactation periods (approximate treatment levels calculated by reviewer: 0, 0.16, 1.56, 15.6 mg/kg/day)¹. In this study 12 adult males/group received the same treatment for 56 days prior to mating and during the mating period (calculated treatment levels: 0, 0.15, 1.45, 14.5 mg/kg/day)¹. The dams were euthanized after the weaning of the pups. Hematology parameters were assessed and the reproductive tissues were dissected and preserved for histological examination. The males were euthanized after the mating period. Hematology parameters were assessed and the reproductive tissues dissected. All of the tissues except the right cauda epididymis were fixed. The sperm were recovered and the motility was assessed. On day 21 of lactation, blood was collected from each of 10 pups/sex/group and hematological parameter and thyroxine (T4) and triiodothyronine (T3) levels were determined. Twenty pups/sex/group were selected on lactation day 21 and maintained on the treatment through post-natal day 40. The serum levels of the T4 and T3 were measured on post-natal day 40. In the 2nd experiment, 12 males/group received 0, 100 or 500 ppm of sodium chlorite in the drinking water for 72 to 76 days (calculated treatment levels: 0, 14.5, 52.2 mg/kg/day)¹. At necropsy blood was drawn and hematology parameters and thyroid hormone levels assessed. Sperm were recovered and counted and their motility and morphology were examined. In a 3rd experiment 12 males/group received 0, 10 or 100 ppm of sodium chlorite in the drinking water in the same manner as the animals were treated in the 2nd experiment (calculated treatment levels: 0, 1.45, 14.5 mg/kg/day)¹. The same parameters were evaluated. In the 1st experiment there was no treatment-related effect upon the adult animals. There was no treatment-related effect upon reproductive and development parameters. Hematologic parameters were not affected by the treatment. The necropsy did not reveal any treatment-related lesions in the reproductive tissue. Absolute and relative reproductive organ weights were not affected by the treatment. In the 2nd and 3rd experiments, there was no apparent treatment-related effect upon the sperm count and the percent of the sperm which were motile at a treatment level up to 500 ppm. However, in the assessment of progressive motility, the velocity of the sperm was reduced in a treatment-related manner with significant differences noted at the 100 and 500 ppm treatment levels in comparison to the control group. There also was a significant increase in the percentage of abnormal sperm at the 100 and 500 ppm treatment levels. In the thyroid hormone evaluation both the T4 and T3 serum concentrations were reduced for the pups at 21 and 40 days of age. This effect was not apparent for the adult animals. However, there was no histological examination of the thyroids from these pups to further assess the potential effects of these lower hormonal levels. **No adverse effect indicated. Parental NOEL:** (M) 10 ppm in the drinking water ((M) 1.45 mg/kg/day) (based upon the effect on sperm morphology and progressive motility at the 100 ppm treatment level), (F) 15.6 mg/kg/day) (based upon the lack of a treatment-related effect on the dams in the 100 ppm treatment group); **Reproductive NOEL:** 100 ppm (15.6 mg/kg/day) (based upon the lack of a treatment-related effect in the 100 ppm treatment group); **Developmental NOEL:** 100 ppm (15.6 mg/kg/day) (based upon the lack of a treatment-related effect in the 100 ppm treatment group). **Summary report.** (██████, 1/19/17)

50288-0266; 296397; "Two-generation Reproduction and Developmental Neurotoxicity Study with Sodium Chlorite in the Rat"; (M.W. Gill, M.S. Swanson, S.R. Murphy, G.P. Bailey; Toxicology/Regulatory Services, Inc., Charlottesville, VA, Vulcan Chemicals, Birmingham, AL,

Elf Atochem North America, Inc., Philadelphia, PA, Quintiles England Ltd., Ledbury, Herefordshire, HR8 1LH, UK; J. Applied Toxicology 20: 291-303 (2000)); In the F0 generation, thirty Sprague-Dawley rats/sex/group received 0, 35, 70 or 300 ppm of sodium chlorite (purity: 81.4%) for 10 weeks during the pre-mating period, mating, gestation and lactation periods. Twenty five offspring/sex/group were selected for the F1 generation at the time of weaning and treated for 10 weeks of pre-mating, mating, gestation and lactation. Due to the reduced number of litters produced in the mating of the F1 generation, a second mating was performed (F2b generation). The reported treatment levels were (M) 0, 4, 8, 30 mg/kg/day, (F) 0, 5, 10, 39 mg/kg/day. Pups in the F1 generation were selected for the developmental neurotoxicity evaluation. Twenty pups/sex/group in the F1 generation were evaluated in the Functional Observational Battery (FOB) on post-natal days (PND) 21 and PND 60. The FOB included open field and handling assessments and responses to various stimuli. Motor activity was measured for 10 animals/sex/group in the F1 generation on PND 17, 21 and 60. A swim maze learning assessment was performed with 10 F1 generation/sex/group on PND 22 and 60. The acoustic startle response was assessed with 20 animals/sex/group in the F2b generation. The neuropathological examination of 10 animals/sex/group/time point in the F1 generation were euthanized on PND 11 and 60. The pups were sacrificed by intracardiac injection of sodium pentobarbitone. The brain of each animal was weighed and the brain and spinal cord were fixed, processed and sectioned for microscopic examination. The young adult animals were perfused whole body and fixed while anesthetized. Nervous tissues from 6 animals/sex/group in the control and 300 ppm groups were processed and examined microscopically. The parental animals in the two generations did not demonstrate any treatment-related clinical signs. The mean body weights and food consumption of the F0 generation were not affected by the treatment during the pre-mating periods. The mean water consumption of both sexes in the 70 and 300 ppm of this generation was less than that of the control group. For the F1 parental generation, the mean body weight and food consumption of the males in the 300 ppm group were less than that of the control group. The mean water consumption of the males in the 35 ppm group and above and the females in the 300 ppm in this generation was less than the control group's water consumption. The mean body weights of the maternal animals in the 300 ppm group at various times during the lactation periods of both generations were less than the control group values ($p < 0.05$, 0.01 , or 0.001). For the fertility parameters there were no treatment-related effects on the estrous cycle, sperm motility and morphology or mating, fertility and gestational indices of both generations. Histological examination of the reproductive tissues did not reveal any treatment-related lesions. Litter sizes, pup weights and pup survival were not affected by the treatment. Among the developmental indices which were evaluated, the time to eye opening seemed to be affected in the F2a offspring with a reduced percentage of pups with open eyes on PND 15 in comparison to that of the control group. Otherwise, there was no apparent effect on this parameter for the F1 and F2b offspring. The mean body weights of both sexes of pups in the 300 ppm group of F1, F2a and F2b generations were less than the control weights during the lactation period. For the F1 generation, the time to preputial separation of the 70 and 300 ppm male pups and time to vaginal opening of the 300 ppm female pups were delayed in comparison to the control group values. These effects were not evident in the F2 generation. The evaluation of hematological parameters of the F1 offspring on PND 25 and as 13 week-old young adults revealed significant reduction in the red blood cell counts (300 ppm females, PND 25 and young adults), reduced hemoglobin concentration (300 ppm males and females, PND 25 and young adults; 35 and 70 ppm females, PND 25), reduced hematocrit (300 ppm males and females, PND 25 and young adults; 35 and 70 ppm females, PND 25 and young adults; 35 and 70 ppm males, young adults), reduced white blood cell count (300 ppm, males and females, PND 25; 70 ppm females, PND 25), and an increased level of methemoglobinemia (300 ppm, males and females, PND 25). The thyroxine and triiodothyronine levels in the serum was not affected by the treatment at either time point. In the developmental

neurotoxic evaluation the FOB did not result in any treatment-related effects on nerve function at 21 or 60 days post-natal. Motor activity assessment did not reveal any treatment-related effects at 17, 21 or 60 days post-natal. Learning was not affected by the treatment as evaluated by the swim maze at 25 and 60 days post-natal. Histopathological examination of the nervous tissues from 11 and 60 day old F1 generation pups did not reveal treatment-related lesions. **No adverse effect indicated. Reproductive Endpoints: Parental NOEL:** (M/F) <35 ppm ((M) <4 mg/kg/day, (F) <5 mg/kg/day) (based upon the treatment-related effect on certain hematological parameters), **Reproductive NOEL:** 300 ppm ((M) 30 mg/kg/day, (F) 39 mg/kg/day) (based upon the lack of treatment-related reproductive effects on the parents in both generations of the 300 ppm group); **Developmental NOEL:** (M/F) 70 ppm (10 mg/kg/day) (based upon the lower mean body weights of the pups in the 300 ppm of both generations); **Developmental Neurotoxicity Endpoints: Maternal NOEL:** <35 ppm (<5 mg/kg/day) (based upon the treatment-related effect on certain hematological parameters); **Developmental Neurotoxicity NOEL:** 300 ppm (39 mg/kg/day) (based upon the lack of effect on the neurologically-related parameters in the development of the offspring in the 300 ppm treatment group of the F1 and F2 generations). **Summary report.** (██████████, 1/25/17).

