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Dear Sir or Madam:

On January 11, 1994, FMC Corporation ("FMC") notified EPA of preliminary information relative to a sensory irritation study in mice, via inhalation exposure, conducted with sodium persulfate. In that same letter to EPA, FMC assured the Agency it would be provided with a complete copy of the final, audited report when it became available. This report is enclosed herewith.

FMC is making no claims of confidentiality for this submission.

Sincerely yours,

Linda M Clark

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STUDY TITLE

**Sodium Persulfate (FMC No. 193-1803): Sensory Irritation Study
in Swiss Webster Mice**

TEST SUBSTANCE

Sodium Persulfate

DATA REQUIREMENT

Not Applicable

AUTHOR

M. S. Werley and W. J. Kintigh

STUDY COMPLETION DATE

May 27, 1994

PERFORMING LABORATORY

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LABORATORY PROJECT ID

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Sodium Persulfate (FMC No. I93-1803): Sensory Irritation Study
in Swiss Webster Mice

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The portions of this study conducted by BRRC meet the requirements of U.S. EPA Toxic Substances Control Act (TSCA) Good Laboratory Practice Standards, 40 CFR Part 792, with one exception.

1. The Sponsor was responsible for physical and chemical characterization of the test substance. The purity analysis was not performed according to Good Laboratory Practice Standards. Test material stability analysis was not performed.

This exception was not expected to compromise the integrity of the results and conclusion of the study.

Study Director:

Michael S. Werley
Michael S. Werley, Ph.D.

5/27/94
Date

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Sodium Persulfate (FMC No. I93-1803): Sensory Irritation Study
in Swiss Webster Mice

SUMMARY

The sensory irritation potential of sodium persulfate (CAS No. 7775-27-1) dust was investigated in male ND4 Swiss Webster mice. Groups of 4 mice were exposed (head-only) to sodium persulfate dust for 30 minutes. Sensory irritation was assessed by monitoring the respiratory rate of each animal prior to the exposure, during the exposure, and during a 10-minute recovery period. The animals were observed for 7 days following the exposure. Monitors for toxic effect included respiratory rate changes, clinical observations during and following exposure, and body weight.

Exposure concentrations of 0.26, 0.77, 1.38, and 3.22 mg/l of sodium persulfate dust were measured. The mass median aerodynamic diameters of sodium persulfate particulates generated during exposures were determined to be 9.0, 7.3, 11.7, and 16.0 μm for the 0.26, 0.77, 1.38, and 3.22 mg/l exposure concentrations, respectively, with geometric standard deviations which ranged from 2.8 to 9.0 μm . Mortality was observed in 25, 50, and 100% of the mice from the 0.77, 1.38, and 3.22 mg/l exposure groups, respectively, during the 7-day postexposure recovery period. Exposure-related clinical signs observed during this study included decreased respiratory rate; blepharospasm; lacrimation; perinasal encrustation, discharge, and wetness; periocular encrustation; and unkempt fur. Abnormal gait and whole body tremors were observed in animals exposed to the highest concentrations of sodium persulfate dust (1.38 and 3.22 mg/l) during the 7-day postexposure period. Exposure-related body weight decreases and decreased body weight gains were observed during the study.

During exposure, the waveform of the respiratory cycle changed from that usually seen in air-exposed animals to include a notching or lengthening of the expiratory portion of the waveform which resulted in a decreased respiratory rate. Such a characteristic waveform is considered to be an indicator of the sensory irritation response. At high exposure concentrations of sodium persulfate dust, the notching was more pronounced and resulted in a decreased respiratory rate. During the recovery period, mean respiratory rates remained depressed in all exposure groups.

A concentration-response curve was plotted with the common logarithm of the exposure concentration as the independent variable and the percent decrease in respiratory rate as the dependent variable. The RD50, or concentration of sodium persulfate dust which produced a 50 percent decrease in respiratory rate, was determined to be 2.25 mg/l, with a 95% confidence interval of 0.95-3.22 mg/l. A predicted safe exposure limit for sodium persulfate dust can be calculated as 0.068 mg/l (68 mg/m³) based upon 0.03 RD50, which has been proposed as a predictor of an acceptable Threshold Limit Value (TLV) (Alarie, 1981). Based on the relatively high estimated TLV, sodium persulfate is considered a slight sensory irritant.

OBJECTIVE

The objective of this study was to evaluate sensory irritation in mice during a single 30-minute exposure to sodium persulfate dust. Sensory irritation was evaluated by determination of a concentration-dependent decrease in respiratory rate. From the concentration-response curve, the concentration which produced a 50 percent decrease in respiratory rate (RD50) was calculated.

BACKGROUND INFORMATION

Sensory irritation occurs when airborne chemicals impinging on the surface of the cornea or upper airways cause stimulation of free nerve endings of the afferent trigeminal nerve, which evokes a painful, burning sensation (Alarie *et al.*, 1973). A series of physiological reflex reactions occurs that includes an inhibition of respiratory rate, as a result of a lengthened expiratory phase of breathing. Alarie (1966) demonstrated that this depression in respiratory rate is dependent on the airborne concentration of the sensory irritant.

A concentration-response curve can be obtained by plotting the percent decrease in respiratory rate from control against the logarithm of the concentration of the chemical. From such plots, the concentration which produces a 50 percent decrease in respiratory rate (RD50) can be determined. RD50 values for different compounds can then be compared as to their ability to evoke sensory irritation. It has been shown that a relationship exists between the RD50 obtained in mice and the human response (burning sensation of the eyes, nose, and throat) (Alarie, 1966, 1973; Kane *et al.*, 1979).

TARGET CONCENTRATION SELECTION

During 2 preliminary exposures, groups of 2 mice each were exposed to an airborne concentration of sodium persulfate dust. The airborne concentration for the second preliminary exposure was then determined gravimetrically and the target concentration for the first definitive exposure was chosen based upon the data from these preliminary exposures. Other exposure concentrations were then chosen so that a concentration-response curve could be constructed.

MATERIALS AND METHODS

The protocol detailing the design and conduct of this study are included in Appendix 2. Protocol deviations are also included in Appendix 2. This study was conducted to comply with the standard test method for estimating sensory irritation of airborne chemicals, Annual Book of ASTM Standards, Designation E981-84, American Society for Testing and Materials, Philadelphia, PA (1984).

Test Substance

Two 1-pound clear glass bottles of sodium persulfate, a white crystalline powder (Lot # E8317-70-030915, CAS No. 7775-27-1), were received on November 10, 1993, from FMC Corporation (FMC Toxicology Laboratory, Princeton, NJ) and assigned BRRC Sample No. 56-417-1 and -2. A second sample of test substance consisting of a clear glass bottle containing 2.816 kg (gross weight) of sodium persulfate powder (Lot # E8317-71-12293, CAS No. 7775-27-1) was

received on December 8, 1993, from FMC Corporation (FMC Toxicology Laboratory, Princeton, NJ) and assigned BRRC Sample No. 56-434. The purity of the test substance was specified as 99% in the MSDS and specified as 98.48% in the Sponsor's certificate of analysis. BRRC Sample No. 56-417 was used in the preliminary level setting exposures, before animal testing was begun. BRRC Sample No. 56-434 was used in the sensory irritation exposures.

Animals and Husbandry

Twenty-eight male ND4 Swiss Webster mice which arrived on November 16, 1993 from Harlan Sprague Dawley, Inc. (Indianapolis, IN) were used for sensory irritation studies consisting of 2 preliminary exposures and 4 exposure groups. All animals were designated by the supplier to be approximately 28 days old and 20-22 g upon arrival.

Animals were housed in a Relocatable Containment System® unit (Hazleton Systems, Inc., Aberdeen, MD) in Room 164D from arrival to termination of the study except during exposures. All animals were assigned unique numbers and identified by cage tags. Animals considered available for use in the study were identified by a tail marking or tattooing procedure.