Chlorine Dioxide

50288-0266; 296393; "Reproductive Effects in Long-Evans Rats to Chlorine Dioxide"; (B.D. Carlton, A.H. Basaran, L.E. Mezza, E.L. George, M.K. Smith; Battelle Columbus Division, Columbus, OH and HERL, USEPA, Cincinnati, OH; Environmental Research 56: 170-177 (1991)); Twelve male Long-Evans rats/group were dosed orally by gavage with 0 (deionized water), 2.5, 5.0 or 10 mg/kg of ClO₂ for 56 days prior to mating and during mating. Twenty four female Long-Evans rats/group were dosed in the same manner for 14 days prior to mating and during mating, gestation and lactation. The males were euthanized after mating and grossly examined for lesions. Serum thyroxine (T4) and triiodothyronine (T3) concentrations were determined. The reproductive organs were processed and examined histologically. Sperm counts, morphology, and motility were assessed. Litters were evaluated for viability, litter size, day of eye opening, body weight gain and gross external abnormalities. Pup weights were recorded on postnatal days 1, 4, 12 and 21. For those retained for hormonal analysis, weights were recorded on postnatal days 28, 34 and 40. Ten pups/sex/group were euthanized on lactation day 21. Each pup was necropsied and the reproductive organ weights were recorded. Thyroid hormone levels were determined in male pups on postnatal days 17, 21 and 40. The dams were euthanized on lactation day 21 and necropsied. The reproductive organs were processed and examined histologically. Thyroidal hormone levels were determined. There was no treatment-related effect on the parental animals. The testes and epididymides of the adult males were not affected by the treatment. The sperm count, morphology and motility were not affected as well. There was no treatment-related effect on the reproductive parameters. In the development of the pups, the mean vaginal weight of the 21-day old female pups in the 10 mg/kg treatment group was less than that of the control group (p<0.05). There was no apparent treatment-related effect on T4 and T3 levels of the adult animals and male pups at the various time points of analysis. **Summary report.** (██████████, 2/13/17)

Sodium Chlorite and Chlorine Dioxide

50288-0266; 296410; "Effect of Chlorine Dioxide and Its Metabolites in Drinking Water on Fetal Development in Rats"; (D.H. Suh, M.S. Abdel-Rahman, R.J. Bull; Toxicology Laboratory, Department of Pharmacology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ; Journal of Applied Toxicology 3: 75-79 (1983)); Six to nine mated female Sprague-Dawley rats/group received 0, 1, 10, or 100 mg/l of chlorine dioxide or 1 or 10 mg/l of sodium chlorite in the drinking water for a 2 ½ month premating period, during mating

and through gestation day 20 (approximate treatment levels: ClO₂, 0, 0.15, 1.5, 15 mg/kg/day, ClO₂⁻, 0.15, 1.5 mg/kg/day, calculated by reviewer). The dams were euthanized and the development of the fetuses were evaluated for treatment-related effects. There was no apparent treatment-related effect on the dams. The mean maternal body weight gain during pregnancy was not affected. The number of implants and live fetuses per dam were lower for the ClO₂100 mg/l group ((p<0.01). Hydronephrosis was noted in 2 of eight litters in the ClO₂100 mg/l group and in 2 of 9 litters of the ClO₂⁻ 10 mg/l group. This malformation was not evident in the control group. Three of 56 fetuses in the ClO₂⁻ 10 mg/l group suffered missing vertebrae and another 7 fetuses in this group were missing sternabrae (it was not apparent as to how many litters were affected). Two of 35 fetuses in the control group exhibited this latter malformation. An anomaly of increased crown-rump length was noted for the ClO₂⁻ 10 mg/l group (p<0.01).

Possible adverse effect: incidence of fetal hydronephrosis and skeletal malformations.

Maternal NOEL: ClO₂, 15 mg/kg/day (based on the lack of treatment-related effects on the dams in the 100 mg/l treatment group), ClO₂⁻, 1.5 mg/kg/day (based upon the lack of treatment-related effects on the dams in the 10 mg/l treatment group); **Developmental NOEL:** ClO₂, 1.5 mg/kg/day (based upon the incidence of fetal hydronephrosis in the 100 mg/l treatment group), ClO₂⁻, 0.15 mg/kg/day (based upon the incidence of fetal hydronephrosis and skeletal malformations in the 10 mg/l treatment group). **Summary report.** (██████████, 2/9/17)

Mouse Reproduction

Sodium Chlorite

50288-0266; 296406; "Effects of Chlorite Exposure on Conception Rate and Litters of A/J Strain Mice"; (G.S. Moore, E.J. Calabrese, D.A. Leonard; Division of Public Health, University of Massachusetts, Amherst, MA; Bulletin of Environmental Contamination and Toxicology 25: 689-696 (1980)); Female A/J mice received 0 (distilled water) or 100 ppm of sodium chlorite in the drinking water from the beginning of gestation through day 28 post-natal (weaning). The treatment levels of sodium chlorite were approximately 20 mg/kg/day during the gestation period and 60 mg/kg/day during the lactation period (calculated by the reviewer). The reported conception rates were 56 and 39% for the control and 100 ppm groups, respectively. The number of live pups at birth per litter was lower in the treatment group, 5.4 vs. 5.0 (NS). The average pup weight at birth was less for the treatment group, 1.27 vs. 1.17 g (NS). The number of dead pups per litter was increased at birth for the treatment group, 1.5 vs. 2.0 (NS). The number of pups/litter which died during the lactation period was greater for the treatment group (1.3 vs. 1.9 (NS). The mean weight of the pups at weaning was less for the treatment group (12.5 vs. 10.7 g (p<0.05). Overall the survival and development of the pups was not affected by the treatment. However, the report did not provide any treatment-related data for the dams.

Summary report. (██████████, 1/31/17)

DEVELOPMENTAL TOXICITY

Rat

Sodium Chlorite

50288-0265; 296195; "Assessment of Maternal Toxicity, Embryotoxicity and Teratogenic Potential of Sodium Chlorite in Sprague-Dawley Rats"; (D. Couri, C.H. Miller, Jr., R.J. Bull, J.M. Delphia, E.M. Ammar; Department of Pharmacology and Department of Anatomy, College of Medicine, Ohio State University, Columbus, Ohio; Environmental Health Perspectives 46: 25-29 (1982)); Up to 13 female pregnant Sprague-Dawley rats were treated with sodium chlorite via intraperitoneal injection (cohort 1), oral gavage (cohort 2) or in the drinking water (cohort 3) between days 8 and 15 of gestation. In the first cohort, the dams were injected with 10, 20 or 50 mg/kg/day of the test material. The second cohort was dosed with 200 mg/kg/day of the test material. The third cohort drank water with 0.1, 0.5 or 2% of the test material (0.1%: 34, 0.5%:

163, 2%: 212 mg/rat/day which translated to approximately 0.1%: 90 to 100, 0.5%: 520 to 540, 2%: 750 to 770 mg/kg/day (calculated by reviewer)). Some of the dams in each group were permitted to deliver and the remainder were euthanized prior to delivery on gestation day 22. Offspring of those litters, which were delivered, were maintained up to postnatal day 29. All of the dams in the 50 mg/kg group (cohort 1) and the 200 mg/kg (cohort 2) died within 2 days after the initiation of dosing. Fifty percent of the dams in the 20 mg/kg group (cohort 1) died as well. The dams in the 10 mg/kg/day group of the first cohort and the 0.5 and 2.0% sodium chlorite in the drinking water treatment groups of the third cohort lost weight during the treatment period. Only the dams in the 0.1% sodium chlorite in the drinking water treatment group of the third cohort did not demonstrate any treatment-related effects. For the neonates, the mean crown-rump length and the mean body weight of the offspring for all of the treatment groups with live litters were less than the control group values ($p < 0.05$ and NS, respectively). The fetal data reported for the litters derived from *cesarean* section was compromised because no control data was available. There was no apparent effect on the growth of the pups up to post-natal day 29. **Possible adverse effect:** retarded development (lower mean crown-rump length and lower mean neonate weights); **Maternal NOEL:** 1% sodium chlorite in the drinking water (90 to 100 mg/kg/day) (based upon the lower mean body weights of the dams in the 0.5% sodium chlorite in drinking water group); **Developmental NOEL:** <1% sodium chlorite in the drinking water (<90 to 100 mg/kg/day) (based upon retarded development (lower mean crown-rump length and mean neonate weights) of the offspring in the 0.1% sodium chlorite in the drinking water. **Summary Report.** (██████████, 1/4/17)

Chlorine Dioxide

50288-0266; 296411; "Effects of Chlorine Dioxide on the Developing Rat Brain"; (G.P. Toth, R.E. Long, T.S. Mills, M.K. Smith; Reproductive and Developmental Biochemistry Branch, Developmental Toxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH, Pathology Associates, Inc., West Chester, OH, Computer Sciences Corporation, Cincinnati, OH, Reproductive and Developmental Biochemistry Branch, Developmental Toxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH; *Journal of Toxicology and Environmental Health* 31: 29-44 (1990)); Long Evans pups (8 pups per litter, 4 males and 4 females) were dosed orally by gavage with 0 (distilled water) or 14 mg/kg/day of chlorine dioxide from post-natal day (PND) 1 through PND 20. A positive control group of pups were dosed in the same manner with 20 mg/kg/day of propylthiouracil (PTU) for the same time period. On PND 11, 21 and 35, a cohort of treatment group was euthanized. The cerebellum, olfactory bulbs, forebrain and liver were dissected. Blood was recovered and the thyroxine (T4), triiodothyronine (T3), and T3 uptake were determined by means of a radioimmunoassay at each of the time points. Hepatic α -glycerophosphate dehydrogenase (α -GPD) activity was assayed as a measure for hypothyroidism. Protein synthesis in the dissected brain regions was assayed by intraperitoneal injection of L-[^{14}C -(U)]-leucine 30 minutes prior to sacrifice. Protein synthesis was expressed as (^{14}C dpm in protein/mg protein/trichloroacetic acid soluble ^{14}C dpm/g of tissue. DNA content was assayed in these brain regions as well. On PND 35, the forebrains of female rat pups were sectioned in regions 2 (parietal cortex), 4 (frontal cortex), and 18 (occipital cortex) and cerebral cortical thickness, dendritic spine counts and dendritic branch counts were determined. The mean body weight of the chlorine dioxide-treated pups was less than that of the control group over the study period ($p < 0.05$). In the regional brain weight determinations, the forebrain weight of the chlorine dioxide-treated pups was less than that of the control group on PND 21 and 35 ($p < 0.01$). The cerebellum and olfactory bulb weights were apparently less affected. The lower forebrain weight correlated with a lower protein content at those two time points for the treated animals ($p < 0.05$ or 0.001). There was no apparent treatment-related effect on the DNA content in these portions of the brain. Incorporation of protein into the brain over a 30-minute interval

was not affected by the treatment. In the characterization of the brain morphology, the dendritic spine count was reduced in the chlorine dioxide-treated group in comparison to the control group ($p < 0.01$). The serum T4 and T3 levels were apparently not affected by the treatment. These results correlated with the lack of a treatment-related effect on α -GPD activity. **Possible adverse effect:** reduced protein content in the forebrain and reduced dendritic spine counts in the occipital cortex. The PTU-treated group suffered lower a mean body weight over the treatment period and reduced regional brain weights, brain protein and DNA content, lower protein synthesis in the brain, reduced serum T4 and T3 levels, and lower hepatic α -GPD activity. **Summary report.** [REDACTED], 2/10/17)

Sodium Chlorite and Chlorine Dioxide

50288-0266; 296409; "Teratologic Evaluation of Alcide Liquid in Rats and Mice. I"; (G.A. Skowronski, M.S. Abdel-Rahman, S.E. Gerges, K.M. Klein; University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Pharmacology Department, Toxicology Laboratory, Newark, NJ; Journal of Applied Toxicology 5: 97-103 (1985)); Alcide liquid is a germicidal agent which is comprised of two parts. Part A consists of sodium chlorite and Part B is lactic acid. When the two components are mixed, chlorine dioxide is produced. Twenty mated female Sprague-Dawley rats and female Swiss Webster mice were dosed orally by gavage with 1.0 ml (rats) or 0.1 ml (mice) of (Part A:Part B:deionized water (1:1:2) (Group 1), (Part A:Part B:deionized water (1:1:4) (Group 2), Placebo, (deionized water) (Group 3), or positive control (rats: 250 mg/kg/day of sodium salicylate) (mice: 100 mg/kg/day of cortisone) (Group 4) from day 6 through day 15 of gestation (treatment levels for the study animals could not be calculated as the sodium chlorite concentration was not reported). The rats and mice were euthanized on gestation days 20 and 18, respectively. The fetuses were assessed as to the presence of any developmental abnormalities. The dams of either species were not affected by the treatment. There was no effect on their mean body weight gains. The mean fetal weights and crown-rump lengths of either species were not affected by the treatment. There was no effect on the development of the rat fetuses. In the mice fetuses there was an incidence of gastrointestinal malformations (gastromegaly, gastric atresia, and duodenum jejunum agenesis). **Possible adverse effect:** incidence of gastrointestinal malformations (gastromegaly, gastric atresia, and duodenum jejunum agenesis) in the mouse fetus. Treatment level of sodium chlorite could not be elucidated. The positive controls were functional for both species. **Summary report.** [REDACTED], 2/9/17).

50288-0266; 296395; "Effects of Alcide Gel on Fetal Development in Rats and Mice. II"; (S.E. Gerges, M.S. Abdel-Rahman, G.A. Skowronski, S. Von Hagen; University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Pharmacology Department Toxicology Laboratory, Newark, NJ; Journal of Applied Toxicology 5: 104-109 (1985)); Alcide gel is a germicidal agent which consists of two parts. Part A consists of sodium chlorite and Part B is lactic acid. When the two components are mixed, chlorine dioxide is produced. When Part A (sodium chlorite) preparation was mixed with Part B (lactic acid), a concentration of 0.4% sodium chlorite resulted in the evolution of 0.025% solution of chlorine dioxide initially. The concentrations of sodium chlorite and chlorine dioxide gradually diminished to 0.28% and 0.02%, respectively, at 60 minutes post-preparation (see vol. no. 50288-0266, rec. no. 296200). The skin of twenty mated female Sprague-Dawley rats/group and twenty mated female Swiss Webster mice/group was exposed to 2 g/kg of Alcide gel (Part A:Part B (1:1) (w/w)) (Group 1), 1 g/kg of Alcide gel (Part A:Part B (1:1) (w/w)) (Group 2), Placebo, 2 g/kg (Part A:Part B (1:1) (w/w)) (active ingredients were not included in the preparations) (Group 3), or 0 (Group 4) (untreated control) from gestation day 6 through gestation day 15 (daily exposure duration was not apparently limited). At least 16 dams/group of both species were pregnant and produced litters for examination. No deaths resulted from the treatment. There were no maternal signs of

toxicity. The development of the fetuses for either species was not affected by the treatment. **No adverse effect was indicated. Summary report.** (██████████, 1/24/17)

Mouse

Sodium Chlorite

50288-0265; 296189; "Toxicological Effects of Chlorite in the Mouse"; (G.S. Moore, E.J. Calabrese; Division of Environmental Health, School of Public Health, University of Massachusetts, Amherst MA; Environmental Health Perspectives 46: 31-37 (1982)); This study was performed in 3 phases. In the 1st phase, approximately 15 A/J and 15 C57L/J mice/group (sex not identified) received 0, 1.0, 10.0 or 100 ppm of sodium chlorite in the drinking water for 30 days (approximately 0.27, 2.7 and 27 mg/kg/day, calculated by reviewer). At the conclusion of the treatment period, blood was collected and a hematological analysis was performed. This analysis included a red blood cell count, hematocrit, and hemoglobin concentration, a white blood cell count and a reticulocyte count. Glucose-6-phosphate dehydrogenase (G6PD) activity and glutathione concentration were determined. Osmotic fragility of the red blood cells was measured. In the 2nd phase mated A/J female mice received 0 or 100 ppm of sodium chlorite in the drinking water from the beginning of gestation through day 28 of lactation. The development of the pups during the 28-day lactation period was assessed. In the 3rd phase, 11 or 12 mice/group/treatment interval (sex and strain were not specified) received 0, 4.0, 20.0 or 100 ppm of sodium chlorite in the drinking water for 30, 90 or 180 days. Upon completion of their respective treatment periods, each animal was euthanized and its kidneys dissected and processed for histological examination. This examination included both light and electron microscopic evaluation. In phase one the G6PD activity and the mean corpuscular volume were increased for both strains in the 100 ppm treatment group ($p < 0.05$). Otherwise, no other parameters were apparently affected by the treatment. In phase two, the mean pup weaning weight and the birth to weaning weight gain of the pups in the treatment group were less than the control values ($p < 0.05$). In phase 3 there was no treatment-related effect on the kidney after 180 days of treatment. **Summary report.** (██████████, 2/14/17)

Rabbit

Sodium Chlorite

**50288-0058 115606 Irvine, L. F. H., "Sodium chlorite: rabbit teratology study (drinking water administration)" Toxicol Laboratories Limited, Herfordshire, 9/21/90. Laboratory Project ID: CMA/3/R. Sixteen or 17 NZW does/group were dosed in drinking water with 0, 200, 600, or 1200 ppm sodium chlorite (80.58% purity, dosing levels adjusted for purity) on gestation days 7-19 in a standard developmental toxicity study. Maternal NOEL = 200 ppm (13.0 mg/kg/day), based on dose-related decrements in water and food consumption. Maternal body weight gain was significantly reduced at 1200 ppm, primarily during the first few days of treatment. Developmental NOEL = 200 ppm (vertebral malformation incidences of 0, 1, 3, and 0 in controls through increasing treatment groups, respectively). There were small (not statistically significant) decrements in fetal body weights at 600 and 1200 ppm, considered to be minor treatment effects. Study is acceptable. No adverse effects are indicated (the equivocal increase in vertebral malformations at 600 ppm lacked dose-response and was in the presence of marked maternal treatment response). (██████████, 1/5/01).

50288-065 130827 Irvine, L. F. H., "Sodium chlorite: rabbit teratology dose ranging study (drinking water administration)." Project ID CMA/2/R, 9/21/90. This was the pilot for study 50288-058 115606, above. Five does/group were dosed at 0, 200, 800, and 1200 on gestation days 7-19. Parameters included hematology at term for does. Fetuses were evaluated for reproduction indices and for external abnormalities. Female body weight, food consumption,

and water consumption were sharply reduced at 800-1200 ppm. Hematology parameters appeared very modestly reduced at 1200 ppm only. There were no apparent treatment effects on fetuses. This study justifies selection of dosages for the primary study. [REDACTED], 1/5/01 (no worksheet).