The animals were housed 2/cage in stainless steel, wire mesh cages 23.5 x 20 x 18 cm. DACB® (Deotized Animal Cage Board; Shepherd Specialty Papers, Inc.) was placed under each cage and changed regularly. Cages were changed and sanitized at least once every 2 weeks. An automatic timer was set to provide fluorescent lighting for a 12-hour photoperiod (approximately 0500 to 1700 hours for the light phase). Temperature and relative humidity were recorded (Cole-Parmer Hygrothermograph® Seven-Day Continuous Recorder, Model No. 8368-00, Cole-Parmer Instrument Co., Chicago, IL). Temperature was routinely maintained at 66-77°F; relative humidity was routinely maintained at 40-70%. Any minor exceptions to these specified ranges were noted in the raw data.

Tap water (Municipal Authority of Westmoreland County, Greensburg, PA) was available ad libitum except during exposures and was delivered using water bottles and by an automatic watering system with demand control valves mounted on each rack. Water analyses were provided by the supplier, and Chester Lab (contaminants, aflatoxin) and RJ Lee Group, Inc. (asbestos) at regular intervals. EPA standards for maximum levels of contaminants were not exceeded. Pelleted, certified AGWAY® PROLAB® Animal Diet Rat, Mouse, Hamster 3000 (Agway Inc.) was available ad libitum except during exposures. Analyses for chemical composition and possible contaminants of each feed lot were performed by Agway Inc., and the results were included in the raw data.

Animal Acclimation

The animals were acclimated to laboratory conditions for at least 14 days prior to exposure to sodium persulfate dust. Table 1 gives the dates of animal receipt, dates of exposure, the age of animals at exposure, and sacrifice dates.

Animal Exposure and Measurement of Respiratory Variables

Mice were exposed by a head-only technique in Room 147. A diagram of the equipment used to monitor respiratory variables is shown in Figure 1. Mice were placed in individual plethysmographs with their heads protruding through flexible rubber neck seals into the center of the glass exposure chamber (vol. = 2.3 liters). The plethysmographs were closed with rubber stoppers to prevent air leaks. Chamber air was obtained from room air, and the airflow rate through the exposure chamber was maintained at 20-30 l/min.

Attached to the top of each plethysmograph was a Gaeltec Gas Differential Pressure Transducer (Model 8T-2, Medical Measurements Inc., Hackensack, NJ) which sensed pressure changes due to the inspiration and expiration of the animal (Figure 1). These respiratory signals were then amplified and displayed on a polygraph recorder (Western Graphtec, Inc., Irvine, CA).

Respiratory signals were converted to digital representations at 200 samples/second by a computer. Every 15 seconds, the respiratory rate for each animal was written to a computer file on disk of an IBM-AT personal computer (Burleigh-Flayer *et al.*, 1988). Respiratory frequency (f) was determined by counting the number of respiratory waves/minute (breaths/minute).

After the mice were placed in the body plethysmographs, they were allowed an acclimation period of at least 10 minutes. Baseline respiratory values of the mice were then determined during a 10-minute preexposure period while being exposed to room air drawn through the chamber. Respiratory variables were collected continuously during the 10-minute preexposure period, the 30-minute exposure period, and the 10-minute recovery period. During the 10-minute recovery period, only room air was introduced into the exposure chamber.

Administration of Test Substance

Aerosol Generation

Sodium persulfate dust was metered from an Accurate auger/feeder (Accurate Dry Material Feeders, Whitewater, WI) using a 3/8-inch diameter rod auger operated at a constant rotational rate for each exposure. Sodium persulfate dust metered from the Accurate feeder tube was introduced into a 1-inch glass inlet tube through a tapered glass funnel and venturi nozzle apparatus. As the powdered test substance dropped through the funnel and venturi nozzle into the glass tube, agitation and dispersion of the material were provided by pressurized air introduced into the end of the tube. Pressure in the air line was maintained at approximately 2.0 psi and was regulated using a pressure regulator (PSIG) connected to the in-house air supply line. A diagram of generation apparatus and exposure chamber is shown in Figure 2.

The particulate generation apparatus (t-tube) was maintained under negative pressure so that airborne particulates of sodium persulfate dust were drawn into the exposure chamber. Various exposure concentrations of sodium persulfate aerosol were generated by adjusting the auger feed rate and chamber airflow rate at 20-30 l/min. Airflow through the exposure chamber (negative pressure) was maintained using the in-house vacuum air line.

Exhaust air was passed through a particulate sump, a water filter, a charcoal filter, and glass flowmeter, before being conducted to the outside.

Chamber Atmosphere Measurements

Chamber concentrations (including preliminary exposures) were determined 2-3 times during each exposure by standard gravimetric techniques. A sample of chamber air was drawn from a port on the top of the exposure chamber. Sample collection times ranged from 5 to 9 minutes. A glass fiber filter (25 mm, type A-E; Gelman Instrument Co., Ann Arbor, MI) contained in a filter holder was used to collect the sodium persulfate dust. The filter cassette was connected in series to a dry gas meter (Rockwell International, Pittsburgh, PA), a critical orifice, and a vacuum pump (Terracon Corp., Waltham, MA). The nominal concentration was calculated by dividing the total amount of sodium persulfate dust delivered from the Accurate feeder to the chamber by the total chamber airflow (airflow/minute x exposure duration in minutes).

During exposures, characteristics of the particle distribution were measured using an Eight-Stage Marple Personal Cascade Impactor (Model 298, Andersen Samplers Inc., Atlanta, GA) equipped with an In-Line Adapter (Model 290-IA, Andersen Samplers Inc., Atlanta, GA). The impactor airflow rate was approximately 1.4 l/min and the sample collection time was 5 minutes. Eight stages of the Marple Impactor were charged with 34 mm Mylar collection substrates (Sierra Model C-290-MY, Andersen Samplers Inc., Atlanta, GA), which had been coated, using an impaction greasing template (Model 290-IGT, Andersen Samplers Inc., Atlanta, GA), with Dow Corning 316 Silicone Release Spray (Dow Corning Corporation, Midland, MI). The backup filter plate was charged with a single, uncoated 34 mm polyvinyl chloride filter (Sierra Model F-290-P5). Following sample collection, the filters were assayed gravimetrically. The mass median aerodynamic diameter and geometric standard deviation were determined for each exposure atmosphere using a probit analysis method (Finney, 1964).

Chamber temperature and room air relative humidity were recorded using a Fluke 51 K/J thermometer (John Fluke Manufacturing Company, Everett, WA) and an Airguide humidity indicator (Airguide Instrument Co., Chicago, IL), respectively. Temperature and relative humidity measurements were recorded 2-6 times during each exposure (including preliminary exposures).

Observations and Measurements

Study Design

Animals were randomly assigned to 4 exposure groups, for exposure to differing exposure concentrations of sodium persulfate dust. During the exposure period and immediately following each exposure, animals were observed for clinical signs of toxicity for up to 1 hour postexposure. After the return of each exposure group to the animal room, animals were observed individually once daily for clinical signs during a 7-day postexposure period.

In-life Evaluations

All animals were visually examined before placement into the body plethysmographs. All animals were individually observed for signs of toxic effects during the exposure, following the exposure, and daily for 7 days postexposure. Animals were observed for signs of irritation (periocular wetness, perinasal wetness) and/or toxicity upon removal from the plethysmograph and once a day for 7 days following the exposure. In addition, daily mortality checks were performed each afternoon.

Body weight data were collected for all animals on the morning prior to initiation of the first exposure and on postexposure Day 7. On postexposure Day 7, animals were sacrificed by CO₂ asphyxiation. No animal necropsies were performed.