Sodium Chlorite and Chlorine Dioxide

50288-0266; 296390; "Teratologic Studies on Alcide Allay Gel in Rabbits"; (M.S. Abdel-Rahman, G.A. Skowronski, S.E. Gerges, S. Von Hagen, R.M. Turkall; Toxicology Laboratory, Pharmacology Department, New Jersey Medical School and Clinical Laboratory Sciences Department, School of Health and Related Professions, University of Medicine and Dentistry of New Jersey, Newark, NJ; Journal of Applied Toxicology 7: 161-165 (1987)); Allay gel is a germicidal agent which consists of two parts. Part A consists of sodium chlorite and Part B is lactic acid. When the two components are mixed, chlorine dioxide is produced. Four groups of 12 pregnant female New Zealand White rabbits comprised the untreated control or were dosed with 2 g/kg of Part A and Part B (1:1) (high dose), 2 g/kg of Part A (NaClO₂ at ¼ the concentration in the high dose) and Part B (1:1) (low dose), or 2 g/kg of Part A and Part B (1:1) (placebo in which no active ingredients were included). The skin of each animal was treated daily in the appropriate manner from gestation day 6 through 18 (note: the treatment site of the dosed animal was wrapped for 6 hours each day). On day 29 of gestation, each of the does were euthanized and their fetuses were examined for abnormalities. Although dermal exposure to sodium chlorite and chlorine dioxide was not assessed in this study, in another study by this laboratory (rec. no. 296200) in which this product was used as the test material, the initial concentrations of the two components were 0.4 and 0.025%, respectively, at the time of mixing. The does in all of the treatment groups did not demonstrate any signs of systemic toxicity. The treatment sites of the high dose groups demonstrated moderate to severe dermal irritation that peaked about day 11 of gestation and ultimately had resolved by day 18. Fetal development of the placebo group and the two treatment groups was apparently affected by the treatment procedure as the mean fetal weights and crown-rump lengths of these groups were less than that of the untreated control group. There was an increased incidence in cranial anomalies (acephalus, cephalocele, hydrocephalus) in the high dose treatment group (untreated group: 2/87, placebo: 1/99, low dose: 0/93, high dose: 7/96). **Possible adverse effect:** increased incidence of cranial anomalies. The per litter incidence could not be ascertained. Authors of the article did not deem this incidence rate to be of toxicological significance. **Summary report.** [REDACTED], 1/18/17)

NEUROTOXICITY

Acute neurotoxicity, rat

No study on file with DPR nor required at this time.

90-day neurotoxicity, rat

No study on file with DPR nor required at this time.

Developmental neurotoxicity, rat

See Record No. 296397 under Rat Reproduction Toxicity.

IMMUNOTOXICITY

Sodium Chlorite

50288-0268; 297615; "Evaluation of the Immunomodulatory Effects of the Disinfectant By-Product Sodium Chlorite in Female B6C3F1 Mice: A Drinking Water Study"; (N.A. Karrow, T.L. Guo, J.A. McCay, G.W. Johnson, R.D. Brown, D.L. Musgrove, D.R. Germolec, R.W. Luebke,

K.L. White; Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, Laboratory of Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, NC, Immunotoxicology Branch, Experimental Toxicology Division, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC; Drug and Chemical Toxicology 24, 239-258 (2001)); Eight female B6C3F1 mice/group received 0, 0.1, 1, 5, 15, or 30 mg/l of sodium chlorite in the drinking water for 28 days (0, 0.02, 0.17, 0.9, 2.6, 5.1 mg/kg/day, calculated by the reviewer). On day 25, five days before necropsy on day 29, each animal received an iv injection of 7.5×10^7 sheep red blood cells (sRBC). One of the positive control groups of 8 females were dosed by intraperitoneal injection with 50 mg/kg/day of cyclophosphamide (CPS) on study days 25 through day 28 as the positive control group. The other positive control group of 8 animals were dosed intravenously with anti-asialo GM1 (AAGM1) rabbit antibody on day 28 for the basal and augmented natural killer activity assessment (see below). The animals were euthanized on study day 29. The thymus, lungs, liver, spleen, and kidneys were weighed. Prior to necropsy, blood was collected by retro-orbital bleeding and hematological parameters assessed. Spleen T cells, B cells, NK cells and macrophages were enumerated. Basal and augmented natural killer cell activity in the spleen was assessed. SRBC specific IgM plaques were determined for each animal by incubating a spleen cell suspension preparation with guinea pig complement and sRBC. An enzyme-linked immunosorbent assay (ELISA) was used to determine the serum titers of the primary IgM response to the sRBC. In a third assay, the spleen cell mixed leucocyte response (MLR) to stimulator DBA/2 spleen cells was determined. In a separate test, the peritoneal macrophage activation assay, the mice were treated with sodium chlorite in the drinking water at the same treatment levels for 32 days. Macrophages were recruited into the peritoneal cavity by an ip injection of 1 ml of thioglycollate 3.5 days prior to euthanasia on study day 33. Peritoneal cells were collected and incubated with B16F10 tumor cells. In the assay the degree to which the tumor cells were suppressed was determined. The mean body weights of all of the treatment groups were greater than that of the control group by the end of the treatment period (NS, $p < 0.01$ or 0.05). The mean relative spleen and thymus weights were not affected by the treatment. Treatment with CPS resulted in reduced relative spleen and thymus weights. The absolute number of $CD8^+$ T cells was increased in the 30 mg/l treatment group. The absolute numbers of $CD4^+$ T cells, B cells, NK cells and macrophages were not affected by the treatment. Treatment with sodium chlorite demonstrated an increased antibody forming cell (AFC) response in the spleen both in specific terms (AFC/ 10^6 spleen cells) and in total spleen activity (AFC/spleen). Treatment with CPS resulted in a drastic reduction of the AFC response. In the spleen cell MLR assay there was no treatment-related effect on the cell mediated response to the DBA/2 spleen cells. CPS inhibited the response. Activation of peritoneal macrophages to kill and/or inhibit the growth of B16F10 tumor cells was not affected by sodium chlorite treatment. Basal and augmented natural killer cell activity in the spleen was likewise not affected by the treatment. Treatment with AAGM1 severely suppressed the response. **No adverse effect indicated. Summary Report.** (██████████, 3/22/17)

ENDOCRINE DISRUPTOR STUDIES

No studies submitted nor required at this time.

Human Toxicity

Sodium Chlorite

50288-0265; 296201; "A Case of Severe Chlorite Poisoning Successfully Treated with Early Administration of Methylene Blue, Renal Replacement Therapy and Red Blood Cell Transfusion: Case Report"; (A. Gehardtova, P. Vavrinc, D. Vavricova-Yaghi, M. Seelen, A. Dobisova, Z. Flassikova, A. Cikova, R.H. Henning, A. Yaghi; University Hospital Bratislava, Nemocnica Ruzinov, ICU, KAIM, Clinic of Anesthesiology and Intensive Care Medicine, Faculty

of Medicine, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University in Bratislava, University in Bratislava, Bratislava, Slovak Republic; Department of Nephrology and the Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; Medicine 93: 1-5 (2014); A 55-year old man attempted suicide by ingesting approximately 100 ml of a 28% formulation of sodium chlorite along with 0.75 liters of whiskey and 4800 mg of ibuprofen (approximate dose of sodium chlorite: 400 mg/kg). Upon arrival at a medical facility, the patient was cyanotic and suffering from 40% methemoglobinemia. Chlorite as an oxidizing agent acts to increase the oxidation state of hemoglobin iron. Tissue hypoxia resulted from this condition. Liver enzymes and the coagulation factors were normal. The lack of injury to the liver would likely preclude the contribution of ibuprofen and alcohol to the clinical injuries suffered by the patient. Methylene blue therapy was instituted and eventually the methemoglobinemia was reduced to 10.2% by 29 hours post-initiation. Overall, the reduction of methemoglobinemia demonstrated biphasic kinetics with the initial and later phases demonstrating half-lives of 15.2 and 65.4 hours, respectively. In time the patient suffered hemolysis and acute kidney failure and received blood transfusions and periodic kidney dialysis during his hospitalization. Eventually, the patient recovered and was discharged. **Possible adverse effects:** severe methemoglobinemia, hemolysis, and acute kidney failure; **Summary report.** (██████████, 1/10/17)

50288-0265; 296202; "A Case of Sodium Chlorite Toxicity Managed with Concurrent Renal Replacement Therapy and Red Cell Exchange"; (A. Romanovsky, D. Djogovic, D. Chin; Division of Critical Care Medicine, University of Alberta, Division of Nephrology, University of Alberta, and Department of Emergency Medicine, University of Alberta, Edmonton, AB, Canada; Journal of Medical Toxicology 9: 67-70 (2013); A patient presented at the local hospital after ingesting a small amount of a 28% sodium chlorite solution which had been further diluted. Methemoglobinemia was 6.7%. Urine was brown in color with hemoglobinuria, a few red blood cells and hemegranular casts. Hemolysis and acute kidney failure necessitated blood transfusions and hemodialysis. Esophagogastroduodenoscopy revealed superficial gastric ulcers. Ultimately the patient was discharged from the hospital 17 days after admission. **Possible adverse effect:** methemoglobinemia, hemolysis and acute renal failure. **Summary Report** (██████████, 1/11/17)

50288-0266; 296401; "Acute Sodium Chlorite Poisoning Associated with Renal Failure"; (J.L. Lin, P.S. Lim; Division of Nephrology, Chang Gung Memorial Hospital, Taipei, Taiwan, Republic of China, Division of Nephrology, Kuang Tien General Hospital, Shalu, Taichung, Taiwan, Republic of China; Renal Failure 15: 645-648 (1993)); A male presented at the hospital after imbibing 100 ml of a 10% sodium chlorite solution (approximate dose: 140 mg/kg, based on a 70 kg bw). Immediate clinical signs included severe methemoglobinemia (59%) and cyanosis. His urine was brown in color with protein and blood. Hemoglobin levels declined from 17.6 g/dl to 7.1 g/dl over the next few hours after admission. As a consequence of massive hemolysis, disseminated intravascular coagulation occurred. Treatment with methylene blue and arteriovenous hemofiltration resulted in reducing the methemoglobin level to 21.1% after 12-hours of care and to 16.9% at 24 hours. However, in the following days severe respiratory failure resulted from pulmonary edema and hemorrhage. In the midst of this, the patient suffered cardiac arrest and was resuscitated. At this point in time, he also suffered acute renal failure. A renal biopsy revealed severe interstitial edema and moderate damage to the tubules with hemorrhage and necrosis also being noted. Hemodialysis was continued for 4 weeks and ultimately after two months of hospitalization, the patient was discharged with normal renal function. **Possible adverse effect:** severe cyanosis, hemolysis and renal failure. **Summary report.** (██████████, 1/27/17)

50288-0267; 296811; "The Effects of Chronic Administration of Chlorite to Glucose-6-Phosphate Dehydrogenase Deficient Healthy Adult Male Volunteers"; (J.R. Lubbers, S. Chauhan, J.K. Miller, J. R. Bianchine; Department of Pharmacology, The Ohio State University, College of Medicine, Columbus, OH; Journal of Environ. Pathol., Toxicol. and Oncol. 5: 239-242 (1984); Three male human volunteers who were deficient in glucose-6-phosphate dehydrogenase activity (< 5 IU/g of hemoglobin) imbibed 500 ml of water with a sodium chlorite concentration of 5 ppm daily for 12 weeks (calculated dose: 0.36 mg/kg/day, based on a 70 kg body weight). They were monitored periodically over the 12-week treatment period and the subsequent 8 weeks post-treatment. Vital signs and 47 quantitative hematological, clinical chemical and urinalytical parameters were measured. A mild reduction in mean corpuscular hemoglobin concentrations was noted between 2 and 4 weeks of treatment for all three of the subjects. The significance of this observation was questioned as no control subjects were included in the study. Otherwise, no other effects were noted. **Summary report.** (██████████, 2/22/17)

Chlorine Dioxide

50288-0268; 297614; "Chlorine Dioxide Water Disinfection: A Prospective Epidemiology Study"; (G.E. Michael, R.K. Miday, J.P. Bercz, R.G. Miller, D.G. Greathouse, D.F. Kraemer, J.B. Lucas; Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH; Archives of Environmental Health 36: 20-27 (1981); A treatment group of 197 human subjects drank water which had been disinfected with chlorine dioxide for 12 weeks (chlorite ion: approximately 5 ppm). A concurrent control group of 112 individuals was included in the study in which they imbibed chlorine dioxide-free water. Specified hematological and clinical chemical parameters were assayed prior to the initiation of the exposure and after the 12-week exposure period. No treatment-related effect on the hematocrit, hemoglobin concentration, red blood cell count, white blood cell count, reticulocyte percentage, mean corpuscular volume, methemoglobin percentage, or blood urea nitrogen, serum creatinine, and total bilirubin concentrations was evident. **No adverse effect evident. Summary Report** (██████████, 3/24/17)

Sodium Chlorite and Chlorine Dioxide

50288-0265; 296193; "Controlled Clinical Evaluations of Chlorine Dioxide, Chlorite and Chlorate in Man"; (J.R. Lubbers, S. Chauhan, J.R. Bianchine; Environmental Health Perspectives 46: 57-62 (1982)); Ten male human volunteers/group drank chlorine dioxide or chlorite among other chlorinated compounds in a two phase study. In the first phase, the volunteers drank 1000 mls of a particular concentration of the respective test material and were observed for an additional two days. On the 4th day, the concentration of the material was increased and the treatment and observation was repeated over the next two days. A maximal treatment level of 24 mg/l and 2.4 mg/l was achieved for chlorine dioxide and chlorite, respectively. The respective doses were 24 and 2.4 mg/person (approximately 0.34 and 0.034 mg/kg based upon a body weight of 70 kg). In phase II the volunteers drank 500 mls of a 5.0 mg/l preparation of either of the two test materials for 12 weeks. The dose levels were 2.5 mg/person or approximately 0.036 mg/kg/day. Physical examinations were performed and blood and urine samples were collected weekly. In the third phase, 3 subjects with a glucose-6-phosphate dehydrogenase (G6PD) deficiency drank 500 mls of a 5.0 mg/l preparation of chlorite daily for 12 weeks. Their health was monitored in the same manner as was employed in Phase II. The treatment level was 2.5 mg/person or approximately 0.036 mg/kg/day. The physical examinations and clinical chemical, hematological and urine analytical parameters which were evaluated did not reveal any treatment-related effects. **No adverse effect indicated. Chlorine Dioxide Acute Human NOEL: 0.34 mg/kg, Chlorite Acute Human NOEL: 0.034 mg/kg; Chlorine Dioxide and Chlorite Subchronic NOEL: 0.036 mg/kg/day;** (all of these values were based on the highest dose tested); **Summary Report.** (██████████, 12/30/16)

50288-0266; 296402; "Effects of the Acute Rising Dose Administration of Chlorine Dioxide, Chlorate and Chlorite to Normal Healthy Adult Male Volunteers"; (J.R. Lubbers, J.R. Bianchine; Department of Pharmacology, The Ohio State University College of Medicine, Columbus, OH; J. Environ. Pathol. Toxicol. Oncol. 5:215-228 (1984)); Ten male human volunteers/group ingested 1000 ml of a progressively increasing concentration of chlorine dioxide or sodium chlorite. The chlorine dioxide concentrations were 0.1, 1.0, 5.0, 10.0, 18.0, 24.0 ppm (1.4 to 340 µg/kg, based on a given weight of 70 kg). The sodium chlorite concentrations ranged were 0.01, 0.1, 0.5, 1.0, 1.80, and 2.40 ppm (0.14 to 34.0 µg/kg, based on a given weight of 70 kg). Each subject received the dose within 4 hours on the day of treatment. A physical examination was performed on days 2 and 3 and blood and urine samples were collected on day 2 and extensive biochemical parameters were evaluated. On the 4th day, the next dose was ingested and the process was repeated until each subject had taken the highest dose and the sample collection and physical examinations were completed. A control group of 10 subjects received demineralized deionized water as their treatment and completed the entire sequence of the dosing procedure. No treatment-related clinical signs or symptoms were noted. None of the hematological or clinical chemical parameters were affected by the treatments. Single dose treatments at approximately 340 µg/kg for chlorine dioxide and 34 µg/kg for sodium chlorite did not result any treatment-related effects. **Summary report.** (██████████, 1/30/17)

50288-0266; 296404; "Effects of the Chronic Administration of Chlorine Dioxide, Chlorite, and Chlorate to Normal Healthy Adult Male Volunteers"; (J.R. Lubbers, S. Chauhan, J.K. Miller, J.R. Bianchine; Department of Pharmacology, The Ohio State University College of Medicine, Columbus, OH; J. Environ. Pathol. Toxicol. Oncol. 5: 229-239 (1984)); Ten male human volunteers/group ingested 0 (vehicle: demineralized, deionized water) or 500 ml of 5 ppm chlorine dioxide or sodium chlorite daily for 12 weeks (0.036 mg/kg/day of both chemicals based on a given body weight of 70 kg bw). Over the treatment period physical examinations, electrocardiograms, vital sign assessment, complete blood and urine analyses, and more specific tests; thyroid function tests, Coombs tests, haptoglobin, methemoglobin, glucose-6-phosphate dehydrogenase, sickle cell preparation, hemoglobin electrophoresis and glutathione were performed at specified time points during the treatment period up to once per week in frequency. Under this treatment condition, no treatment-related effects were identified. **Summary report.** (██████████, 1/30/17)

Mechanistic Studies

Sodium Chlorite

50288-0267; 296810; "Oxidative Damage to the Erythrocyte Induced by Sodium Chlorite, *In Vivo*"; (W.P. Heffernan, C. Guion, R.J. Bull; Toxicological Assessment Branch Laboratory Studies Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH; Journal of Environmental Pathology and Toxicology 2: 1487-1499 (1979)); In this report male CD rats and male mixed breed cats were dosed with sodium chlorite under a variety of treatment scenarios in order to understand the oxidative effect of the chemical on the red blood cell. In one study, rats received 0, 100, 250 or 500 ppm of sodium chlorite in the drinking water for 90 days (dose could not be ascertained). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights. However, during the first 30 days of treatment, the red blood cell count, hemoglobin concentration and hematocrit all declined in a dose-related manner. As the treatment progressed, these parameters gradually recovered to near control levels. In a second study, the rats received 0, 10, 50 or 100 ppm of sodium chlorite in the drinking water for 90 days. Serum glutathione (GSH) and 2,3-diphosphoglycerate (2,3-DG) levels were assayed throughout the study. The serum GSH level was reduced in a dose-related manner with a 19 and 34% decline at 50 and

100 ppm, respectively, after 30 days of treatment. After 90 days of treatment, the GSH levels remained depressed. There was a slight elevation of the 2,3-DG levels in the serum over the course of the study. In a third study, the effect of sodium chlorite-induced depletion of GSH on the catalase-mediated metabolism of hydrogen peroxide was evaluated. Rats received 0 or 100 mg/l of ClO_2^- in the drinking water for 30 days. Upon completion of the *in vivo* treatment, red blood cells were recovered from both groups and incubated *in vitro* with sodium chlorite, 0.5 mM for one hour. The presence of the sodium chlorite in the incubation resulted in an increased formation of hydrogen peroxide. However, in the treated animals which were suffering from depletion of GSH, the formation of H_2O_2 was increased 5-fold over that of the control group. In the 4th study the formation of methemoglobin after treatment with sodium chlorite was assessed. In the rats receiving the test chemical in the drinking water, no formation of the oxidized hemoglobin was evident. In this study 4 male rats/group were dosed by intraperitoneal injection with 0, 1, 10, 20, 30 or 50 mg/kg of ClO_2^- . The percentage of methemoglobin was assayed at 30 and 60 minutes post-dose. The methemoglobin levels were increased in a dose-related manner with a maximal level approaching 60% of total pigment in the red blood cells at 30 minutes. The maximal level declined to approximately 35% at 60 minutes. The hemoglobin concentration was reduced from the control value at even the 1 mg/kg treatment level. A further assessment of methemoglobin formation was performed by dosing cats orally by gavage with either 20 or 64 mg/kg of sodium chlorite. Methemoglobinemia was assessed up to 6 hours post-dose. Maximal levels of methemoglobin were achieved at 1 to 2 hours post-dose and declined thereafter. The half-life of methemoglobin disappearance was approximately 2.5 hours. However, when the cats received up to 1000 mg/l of sodium chlorite in the drinking water, no increase in methemoglobinemia was apparent. However, a significant reduction in the hemoglobin concentration and hematocrit were evident. In the final study, the turnover of red blood cells was assessed by determining the half-life of ^{51}Cr -labeled red blood cells in cats. At treatment levels of 0, 10, 100, 250, or 500 ppm of ClO_2^- in the drinking water (duration of the treatment period was not reported) (0, 0.6, 3.0, 6.0, 7.0 mg/kg/day), the half-life of the labeled red blood cells was reduced in a dose-related manner from 8.53 days to 6.02 days at the 500 ppm treatment level. Based on the results of these studies, the hemoglobin in the red blood cells is susceptible to oxidation to methemoglobin by sodium chlorite. This effect is apparent when bolus doses are administered either by orally or by injection and is quickly reversed. Treatment in the drinking water at even 1000 mg/l of sodium chlorite does not result in the elevation of the methemoglobin level. However, treatment at 100 mg/l in the drinking water did reduce the red blood cell count, hemoglobin and hematocrit and serum glutathione level. The half-life of the red blood cells were likewise affected. **Summary report.** (██████████, 2/22/17)