Data Analyses

A preexposure value for respiratory rate of each mouse was calculated by averaging the approximately 40, 15-second preexposure intervals. Percent changes from the mean preexposure value were calculated for each 15-second interval of the exposure period and the 10-minute recovery period. A percent decrease in respiratory rate was determined by averaging these changes during the 15-second exposure intervals, when the decrease had reached a sustained maximum or plateau. A plateau response was defined as a maximal percent decrease sustained for at least 1 minute (ASTM, 1984). A mean percent decrease for all 4 mice was then calculated. Linear regression was performed on the data, with the common logarithm of the exposure concentration as the independent variable and the mean percent decrease in the respiratory rate for 4 animals as the dependent variable, using the method of least squares (Draper and Smith, 1966). From the concentration-dependent decrease of respiratory rate regression line, the concentration which produced a 50 percent decrease in respiratory frequency (f) was calculated along with a 95 percent confidence interval (Draper and Smith, 1966).

RETENTION OF RECORDS

All raw data, documentation, the protocol and any amendments, specimens, and a copy of the final report generated as a result of this study will be retained in the BRRC Archives for at least 5 years. A reserve sample of test substance from each container used during the study will also be stored in the BRRC Archives.

RESULTS AND DISCUSSION

Chamber Atmosphere

Detailed results and discussion of the chamber atmosphere measurements are included in Appendix 1.

Preliminary exposures were conducted as a range-finder for the main study. During the preliminary studies suitable methods of test substance generation and useful exposure concentrations for the initiation of the sensory irritation response were determined. The first probe study demonstrated that use of a chromatography tank would not be useful to generate airborne exposure

concentrations needed to initiate the sensory irritation response. The second probe study showed that a mean exposure concentration of 0.34 mg/l would produce the sensory irritation response in mice. Concentrations of sodium persulfate dust generated during the main study are presented in Appendix 1. The mean exposure concentrations (\pm SD) of sodium persulfate generated were 0.26 (\pm 0.07), 0.77 (\pm 0.20), 1.38 (\pm 0.02), and 3.22 (\pm 0.99) mg/l. The nominal concentrations were calculated for each exposure from the quantity of test substance delivered and the chamber airflow rate. The nominal concentrations were 35.6, 167.8, 386.7, and 642.2 mg/l, respectively, for the 0.26, 0.77, 1.38, and 3.22 mg/l exposures.

Particle sizes determined for sodium persulfate dust were 9.0, 7.3, 11.7, and 16.0 μ m for the 0.26, 0.77, 1.38, and 3.22 mg/l exposures, respectively. The geometric standard deviations for these exposures were 9.0, 3.0, 2.8, and 3.6 μ m for the 0.26, 0.77, 1.38, and 3.22 mg/l exposures, respectively.

The chamber temperature and relative humidity were measured during each exposure. The chamber temperature had a range of 20.8-21.5°C, and the room air relative humidity ranged from 48 to 52% (Appendix 1, Table 2).

Clinical Observations and Mortality

Summaries of the clinical observations are presented in Table 3. During the first probe study, animals had no clinical signs; this lack of signs persisted following exposure for the 7 Day postexposure period. During the second probe study, animals had white powder on the face. Following exposure, no signs were observed, but on Day 1 periocular wetness was observed. From Days 2-7, these animals appeared normal.

During exposure to 0.26 mg/l of sodium persulfate dust, blepharospasm and white powder on fur were noted in all animals, and 4 of 4 mice exhibited lacrimation. One of 4 mice exhibited lacrimation immediately following the exposure. All animals had periocular wetness, blepharospasm, and white powder on the face at the postexposure observation. All mice were normal during the postexposure period (Days 1-7).

Similar to the 0.26 mg/l exposure, 0.77 mg/l of sodium persulfate dust caused blepharospasm and lacrimation in all animals during exposure. Following the exposure, all animals had lacrimation, white powder and unkempt fur on the face. One mouse exhibited decreased respiration and a white eye opacity of the right eye, and the same mouse had a red opacity of the left eye. On postexposure Day 1, 2 mice had blepharospasm, and 1 animal was found dead. On Days 3-7, all remaining animals were normal.

During exposure to 1.38 mg/l of sodium persulfate dust, all animals exhibited blepharospasm, lacrimation, and white powder on the fur. Immediately after the exposure, 1 mouse had periocular encrustation and 4 of 4 had perinasal encrustation, lacrimation and unkempt fur. One mouse exhibited a white opacity of both eyes. On Day 1 postexposure, 1 animal had a tremor of the whole body and an abnormal gait, and all animals had blepharospasm of 1 or both eyes. At Day 2, these clinical signs persisted. At Day 3, 1 animal exhibited whole body tremors, blepharospasm, and abnormal gait; 2 mice were normal; and 1 mouse was found dead. On Day 4, 1 mouse was found dead while 2 mice were normal. The remaining 2 mice were normal on Days 5-7.

During exposure to 3.22 mg/l of sodium persulfate dust, animals exhibited blepharospasm, lacrimation, head tremors, and white powder on the fur. Later, near the end of the exposure period, animals had perinasal discharge and wetness. Immediately following the exposure, all animals had periocular encrustation and blepharospasm. All animals were moribund and 1 mouse appeared to be unconscious. Three of 4 had whole body tremors and decreased respiration, and 1 mouse exhibited abdominal respiration. Later (about 3.0 hours after exposure), the unconscious mouse was found dead after regaining consciousness in the interim time period. On Day 1 postexposure, another mouse was found dead. The 2 remaining mice had periocular encrustation, unkempt fur, whole body tremors, abnormal gait, and blepharospasm. On Day 2, the remaining mice exhibited tremors. On Day 3, 1 mouse was found dead, and the other mouse had tremors. The last mouse in this group was found dead on Day 4.

In summary, exposure to sodium persulfate dust caused mortality at the 0.77 (1 of 4), 1.38 (2 of 4), and 3.22 (4 of 4) mg/l exposure concentrations. Exposure-related clinical signs included blepharospasm, lacrimation, perinasal encrustation, perinasal discharge and wetness, periocular encrustation, unkempt fur, abnormal gait, whole body tremors and decreased respiration rate. The ocular opacity finding, observed in a few animals exposed to 0.77 and 1.38 mg/l of sodium persulfate dust, is not believed to be exposure related due to the lack of a concentration-related response. The observed ocular opacities may have resulted from high velocity air laden with the test substance being conducted past the animals' eyes as they were housed in the body plethysmographs. This airstream flowing over the animals may have caused a reversible drying of the cornea.

Body Weights

Individual animal body weight data are presented in Table 2.

Probe study animals had mean body weight gains of 0.45 and 0.05 grams, respectively, on Day 7 following the first and second probe studies.

Mean body weight gains of 0.55 and 1.13 g were observed for the 0.26 and 0.77 mg/l exposure groups, respectively, on postexposure Day 7. On postexposure Day 7, the mean body weight gain in the 1.38 mg/l group was -0.80 g. A decrease in mean body weight and body weight gain was noted in male ND4 Swiss Webster mice exposed to 1.38 mg/l sodium persulfate dust at Day 7 postexposure, and is believed to be related to sodium persulfate exposure. However, a trend in the body weight and body weight gain data is difficult to assess since a limited number of data points are available to make this judgment, due to the mortality in the highest exposure group.

Respiratory Frequency

The individual percent decrease in respiratory rate data are presented in Table 4. Mean time-response curves for f (respiratory frequency) during exposure to different concentrations of sodium persulfate dust are shown in Figure 3. The maximal percent decrease in f for each sodium persulfate exposure group, along with the exposure intervals used to determine the

percent decrease, can be seen in Table 5. These data are shown in Figure 4, with the common logarithm of the exposure concentration as the independent variable (X) and the mean percent decrease in f from baseline as the dependent variable (Y).