Chlorine Dioxide

50288-0265; 296197; "Effects of ClO_2 on the Absorption and Distribution of Dietary Iodide in the Rat"; (R.M. Harrington, H.G. Shertzer, J.P. Bercz; Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH, U.S. Environmental Protection Agency, Health Effects Research Laboratory, Toxicology and Microbiology Division, Cincinnati, OH; *Fundamental Applied Toxicology* 5: 672-678 (1985)); In previous research work, treatment with chlorine dioxide had apparently caused a decrease of thyroxine (T4) in non-human primates. In this study the retention and/or uptake of $^{131}\text{I}^-$ from the gastrointestinal tract of the adult male Sprague Dawley rat was investigated. Rats were fasted for 24 hours prior to being dosed with 5×10^5 cpm of Na^{131}I /kg followed by 0.25 ml of either water or 25 ppm (6.25 μg) or 100 ppm of ClO_2 (25 μg). The radiolabel was recovered from the gastrointestinal tract, blood and thyroid gland up to 24 hours post-dose (up to 1 hour post-dose for the 100 ppm treatment group). In a follow-up assay, one group of rats received powdered chow in which Na^{131}I had been mixed and treated with 100 ppm of ClO_2 . The control group received the untreated chow and a comparable dose of Na^{131}I . Similarly the radiolabel was recovered from the gastrointestinal tract and thyroid

gland at 24 hours post-dose. In addition feces and urine were collected up to 24 hours post-dose. In the former assay, treatment with ClO₂ resulted in the increased retention of the radiolabel in the stomach, small intestine and esophagus and reduced recovery from the blood and thyroid gland at 1 hour post-dose. An increased retention of the radiolabel was observed up to 6 hours post-dose in the gastrointestinal tract of the low dose ClO₂ group. The radiolabel recovered in the blood and thyroid gland were largely equivalent for the two groups by 6 hours post-dose. Treatment with 100 ppm of ClO₂ resulted in largely the same distribution of radiolabel as was observed in the lower treatment group at one hour post-dose. In the latter assay, the iodide in the modified chow was apparently sufficiently bound to increase the retention of the radiolabel in the ileum and colon and resulted in significant recovery in the feces at 24 hours post-dose. Retention of the radiolabel in the thyroid was reduced in comparison with treatment with the free iodide. Study results indicated that dietary chlorine dioxide can result in a reduction in the short-term uptake of iodide from the gastrointestinal tract. **Summary Report.** (██████, 1/5/17)

50288-0265; 296204; "Epidermal Hyperplasia in Mouse Skin Following Treatment with Alternative Drinking Water Disinfectants"; (M. Robinson, R.J. Bull, M. Schamer, R.E. Long; Toxicology and Microbiology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH, College of Pharmacy, Washington State University, Pullman, WA, Pathology Associates, Ijamsville, MD; Environmental Health Perspectives 69: 293-300 (1986)); Among other disinfectants, the effects of chlorine dioxide on murine skin was investigated in this study. In the 1st phase of the study, the skin of five female SENCAR mice/group were exposed whole body except for the head to 0 (distilled water), 1, 10, 100, 300, or 1000 ppm of chlorine dioxide daily for 10 minutes for 4 days. On day 5 the animals were euthanized and a section of dorsal skin was dissected and fixed for microscopic examination. The thickness of the skin and the density of cells in the examined section were determined. Only at the 1000 ppm level was a treatment-related increase in skin thickness observed. An increase in cell density was noted at the 300 and 1000 ppm treatment levels. In the 2nd phase of the study, the skin of 5 female mice/group/time point was exposed to 0 or 1000 ppm of chlorine dioxide for 10 minutes. The animals were euthanized at 1, 3, 4, 5, 8, 10 and 12 days post-dose. The skin of the treated animals demonstrated an increase in thickness throughout the observation period (p<0.05). Single or subacute dermal exposures to chlorine dioxide concentrations in the range of 300 to 1000 ppm for short time intervals resulted in an increased hyperplastic response. **Summary Report.** (██████, 1/12/17)

50288-0266; 296399; "Effects of Chlorine Dioxide on the Thyroid Function in the African Green Monkey and the Rat"; (R.M. Harrington, H.G. Shertzer, J.P. Bercz; Toxicology and Microbiology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH and Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH; Journal of Toxicology and Environmental Health 19: 235-242 (1986)); Six female African Green monkeys received 100 ppm of chlorine dioxide in the drinking water for 8 weeks in two study phases. In the first phase the thyroid uptake of iodine was assayed prior to dosing initiation and at 4 and 8 weeks of treatment and at 3 months after dosing cessation. This assessment was performed by injecting Na¹³¹I (1x10⁶ cpm) intravenously and at 24 hours post-injection, the presence of radiolabel in the thyroid was measured by a non-invasive technique. In the second phase, thyroxine (T4) serum levels were assayed prior to study initiation and at 4 and 8 weeks of dosing. Thyroid uptake of iodine was assayed at those time points as well. In the second part of the study, 12 male Sprague-Dawley rats/group received 0, 100 or 200 ppm of chlorine dioxide in the drinking water for 8 weeks. Serum thyroxine (T4) levels were assayed prior to study initiation and at 4 and 8 weeks of dosing. At 8 weeks, each animal was injected ip with Na¹³¹I (5x10⁵ cpm) and 24 hours post-injection were

euthanized. The radiolabel in the thyroid gland was assayed. In the first phase with the monkeys, the thyroid uptake of iodine was increased by 70% after 8 weeks of treatment. At 3 months after the cessation of dosing, the uptake had returned to the baseline measured prior to the treatment initiation. In the second phase the iodine uptake into the thyroid increased after 8 weeks of treatment as well. The mean serum thyroxine level measurement was inconclusive. The T4 serum concentration first declined below the level measured at the initiation of the treatment after 4 weeks of treatment and then increased above the baseline after 8 weeks. In the rat treatment study the serum thyroxine levels were reduced in a treatment-related manner over the 8 week treatment period. Iodine uptake by the thyroid was not apparently affected by the treatment. The overall report results were inclusive as to whether chlorine dioxide exerted a treatment-related effect on the thyroid. **Summary report.** (██████, 1/26/17)

50288-0266; 296407; "Effects of Chlorine Dioxide on Thyroid Function in Neonatal Rats"; (J. Orme, D.H. Taylor, R.D. Laurie, R.J. Bull; Department of Zoology, Miami University, Oxford, OH, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH; J. Toxicology and Environmental Health 15: 315-322 (1985)); This study was performed in two phases. In phase one 8 male Sprague-Dawley pups/litter were dosed by oral gavage with 0 (distilled water) or 14 mg/kg/day of chlorine dioxide from post-natal day 5 through 20. Locomotor activity was assessed for the litters from lactation day 10 through 21. Pup body weights were recorded weekly and the age of eye opening was recorded. At the time of weaning on day 21, blood was drawn from each pup and serum thyroxine (T4) and triiodothyronine (T3) levels were measured. In phase two adult females received 0 (distilled water), 2, 20 or 100 mg/l of chlorine dioxide in the drinking water from 2 weeks prior to mating until the pups were weaned at 21 days post-natal (treatment level: 0.3, 3.0, 15.2 mg/kg/day, calculated by reviewer). A positive control group received 5 mg/l of propylthiouracil (PTU) in the drinking water over the same time period. Maternal food and water consumption were monitored. Dam and pup body weights were recorded weekly and the age of pup eye opening was recorded. Locomotor activity was assessed for the litters from lactation day 10 through 21. At the time of weaning on day 21, blood was drawn from each pup and dam. Serum thyroxine (T4) and triiodothyronine (T3) levels were measured. In phase one the mean body weights of the 14 mg/kg pups were less than those of the control animals on post-natal days 14 and 21 ($p < 0.05$). Time to eye opening was not affected. The activity of these pups was less than that of the control pups on post-natal days 18 and 19 ($p < 0.05$). The mean serum T4 level of the 14 mg/kg pups was less than that of the control group animals ($p < 0.05$). The T3 level was not affected by the treatment. In phase two the mean body weights of the treated dams were not affected. The mean pup weights were not affected throughout the lactation period. The mean locomotor activity of the 100 mg/l treatment group was less than that of the control group by day 20 post-natal (NS). At the 100 mg/l treatment level, the pups' serum T4 level was less than that of the control group and the T3 level was greater than control group ($p < 0.05$). The T4 and T3 levels of the dams in this group were not affected by the treatment. The pups in the PTU treatment group had lower mean body weights, exhibited lower locomotor activity over the course of the lactation period and had delayed eye opening. They demonstrated lower levels of both T4 and T3 ($p < 0.01$). The T4 and T3 levels of the dams in this group were not affected. The elevated T3 and reduced T4 levels of the pups in the 14 mg/kg direct treatment group and the pups in the indirect 100 mg/l treatment group is possibly indicative of an altered availability of iodide. **Summary report.** (██████, 2/6/17)

Mechanistic Studies

Sodium Chlorite

50288-0267; 296810; "Oxidative Damage to the Erythrocyte Induced by Sodium Chlorite, *In Vivo*"; (W.P. Heffernan, C. Guion, R.J. Bull; Toxicological Assessment Branch Laboratory Studies Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH; Journal of Environmental Pathology and Toxicology 2: 1487-1499 (1979)); In this report male CD rats and male mixed breed cats were dosed with sodium chlorite under a variety of treatment scenarios in order to understand the oxidative effect of the chemical on the red blood cell. In one study, rats received 0, 100, 250 or 500 ppm of sodium chlorite in the drinking water for 90 days (dose could not be ascertained). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights. However, during the first 30 days of treatment, the red blood cell count, hemoglobin concentration and hematocrit all declined in a dose-related manner. As the treatment progressed, these parameters gradually recovered to near control levels. In a second study, the rats received 0, 10, 50 or 100 ppm of sodium chlorite in the drinking water for 90 days. Serum glutathione (GSH) and 2,3-diphosphoglycerate (2,3-DG) levels were assayed throughout the study. The serum GSH level was reduced in a dose-related manner with a 19 and 34% decline at 50 and 100 ppm, respectively, after 30 days of treatment. After 90 days of treatment, the GSH levels remained depressed. There was a slight elevation of the 2,3-DG levels in the serum over the course of the study. In a third study, the effect of sodium chlorite-induced depletion of GSH on the catalase-mediated metabolism of hydrogen peroxide was evaluated. Rats received 0 or 100 mg/l of ClO_2^- in the drinking water for 30 days. Upon completion of the *in vivo* treatment, red blood cells were recovered from both groups and incubated *in vitro* with sodium chlorite, 0.5 mM for one hour. The presence of the sodium chlorite in the incubation resulted in an increased formation of hydrogen peroxide. However, in the treated animals which were suffering from depletion of GSH, the formation of H_2O_2 was increased 5-fold over that of the control group. In the 4th study the formation of methemoglobin after treatment with sodium chlorite was assessed. In the rats receiving the test chemical in the drinking water, no formation of the oxidized hemoglobin was evident. In this study 4 male rats/group were dosed by intraperitoneal injection with 0, 1, 10, 20, 30 or 50 mg/kg of ClO_2^- . The percentage of methemoglobin was assayed at 30 and 60 minutes post-dose. The methemoglobin levels were increased in a dose-related manner with a maximal level approaching 60% of total pigment in the red blood cells at 30 minutes. The maximal level declined to approximately 35% at 60 minutes. The hemoglobin concentration was reduced from the control value at even the 1 mg/kg treatment level. A further assessment of methemoglobin formation was performed by dosing cats orally by gavage with either 20 or 64 mg/kg of sodium chlorite. Methemoglobinemia was assessed up to 6 hours post-dose. Maximal levels of methemoglobin were achieved at 1 to 2 hours post-dose and declined thereafter. The half-life of methemoglobin disappearance was approximately 2.5 hours. However, when the cats received up to 1000 mg/l of sodium chlorite in the drinking water, no increase in methemoglobinemia was apparent. However, a significant reduction in the hemoglobin concentration and hematocrit were evident. In the final study, the turnover of red blood cells was assessed by determining the half-life of ^{51}Cr -labeled red blood cells in cats. At treatment levels of 0, 10, 100, 250, or 500 ppm of ClO_2^- in the drinking water (duration of the treatment period was not reported) (0, 0.6, 3.0, 6.0, 7.0 mg/kg/day), the half-life of the labeled red blood cells was reduced in a dose-related manner from 8.53 days to 6.02 days at the 500 ppm treatment level. Based on the results of these studies, the hemoglobin in the red blood cells is susceptible to oxidation to methemoglobin by sodium chlorite. This effect is apparent when bolus doses are administered either by orally or by injection and is quickly reversed. Treatment in the drinking water at even 1000 mg/l of sodium chlorite does not result in the elevation of the methemoglobin level. However, treatment at 100 mg/l in the drinking water did reduce the red

blood cell count, hemoglobin and hematocrit and serum glutathione level. The half-life of the red blood cells were likewise affected. **Summary report.** (██████████, 2/22/17)

Chlorine Dioxide

50288-0265; 296197; "Effects of ClO₂ on the Absorption and Distribution of Dietary Iodide in the Rat"; (R.M. Harrington, H.G. Shertzer, J.P. Bercz; Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH, U.S. Environmental Protection Agency, Health Effects Research Laboratory, Toxicology and Microbiology Division, Cincinnati, OH; Fundamental Applied Toxicology 5: 672-678 (1985)); In previous research work, treatment with chlorine dioxide had apparently caused a decrease of thyroxine (T₄) in non-human primates. In this study the retention and/or uptake of ¹³¹I⁻ from the gastrointestinal tract of the adult male Sprague Dawley rat was investigated. Rats were fasted for 24 hours prior to being dosed with 5x10⁵ cpm of Na¹³¹I/kg followed by 0.25 ml of either water or 25 ppm (6.25 µg) or 100 ppm of ClO₂ (25 µg). The radiolabel was recovered from the gastrointestinal tract, blood and thyroid gland up to 24 hours post-dose (up to 1 hour post-dose for the 100 ppm treatment group). In a follow-up assay, one group of rats received powdered chow in which Na¹³¹I had been mixed and treated with 100 ppm of ClO₂. The control group received the untreated chow and a comparable dose of Na¹³¹I. Similarly the radiolabel was recovered from the gastrointestinal tract and thyroid gland at 24 hours post-dose. In addition feces and urine were collected up to 24 hours post-dose. In the former assay, treatment with ClO₂ resulted in the increased retention of the radiolabel in the stomach, small intestine and esophagus and reduced recovery from the blood and thyroid gland at 1 hour post-dose. An increased retention of the radiolabel was observed up to 6 hours post-dose in the gastrointestinal tract of the low dose ClO₂ group. The radiolabel recovered in the blood and thyroid gland were largely equivalent for the two groups by 6 hours post-dose. Treatment with 100 ppm of ClO₂ resulted in largely the same distribution of radiolabel as was observed in the lower treatment group at one hour post-dose. In the latter assay, the iodide in the modified chow was apparently sufficiently bound to increase the retention of the radiolabel in the ileum and colon and resulted in significant recovery in the feces at 24 hours post-dose. Retention of the radiolabel in the thyroid was reduced in comparison with treatment with the free iodide. Study results indicated that dietary chlorine dioxide can result in a reduction in the short-term uptake of iodide from the gastrointestinal tract. **Summary Report.** (██████████, 1/5/17)

50288-0265; 296204; "Epidermal Hyperplasia in Mouse Skin Following Treatment with Alternative Drinking Water Disinfectants"; (M. Robinson, R.J. Bull, M. Schamer, R.E. Long; Toxicology and Microbiology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH, College of Pharmacy, Washington State University, Pullman, WA, Pathology Associates, Ijamsville, MD; Environmental Health Perspectives 69: 293-300 (1986)); Among other disinfectants, the effects of chlorine dioxide on murine skin was investigated in this study. In the 1st phase of the study, the skin of five female SENCAR mice/group were exposed whole body except for the head to 0 (distilled water), 1, 10, 100, 300, or 1000 ppm of chlorine dioxide daily for 10 minutes for 4 days. On day 5 the animals were euthanized and a section of dorsal skin was dissected and fixed for microscopic examination. The thickness of the skin and the density of cells in the examined section were determined. Only at the 1000 ppm level was a treatment-related increase in skin thickness observed. An increase in cell density was noted at the 300 and 1000 ppm treatment levels. In the 2nd phase of the study, the skin of 5 female mice/group/time point was exposed to 0 or 1000 ppm of chlorine dioxide for 10 minutes. The animals were euthanized at 1, 3, 4, 5, 8, 10 and 12 days post-dose. The skin of the treated animals demonstrated an increase in thickness throughout the observation period (p<0.05). Single or subacute dermal exposures to chlorine dioxide

concentrations in the range of 300 to 1000 ppm for short time intervals resulted in an increased hyperplastic response. **Summary Report.** (██████████, 1/12/17)