Mean time-response curves for f (respiratory frequency) during exposure to different aerosol concentrations of sodium persulfate are shown in Figure 3. The decrease in f resulted from a lengthening of the expiratory phase of breathing. During exposure, the waveform of the respiratory cycle changed from that usually seen in air-exposed animals to include a notching or lengthening of the expiratory portion of the waveform which results in a decreased respiratory rate. Representative waveforms are shown in Figure 5. Such a characteristic waveform is considered to be an indicator of the sensory irritation response. At high exposure concentrations of sodium persulfate dust, the notching was more pronounced and resulted in a decreased respiratory rate. The depression in f occurred with the onset of sodium persulfate exposure, reaching a maximum about midway through the exposure period (15-20 minutes). However, individual animals in each of the 0.26, 0.77, 1.38, and 3.22 mg/l exposure groups exhibited respiratory rate decreases which were atypical of responses observed for the group. For example, in the 0.77 and 1.38 mg/l exposure groups, 1 animal in each group exhibited respiratory rate decreases of 89.1 and 80.3%, respectively. Two animals in the 3.22 mg/l exposure group had decreases of 81.4 and 91.6%. In these same groups just described, however, other individuals had an attenuated response. In the 0.77, 1.38, and 3.22 mg/l groups, some individual mice had respiratory rate decreases of only 13.2, 13.5, and 17.6%, respectively. This wide range of respiratory rate decreases in animals from the same exposure group is indicative of great biologic variability in the sensory irritation response upon sodium persulfate dust exposure. While such an observation is not very common in these studies, this finding cannot provide any more expansive conclusions regarding the test substance.

During exposure, once the maximal response was reached, it was sustained for the duration of the exposure period. Following the exposure period, the respiratory frequency of mice exposed to sodium persulfate dust remained depressed during the 10-minute recovery period. For all exposure groups, there was no increase or only a slight increase in the respiratory rate during the recovery period (Figure 3). Normally, removal of the test substance from the exposure chamber atmosphere results in a rebound in the respiratory rate towards control levels. However, this rebound was not observed in this study.

The individual percent decrease in respiratory rate data are presented in Table 4. The maximal percent decrease in f for each sodium persulfate exposure group, along with the exposure intervals used to determine the percent decrease, can be seen in Table 5.

During the first preliminary exposure, the exposure was aborted after about 18 minutes since a marked response was not observed and too much test material was being used in the generation apparatus. However, abortion of the procedure at that time was still too early to observe significant changes in the respiratory rate. During the second preliminary exposure, the maximal respiratory rate decrease (calculated manually) was approximately 35.9% in 1

animal. A notching of the respiratory waveform indicative of the sensory irritation response was observed in this animal. An equipment malfunction during data collection caused the loss of the respiratory signal in the second animal.

Mean respiratory rate decreases in mice exposed to sodium persulfate dust were 9.3, 39.2, 36.3, and 56.2% for the 0.26, 0.77, 1.38, and 3.22 mg/l exposure concentrations, respectively. These data are shown in Figure 4, with the common logarithm of the exposure concentration as the independent variable (X) and the mean percent decrease in f from baseline as the dependent variable (Y). This relationship was found to be linear by analysis of variance. The correlation coefficient between these two variables was 0.955, indicating that the two variables are strongly related. Since analysis of variance indicated that the linear model was adequate, the equation of the line was calculated so that an estimate of the RD50 could be determined. Using the method of least squares regression analysis, the equation of the "best-fit" line was determined to be $Y = 40.3803(\log X) + 35.7628$. Using analysis of variance, the slope of the line was significantly different from zero. The concentration which produced a 50% decrease in f or RD50 calculated from this equation was 2.25 mg/l (2252 mg/m³) with a 95 percent confidence interval of 0.95-3.22 mg/l for the true mean value of Y for a given X.

CONCLUSIONS

Inhalation exposures for 30 minutes to sodium persulfate dust produced a decrease in respiratory rate in ND4 Swiss Webster mice, indicating a sensory irritation response. In sodium persulfate exposed animals, dust concentrations of 0.26, 0.77, 1.38, and 3.22 mg/l produced approximate mean percent decreases in the respiration rate of 9.3, 39.2, 36.3, and 56.2%, respectively. During each exposure, much individual biologic variation in the respiratory response was noted as indicated by the range of respiratory rate decreases for animals in each group. The greatest range of response was observed in the 0.77 mg/l group, with 1 animal exhibiting a respiratory rate decrease of 89.1% while another animal showed a 13.2% decrease. Similarly, large ranges of response were also observed in animals from the 1.38 and 3.22 mg/l exposure groups. An evaluation of animal position by plethysmograph location in the exposure chamber indicates that the observed respiratory rate variation is not a function of animal position. In 4 exposure groups exposed to differing sodium persulfate concentrations, large decreases in respiratory rate were recorded for animals in plethysmographs 2, 3, and 4. These decreases were not quite as large for animals housed in plethysmograph 1, but, in some cases, the decreases for animals in plethysmograph 1 are still greater than those observed for animals in the other plethysmographs. This observation suggests that plethysmograph location had no impact upon the respiratory response attained under the conditions of this study.

Exposure to the sodium persulfate dust produced a characteristic notching of the recorded respiratory waveform coincident with a pause in the expiratory phase of the respiratory cycle, indicative of sensory irritation. It appears as though a maximal response was observed in approximately 15-20 minutes. Following the 30-minute exposure period, respiratory rates remained depressed

in all exposure groups. At the end of the recovery period, respiratory rates were well below control respiratory rates obtained during the preexposure period in the 0.77, 1.38, and 3.22 mg/l exposure groups, and little recovery was apparent.

Mortality response was observed in 1/4, 2/4, and 4/4 mice from the 0.77, 1.38, and 3.22 mg/l exposure groups, respectively. Exposure-related clinical findings observed during this study included decreased respiratory rate; blepharospasm; lacrimation; perinasal encrustation, discharge, and wetness; periocular encrustation; and unkempt fur. Abnormal gait and whole body tremors were observed in animals exposed to the highest concentrations of sodium persulfate dust (1.38 and 3.22 mg/l). Body weight decreases and attenuated body weight gains were observed during the study.

The RD50 for sodium persulfate exposures, derived from the "best fit" linear regression line, was 2.25 mg/l. Mean respiratory rate decreases during exposure to sodium persulfate dust ranged from 9.3 to 56.2% for exposure concentrations which ranged from 0.26 to 3.22 mg/l. Analysis of variance, used to test linearity and slope of the linear regression line, showed that the data approximated a straight line, and the slope of the line was significantly different from zero.

The 0.03 RD50 level has been proposed as a predictor of an acceptable Threshold Limit Value (TLV) (Alarie, 1981) due to a good correlation between the 0.03 RD50 and the TLVs for a wide variety of chemicals (Kane *et al.*, 1979; Alarie, 1981). Based on this proposed relationship, a predicted safe exposure limit for sodium persulfate dust can be calculated as 0.068 mg/l (68 mg/m³). Based on the relatively high estimated TLV, sodium persulfate is considered a slight sensory irritant.

REVIEW AND APPROVAL

Study Director: Michael S. Werley 5/27/94
Michael S. Werley, Ph.D. Date

Senior Manager: Heather D. Burleigh-Flayer 5/27/94
Heather D. Burleigh-Flayer, Ph.D. Date

Director: John P. Van Miller 5/27/94
John P. Van Miller, Ph.D., DABT Date

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Study Director: M. S. Werley
Study Coordinator: M. L. Steel
Supervisors: J. C. Norris
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Additional personnel are listed in the raw data.

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TABLE 1
SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

DATES OF ANIMAL RECEIPT, DATES OF EXPOSURE, AGE OF ANIMALS
AT EXPOSURE, AND SACRIFICE DATES

Concentration of Sodium Persulfate Dust (mg/l)	Date Received	Date of Exposure	Approximate Age at Exposure (Days)	Terminal Sacrifice Date
0.26	11-16-93	12-16-93	62	12-23-93
0.77	11-16-93	12-14-93	60	12-21-93
1.38	11-16-93	12-14-93	60	12-21-93
3.22	11-16-93	12-16-93	62	12-23-93

TABLE 2
 SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

INDIVIDUAL BODY WEIGHT DATA (GRAMS)

Concentration of Sodium Persulfate Dust (mg/l)	Animal Number	<u>Body Weight (g) at Day</u>		Body Weight Change (g)
		0	7	
0.26	93-10237	26.3	26.1	-0.2
	93-10238	23.1	23.4	+0.3
	93-10257	26.3	27.5	+1.2
	93-10258	23.9	24.8	+0.9
0.77	93-10255	23.1	23.9	+0.8
	93-10256	23.2	24.5	+1.3
	93-10261	23.8	*	---
	93-10262	25.0	26.3	+1.3

TABLE 2 (Continued)
 SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

INDIVIDUAL BODY WEIGHT DATA (GRAMS)

Concentration of Sodium Persulfate Dust (mg/l)	Animal Number	Body Weight (g) at Day		Body Weight Change (g)
		0	7	
1.38	93-10259	24.7	23.7	-1.0
	93-10260	25.6	25.0	-0.6
	93-10251	25.5	*	---
	93-10252	25.7	*	---
				S.D. 0.283
3.22	93-10241	26.0	*	
	93-10239	24.3	*	
	93-10245	26.0	*	
	93-10246	24.2	*	

* - Animals died before postexposure Day 7.

TABLE 3
 SODIUM PERSULFATE (FMC NO. 193-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

SUMMARY OF CLINICAL SIGNS AND MORTALITY DATA

Concentration of Sodium Persulfate Dust (mg/l)	Clinical Observations Following Exposure	Total Incidence of Mortality During and Following Exposure
0.26	<p>At 9 minutes into the exposure period, mice had white powder on the fur of the face, and blepharospasm. Lacrimation was observed at 19 minutes into exposure. These signs persisted throughout the remaining exposure and recovery periods. Immediately following exposure, all animals had periorcular wetness, 1 mouse had lacrimation, all animals had blepharospasm, and all animals had white powder on the face. All animals appeared normal during the 7-day postexposure period.</p>	0/4
0.77	<p>At 10 minutes into the exposure period, mice had white powder on the fur of the face, and blepharospasm. Lacrimation was observed at 20 minutes into exposure. These signs persisted throughout the remaining exposure and recovery periods. Immediately following exposure, all animals had lacrimation, white powder and unkempt fur on the face. One mouse had decreased respiration, a white opacity of the right eye, and a red opacity of the left eye. On postexposure Day 1, 1 mouse was normal, 1 mouse was found dead, and 2 mice had blepharospasm of 1 eye. On Day 2, the Day 1 blepharospasm findings persisted. On Days 3-7, all animals appeared normal.</p>	1/4

TABLE 3 (Continued)
SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

SUMMARY OF CLINICAL SIGNS AND MORTALITY DATA

Concentration of Sodium Persulfate Dust (mg/l)	Clinical Observations Following Exposure	Total Incidence of Mortality During and Following Exposure
1.38	At 10 minutes into the exposure period, mice had white powder on the fur of the face, blepharospasm and lacrimation. These signs persisted throughout the remaining exposure and recovery periods. Immediately following exposure, all animals had perinasal encrustation, lacrimation and unkempt fur. One mouse had periorbital encrustation, another mouse had a white opacity of both eyes. On postexposure Day 1, 1 mouse had whole body tremors and abnormal gait. All animals had blepharospasm of 1 or both eyes. These signs persisted on Day 2. On Day 3, 1 mouse was found dead, another mouse had whole body tremors abnormal gait, and blepharospasm of both eyes. Two mice were normal. On Day 4, 1 mouse was found dead, and 2 mice were normal. On Days 5-7, the remaining 2 mice were normal.	2/4

TABLE 3 (Continued)
SODIUM PERSULFATE (FMC NO. 193-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

SUMMARY OF CLINICAL SIGNS AND MORTALITY DATA

Concentration of Sodium Persulfate Dust (mg/l)	Clinical Observations Following Exposure	Total Incidence of Mortality During and Following Exposure
3.22	<p>At 9 minutes into the exposure period, mice had white powder on the fur of the face, blepharospasm, lacrimation and head tremors. At 29 minutes into exposure, perinasal discharge and wetness was also noted. These signs persisted throughout the remaining exposure and recovery periods. Immediately following exposure, all animals were moribund, and all animals had blepharospasm and periorcular encrustation. Three mice had whole body tremors and decreased respiration. One mouse had abdominal breathing. One mouse was not conscious upon removal from the chamber; this mouse later died at about 3 hours after exposure after regaining consciousness. On postexposure Day 1, 1 mouse was found dead, 2 mice had abnormal gait, whole body tremors, unkempt fur, periorcular encrustation and blepharospasm of 1 or both eyes. On Day 2, 2 mice had tremors. On Day 3, 1 mouse had tremors and 1 mouse was found dead. On Day 4, 1 mouse was found dead.</p>	4/4

TABLE 4
 SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

INDIVIDUAL PERCENT DECREASE IN RESPIRATORY RATE

Exposure Concentration of Sodium Persulfate Dust (mg/l)	Animal Number	% Decrease in Respiratory Rate
0.26	93-10237	8.6
	93-10238	2.6
	93-10257	13.3
	93-10258	12.4
0.77	93-10255	33.1
	93-10256	13.2
	93-10261	89.1
	93-10262	21.3
1.38	93-10259	13.5
	93-10260	19.2
	93-10251	32.3
	93-10252	80.3
3.22	93-10241	34.2
	93-10239	81.4
	93-10245	91.6
	93-10246	17.6

TABLE 5
SODIUM PERSULFATE (FMC NO. 193-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

MEAN MAXIMAL PERCENT DECREASE IN RESPIRATORY RATE OF MICE
AT EACH EXPOSURE CONCENTRATION

Exposure Concentration of Sodium Persulfate (mg/l) (X)	Mean Maximal Percent Decrease in Respiratory Rate (Y)
0.26	9.3 ± 4.86
0.77	39.2 ± 34.27
1.38	36.3 ± 30.36
3.22	56.2 ± 35.88

Equation of the Line (using the mean group response): $Y = 40.3803(\log X) + 35.7628$

Correlation Coefficient (using the mean group response): $r = 0.955$

RD50: 2.25 mg/l (2252 mg/m³)

RD50 95% Confidence Interval: 0.95-3.22 mg/l (True mean of Y for a given X)

Test for Linearity: Relationship is linear ($p < 0.05$)

Test for Slope: Significantly different from zero ($p < 0.05$)

15-Second Intervals Used to Determine the Maximal Percent Decrease in Respiratory Rate: 140-160
(Intervals 1-41 are preexposure intervals).

FIGURE 1
SODIUM PERSULFATE (FMC NO. 193-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