50288-0266; 296399; "Effects of Chlorine Dioxide on the Thyroid Function in the African Green Monkey and the Rat"; (R.M. Harrington, H.G. Shertzer, J.P. Bercz; Toxicology and Microbiology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH and Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH; Journal of Toxicology and Environmental Health 19: 235-242 (1986)); Six female African Green monkeys received 100 ppm of chlorine dioxide in the drinking water for 8 weeks in two study phases. In the first phase the thyroid uptake of iodine was assayed prior to dosing initiation and at 4 and 8 weeks of treatment and at 3 months after dosing cessation. This assessment was performed by injecting Na¹³¹I (1x10⁶ cpm) intravenously and at 24 hours post-injection, the presence of radiolabel in the thyroid was measured by a non-invasive technique. In the second phase, thyroxine (T4) serum levels were assayed prior to study initiation and at 4 and 8 weeks of dosing. Thyroid uptake of iodine was assayed at those time points as well. In the second part of the study, 12 male Sprague-Dawley rats/group received 0, 100 or 200 ppm of chlorine dioxide in the drinking water for 8 weeks. Serum thyroxine (T4) levels were assayed prior to study initiation and at 4 and 8 weeks of dosing. At 8 weeks, each animal was injected ip with Na¹³¹I (5x10⁵ cpm) and 24 hours post-injection were euthanized. The radiolabel in the thyroid gland was assayed. In the first phase with the monkeys, the thyroid uptake of iodine was increased by 70% after 8 weeks of treatment. At 3 months after the cessation of dosing, the uptake had returned to the baseline measured prior to the treatment initiation. In the second phase the iodine uptake into the thyroid increased after 8 weeks of treatment as well. The mean serum thyroxine level measurement was inconclusive. The T4 serum concentration first declined below the level measured at the initiation of the treatment after 4 weeks of treatment and then increased above the baseline after 8 weeks. In the rat treatment study the serum thyroxine levels were reduced in a treatment-related manner over the 8 week treatment period. Iodine uptake by the thyroid was not apparently affected by the treatment. The overall report results were inclusive as to whether chlorine dioxide exerted a treatment-related effect on the thyroid. **Summary report.** (██████████, 1/26/17)

50288-0266; 296407; "Effects of Chlorine Dioxide on Thyroid Function in Neonatal Rats"; (J. Orme, D.H. Taylor, R.D. Laurie, R.J. Bull; Department of Zoology, Miami University, Oxford, OH, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH; J. Toxicology and Environmental Health 15: 315-322 (1985)); This study was performed in two phases. In phase one 8 male Sprague-Dawley pups/litter were dosed by oral gavage with 0 (distilled water) or 14 mg/kg/day of chlorine dioxide from post-natal day 5 through 20. Locomotor activity was assessed for the litters from lactation day 10 through 21. Pup body weights were recorded weekly and the age of eye opening was recorded. At the time of weaning on day 21, blood was drawn from each pup and serum thyroxine (T4) and triiodothyronine (T3) levels were measured. In phase two adult females received 0 (distilled water), 2, 20 or 100 mg/l of chlorine dioxide in the drinking water from 2 weeks prior to mating until the pups were weaned at 21 days post-natal (treatment level: 0.3, 3.0, 15.2 mg/kg/day, calculated by reviewer). A positive control group received 5 mg/l of propylthiouracil (PTU) in the drinking water over the same time period. Maternal food and water consumption were monitored. Dam and pup body weights were recorded weekly and the age of pup eye opening was recorded. Locomotor activity was assessed for the litters from lactation day 10 through 21. At the time of weaning on day 21, blood was drawn from each pup and dam. Serum thyroxine (T4) and triiodothyronine (T3) levels were measured. In phase one the mean body weights of the 14 mg/kg pups were less than those of the control animals on post-natal days 14 and 21 (p<0.05). Time to eye opening was not affected. The activity of these pups was less than that

of the control pups on post-natal days 18 and 19 ($p < 0.05$). The mean serum T4 level of the 14 mg/kg pups was less than that of the control group animals ($p < 0.05$). The T3 level was not affected by the treatment. In phase two the mean body weights of the treated dams were not affected. The mean pup weights were not affected throughout the lactation period. The mean locomotor activity of the 100 mg/l treatment group was less than that of the control group by day 20 post-natal (NS). At the 100 mg/l treatment level, the pups' serum T4 level was less than that of the control group and the T3 level was greater than control group ($p < 0.05$). The T4 and T3 levels of the dams in this group were not affected by the treatment. The pups in the PTU treatment group had lower mean body weights, exhibited lower locomotor activity over the course of the lactation period and had delayed eye opening. They demonstrated lower levels of both T4 and T3 ($p < 0.01$). The T4 and T3 levels of the dams in this group were not affected. The elevated T3 and reduced T4 levels of the pups in the 14 mg/kg direct treatment group and the pups in the indirect 100 mg/l treatment group is possibly indicative of an altered availability of iodide. **Summary report.** (██████████, 2/6/17)

SUPPLEMENTAL STUDIES

50288-059 115608 A Chemical Manufacturers Association document with 17 tabbed sections occasionally referred to studies of potential interest to SB-950. Tab 4 provides a 1-page summary of an unspecified mouse oncogenicity study, which appears to be Kurokawa *et al.* (1986), based on similarity to the description of that study in Record No. 115609, below. Summary does not identify oncogenicity effects. There were no other noteworthy entries. ██████████, insufficient information to review, hence no worksheet, 1/8/01.

50288-059 115609 "A review of the uses, chemistry and health effects of chlorine dioxide and the chlorite ion," Chlorine Dioxide Panel of Chemical Manufacturers Association, April 1989. Pages 19-34 discuss several studies which relate to SB-950. Although nothing in this record is a full study, some conclusions are: (1) Chlorine dioxide and chlorite have the potential to cause methemoglobinemia and hemolytic anemia, (2) Chlorine dioxide oral doses in rat metabolism studies [non-enzymatic redox-type reactions] lead primarily to chloride ions, with much lesser amounts of chlorite, and very small amounts of ClO_3^- (chlorate) being excreted in urine (the major route of elimination), (3) Subchronic studies using African green monkeys indicated a transient reduction in thyroxine following doses of 100 ppm chlorine dioxide in drinking water, (4) Rabbits exposed to chlorine dioxide in air for 5 hr/day for 4 weeks at 2.5 to 10 ppm suffered bronchopneumonia and increased leukocyte counts. At the lowest dose tested in that study (2.5 ppm) there were only unspecified "reversible pulmonary lesions" detected. (5) A chronic rat drinking water study (duration of 11 months, by Allen and Jandle, 1960) found a number of changes which appear to have been subchronic or subacute in duration. Following treatment with 1, 10, 100, or 1000 mg/L of chlorine dioxide or 10 or 100 mg/L of chlorite, common signs were decreased blood glutathione, osmotic fragility of blood cells, decreased thymidine incorporation in liver and kidney tissues, and increased thymidine incorporation in intestinal mucosa. (6) Several kinds of genetic toxicity tests were performed, and some of these were positive for chlorine dioxide or chlorite, including a mouse micronucleus test using either compound by the ip route. The micronucleus test was negative when chlorite was tested by oral dosing. (7) A drinking water mouse oncogenicity study by Kurokawa *et al.* using sodium chlorite (1986) was determined by investigators to be negative for oncogenicity. A re-analysis of data from the above study by Yokose *et al.* (1987) concluded that "clear evidence of carcinogenic activities of sodium chlorite in B6C3F1 mice was not observed." (8) Water disinfected with unspecified amounts of chlorine dioxide was administered subcutaneously to Sencar mice, followed by application of phorbol myristate acetate (PMA) as a tumor promotor. Chlorine dioxide was stated to have been negative in this test (Bull *et al.*, 1980). (9) A developmental drinking water study by Suh *et al.* (1983) using chlorine dioxide at 0, 1, 10, or 100 ppm reported

a decrement in total implants and live fetuses per dam at 100 ppm, but not at lower dose levels. (10) A non-standard reproduction study in Long-Evans rats by Carlton *et al.* (1987) found no changes in the reproductive parameters examined following treatment with 0, 1, 10, or 100 ppm of sodium chlorite (presumably in drinking water), however T3 and T4 in blood of 100 ppm pups was decreased (apparent NOEL = 10 ppm). (11) A reproduction study by Couri *et al.* (1982) used 0.1, 0.5, or 2.0% sodium chlorite in drinking water. The highest dose led to increased stillbirths and decreased litter size. All groups had reduced crown-rump lengths. No other responses were identified. (12) Female A/J mice were dosed with 0 or 100 ppm chlorite (in drinking water??) from mating through lactation [Moore and Calabrese (1982)]. Pup growth rates and weanling weights were reduced at 100 ppm. Taylor and Pfohl (1985) performed a study in which neonatal rats were exposed to chlorine dioxide either by gavage [14 mg/kg: age of pups exposed not specified, apparently a single dose] or indirectly via milk from dams drinking water with 2, 20, or 100 ppm chlorine dioxide. Gavage-treated pups and pups of dams treated at 100 ppm had decreased locomotor activity and decreased T4 in blood at day 21. Another component of this study suggested delayed locomotor development and reduced brain weights under unspecified treatment conditions. Clinical and epidemiological studies were also reviewed. None of these studies described briefly in this record would appear to address modern data requirements for chlorine dioxide or for chlorite. [REDACTED], 1/24/01 (no worksheet).

50288-018 130836 Cavagnaro, J. and B. H. Keech, "Cytotoxicity testing of biomaterials: agar-overlay screening assay," Hazleton Biotechnologies Corp., 2/17/86, Project No. 2295-102. Ten polymers were treated with chlorine dioxide (6 hr, about 60 mg/L), then aerated for 18 hr prior to placement on agar overlaying Mouse Fibroblast L-929 cells. Cells were stained with neutral red dye prior to exposure to the 1 cm² polymer samples. Decoloration of stained monolayers under the samples represented cytotoxicity. Three trials were conducted. Two polymers were cytotoxic in this assay (Lexan 9440-112 and Lexan 9030-112). All other polymers were negative under study conditions. Study is not required under SB-950 and there is no DPR worksheet. [REDACTED], 1/24/01.

50288-059 115610 "Chlorine dioxide: drinking water issues." Second International Symposium, Houston, TX, May, 1992. This record contains largely reproductions of overlays used in the symposium. The record describes physical characteristics of chlorine dioxide, processing techniques, worker safety information, and brief references to some laboratory animal studies. No worksheet. [REDACTED], 1/24/01.