SCHEMATIC OF THE EQUIPMENT USED TO MONITOR RESPIRATORY VARIABLES DURING EXPOSURE

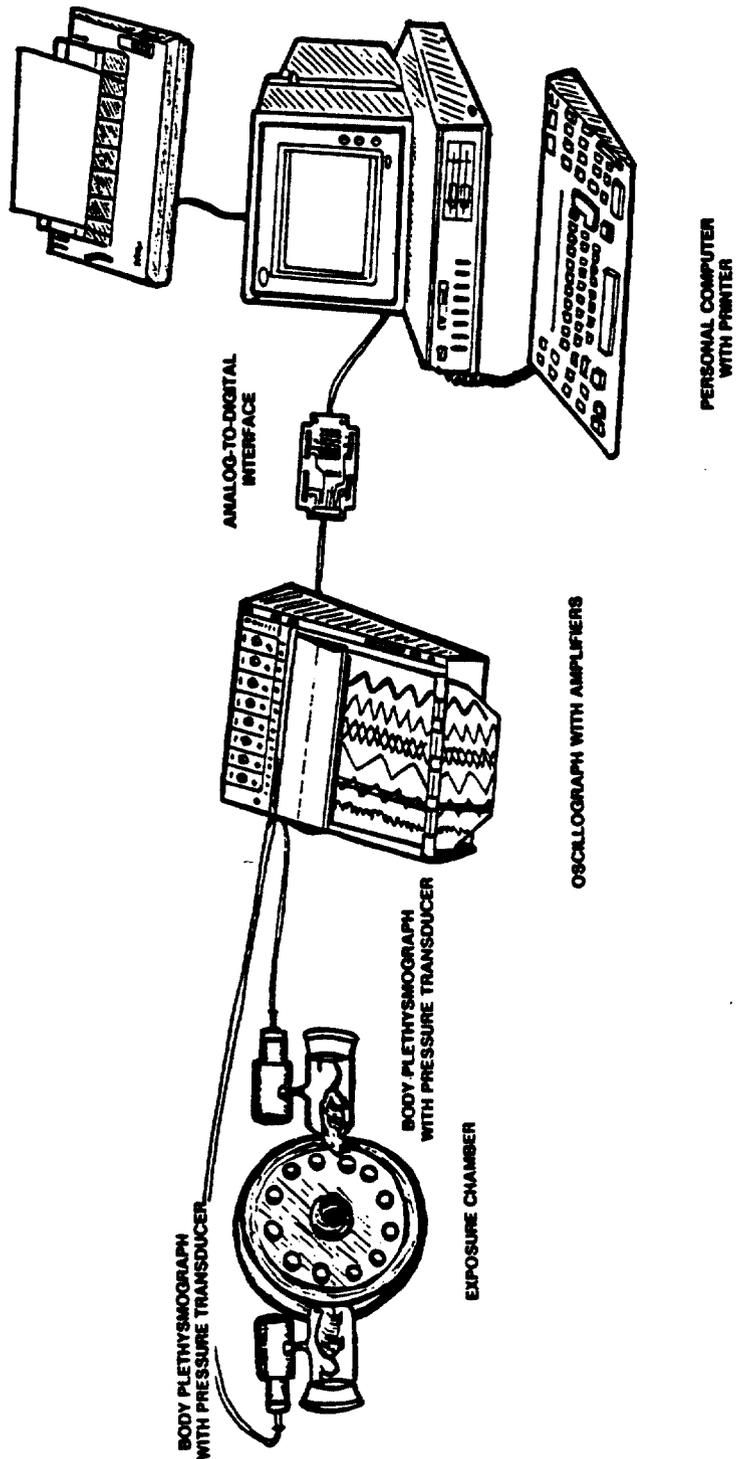


FIGURE 2
SODIUM PERSULFATE (FMC NO. 193-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

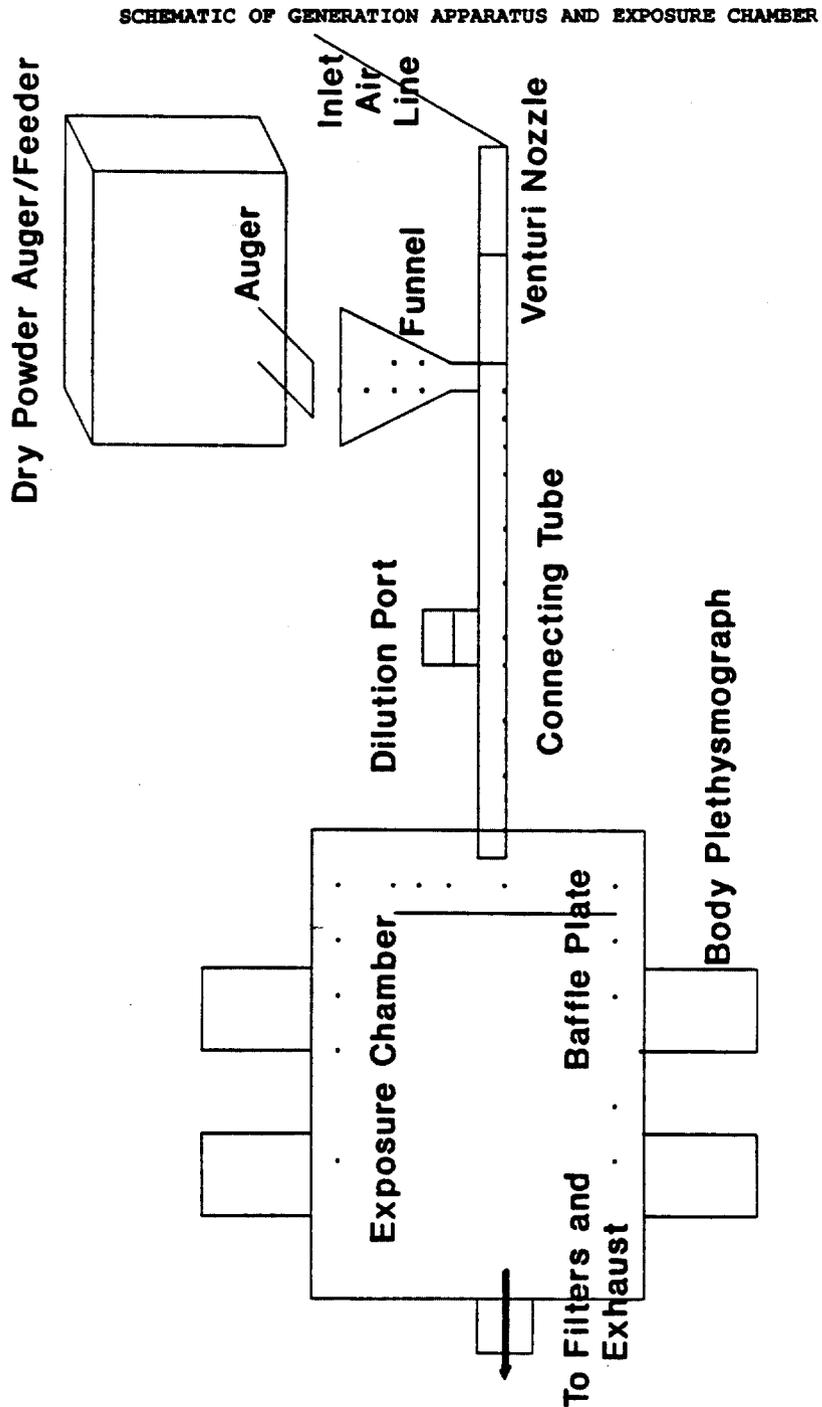


Figure 3
Sodium Persulfate (I93-1803):
Sensory Irritation Study in Swiss Webster Mice
Mean Time-Response Patterns during Exposure

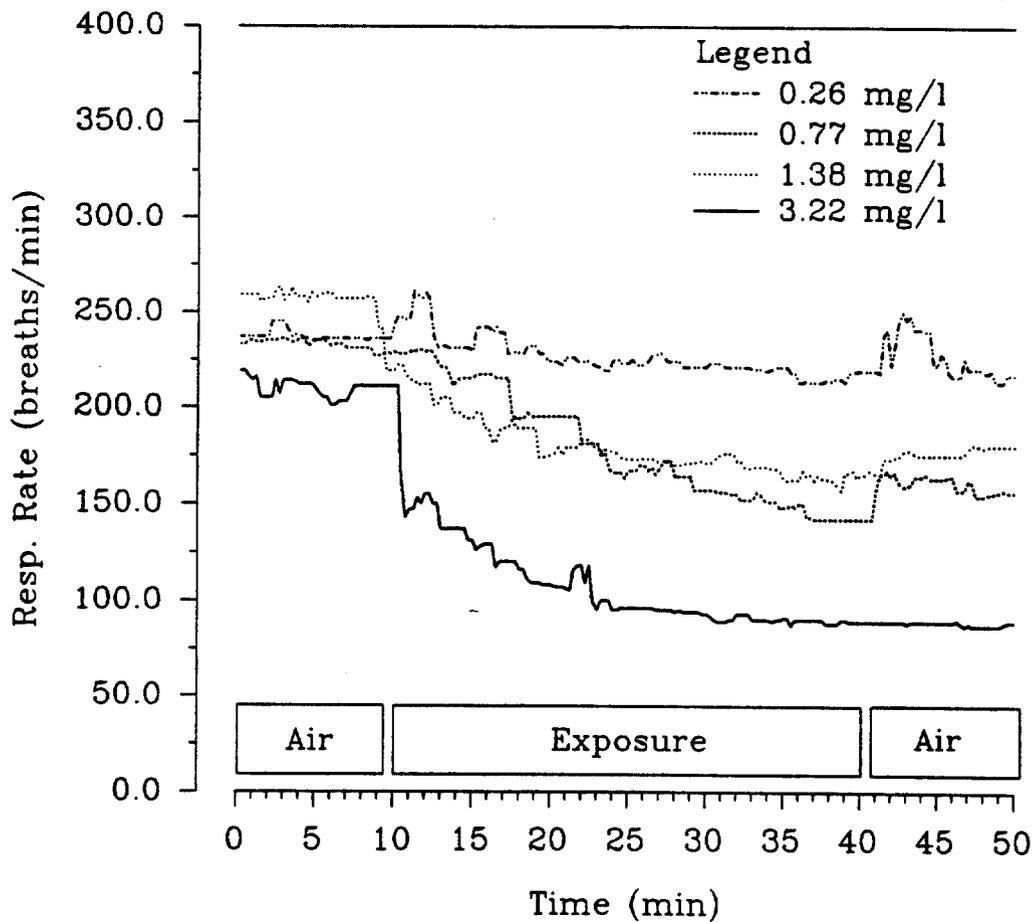
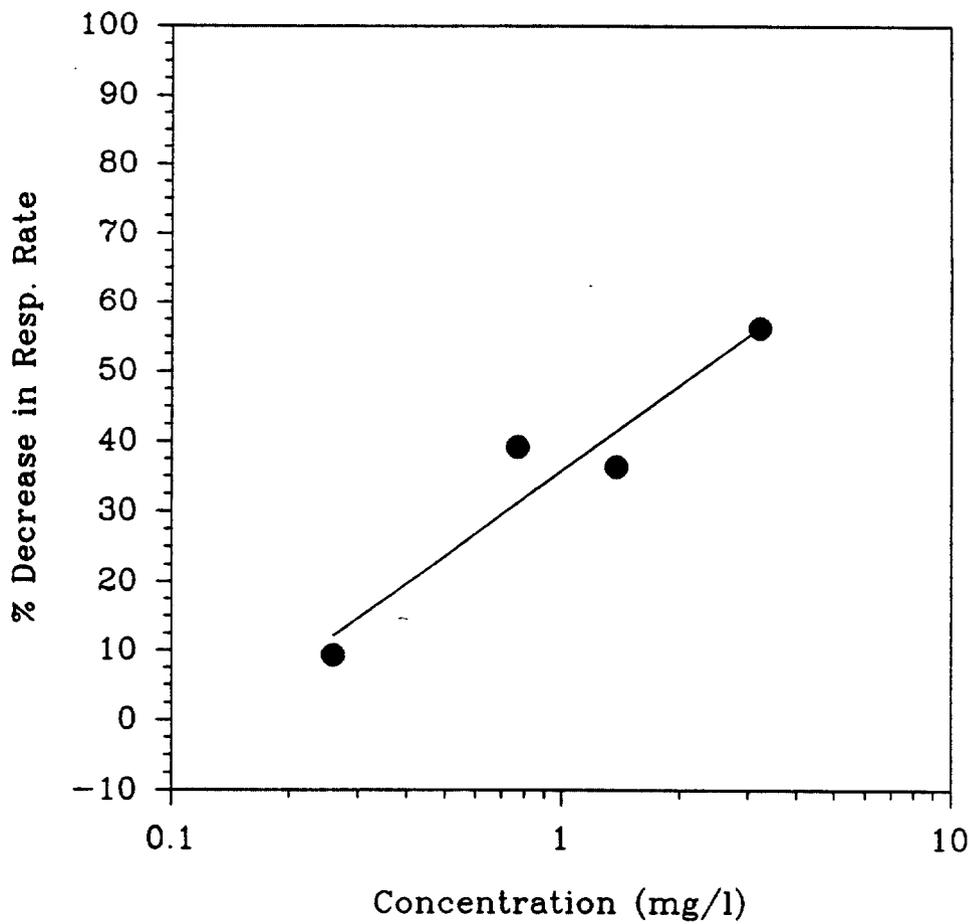


Figure 4
Sodium Persulfate (I93-1803):
Sensory Irritation Study in Swiss Webster Mice
Decrease in Respiratory Rate vs the
Logarithm of the Exposure Concentration



/plots/hbf/cranap.spg

FIGURE 5
SODIUM PERSULFATE (FMC NO. 193-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

RESPIRATORY WAVEFORMS RECORDED UNDER CONTROL AND EXPOSURE CONDITIONS IN SODIUM PERSULFATE-EXPOSED
SWISS WEBSTER MICE

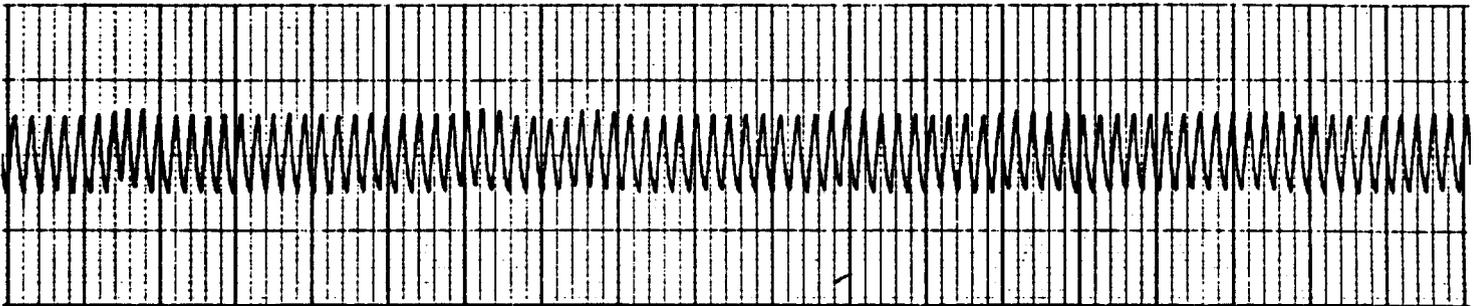


Figure 5A. Polygram depicting normal respiratory cycles for 1 mouse, obtained during 10-minute preexposure interval. The chart speed was 500 mm/min.



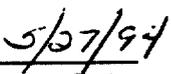
Figure 5B. Polygram depicting a marked sensory irritation response in 1 mouse during exposure to 3.22 mg/l of sodium persulfate during the 30-minute exposure interval. Note the appearance of notching during the expiratory (downward) phase of the respiratory cycle. The chart speed was 500 mm/min.

Sodium Persulfate: Sensory Irritation Study in Swiss Webster Mice

QUALITY ASSURANCE UNIT INSPECTION SUMMARY

<u>Inspection Date(s)</u>	<u>Inspection Type</u>	<u>Date QAU Report Issued To</u>	
		<u>Study Director</u>	<u>Management</u>
11-17-93	EVENT-ANIMAL RECEIPT	11-17-93	12-13-93
11-18-93 to 11-20-93	PROTOCOL	11-22-93	12-02-93
12-21-93	EVENT-BODY WEIGHTS 7 DAY	12-21-93	12-23-93
02-10-94 to 02-16-94	RAW DATA, REPORT	02-16-94	03-09-94
03-05-94	PROTOCOL AMENDMENT #1	03-07-94	03-07-94
03-15-94	PROTOCOL AMENDMENT #1 REVISED	03-15-94	03-15-94
05-27-94	ARCHIVES	05-27-94	05-27-94


Linda J. Calisti, Manager
Good Laboratory Practices/Quality Assurance


Date

FMC Corporation

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**BRRC Report 93N1343
FMC No. I93-1803**



QUALITY ASSURANCE STATEMENT

**FMC STUDY NUMBER
I93-1803**

This report and raw data were reviewed for accuracy and compliance with the study protocol, FDA Good Laboratory Practice Regulations, EPA Good Laboratory Practice Standards and OECD Principles of Good Laboratory Practice by the FMC Toxicology Department's Quality Assurance Unit. Revisions were made where necessary.

A handwritten signature in black ink that reads 'William D. Barta'. The signature is written in a cursive style and is positioned above a horizontal line.

**William D. Barta
Quality Assurance Supervisor**

A handwritten date '5/25/94' in black ink, positioned above a horizontal line.

Date

**Sodium Persulfate (FMC No. I93-1803): Sensory Irritation Study
in Swiss Webster Mice**

Chamber Atmosphere Report

(11 Pages)

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SUMMARY

The concentration of sodium persulfate particulates present in the exposure chamber was monitored during each of the 4 dust exposures by gravimetric methods. The mean chamber concentrations (\pm SD) for the exposures to sodium persulfate determined gravimetrically were 0.26 (\pm 0.07), 0.77 (\pm 0.20), 1.38 (\pm 0.02), and 3.22 (\pm 0.99) mg/l (Table 4). The corresponding nominal concentrations were 35.6, 167.8, 386.7, and 642.2 mg/l, respectively, for the 0.26, 0.77, 1.38, and 3.22 mg/l exposures. Nominal concentrations are presented in Table 3. The particle size distribution was also determined for each exposure (Table 5). For the 0.26, 0.77, 1.38, and 3.22 mg/l exposure levels, the values for the mass median aerodynamic diameters were 9.0, 7.3, 11.7, and 16.0 μ m, respectively, with geometric standard deviations which ranged from 2.8 to 9.0 μ m. The chamber temperature and room air relative humidity were measured during each exposure. The chamber temperature had a range of 20.8-21.5°C, and the room air relative humidity ranged from 48 to 52% (Table 2).

MATERIALS AND METHODS

Test Substance

Two 1-pound clear glass bottles of sodium persulfate, a white crystalline powder (Lot # E8317-70-030915, CAS No. 7775-27-1), were received on November 10, 1993, from FMC Corporation (FMC Toxicology Laboratory, 301 College Road East, Princeton, NJ) and assigned BRRC Sample No. 56-417-1 and -2. BRRC Sample No. 56-417 was used in the preliminary level setting exposures, before animal testing was begun. A second sample of test substance consisting of a clear glass bottle containing 2.816 kg (gross weight) of sodium persulfate powder (Lot # E8317-71-12293, CAS No. 7775-27-1) was received on December 8, 1993, from FMC Corporation (FMC Toxicology Laboratory, 301 College Road East, Princeton, NJ) and assigned BRRC Sample No. 56-434. The purity of the test substance was specified as 99% in the MSDS and specified as 98.48% in the Sponsor's certificate of analysis. BRRC Sample No. 56-434 was used in the sensory irritation exposures. Chemical and physical properties of sodium persulfate are presented in Table 1.

CHAMBER ATMOSPHERE ANALYSIS

The concentration of particulates for each exposure was analyzed by gravimetric methods. The concentration of airborne sodium persulfate dust was measured 2-3 times during each exposure. The sample collection times for the gravimetric samples were 5-9 minutes using a sampling volume of 6.09-11.24 liters of chamber air. Temperature and relative humidity measurements were recorded 2-6 times during each exposure (including preliminary exposures). These data are presented in Table 4.

The data for calculation of the nominal and gravimetric concentrations of sodium persulfate are presented in Tables 3 and 4, respectively. The nominal concentrations were 35.6, 167.8, 386.7, and 642.2 mg/l, respectively, for the 0.26, 0.77, 1.38, and 3.22 mg/l exposures. Differences between the gravimetric and nominal concentration are typically observed in dust studies

because of significant losses of the test substance in the generation equipment and conducting tubing to the chamber, as well as on the animals, cages, and chamber wall surfaces. Also, large particles do not remain airborne and do not contribute to the measured exposure concentration. The data for the particle size analyses were obtained once during each exposure. A summary of the particle size distribution for each exposure is presented in Table 5. For the 0.26, 0.77, 1.38, and 3.22 mg/l exposure levels, the values for the mass median aerodynamic diameters were 9.0, 7.3, 11.7, and 16.0 μm , respectively, with geometric standard deviations which ranged from 2.8 to 9.0 μm .

TABLE 1
SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

CHEMICAL AND PHYSICAL PROPERTIES

Chemical Name:	Sodium Persulfate
CAS Registry Number:	7775-27-1
Molecular Formula	No data
Molecular Weight	No data
Specific Gravity (H ₂ O = 1)	2.6
Appearance and Odor	White, crystalline powder; odor - none
Vapor Pressure at 20°C	Not applicable
Solubility in Water, % by Weight	43% at 25 °C.
Evaporation Rate (butyl acetate = 1)	Not applicable
Flash Point	Noncombustible

TABLE 2
 SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

SUMMARY OF INDIVIDUAL TEMPERATURE AND RELATIVE HUMIDITY DATA

Exposure Concentration of Sodium Persulfate (mg/l)	Temperature (°C)	Relative Humidity (%)
0.26	20.9	52
	21.4	52
	21.1	52
	21.2	52
	21.3	52
	21.3	52
Mean	21.2	52.0
S.D.	0.18	0.00
0.77	21.1	50
	21.1	50
	21.0	50
	20.8	49
	20.8	48
	20.8	48
Mean	20.9	49.2
S.D.	0.15	0.98

TABLE 2 (Continued)
 SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

SUMMARY OF INDIVIDUAL TEMPERATURE AND RELATIVE HUMIDITY DATA

Exposure Concentration of Sodium Persulfate (mg/l)	Temperature (°C)	Relative Humidity (%)
1.38	21.1	48
	21.3	48
	21.2	48
	21.3	48
	21.2	48
	21.2	48
Mean	21.2	48.0
S.D.	0.08	0.00
3.22	21.0	52
	21.5	52
	21.5	52
	21.4	52
	21.4	52
	21.4	52
Mean	21.4	52.0
S.D.	0.19	0.00

TABLE 3
SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
IN SWISS WEBSTER MICE

NOMINAL CHAMBER CONCENTRATION

Mean Gravimetric Concentration (mg/l)	Exposure Duration (min)	Chamber Airflow Rate (l/min)	Weight of Test Substance Used (g)	Nominal Concentration (mg/l)	Analytical/ Nominal Ratio
0.26	30	30	32	35.6	0.007
0.77	30	30	151	167.8	0.005
1.38	30	30	348	386.7	0.004
3.22	30	30	578	642.2	0.005

TABLE 4
 SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

GRAVIMETRIC DATA

Sample Number	Time into Exposure (min)	Sampling Volume (liters)	Sampling Duration (min)	Weight of Sample (mg)	Gravimetric Concentration (mg/l)
0.26 mg/l Group					
1	2	6.4570	5.0	1.83	0.28
2	10	8.6942	5.0	2.80	0.32
3	22	8.8642	5.0	1.66	0.19
				Mean:	0.26
				SD:	0.07
0.77 mg/l Group					
1	3	6.2021	5.0	6.21	1.00
2	9	9.0341	5.0	5.97	0.66
3	21	9.4306	5.0	6.26	0.66
				Mean:	0.77
				SD:	0.20

TABLE 4 (Continued)
 SODIUM PERSULFATE (FMC NO. I93-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

GRAVIMETRIC DATA

Sample Number	Time into Exposure (min)	Sampling Volume (liters)	Sampling Duration (min)	Weight of Sample (mg)	Gravimetric Concentration (mg/l)
1.38 mg/l Group					
1	2	9.2323	5.0	12.68	1.37
2	8	9.0341	5.0	12.69	1.40
3	22	9.4872	5.0	13.12	1.38
				Mean:	1.38
				SD:	0.02
3.22 mg/l Group					
1	2	11.2430	5.0	24.97	2.22
2	9	6.0888	5.0	25.56	4.20
3	21	6.3437	5.0	20.63	3.25
				Mean:	3.22
				SD:	0.99

TABLE 5
 SODIUM PERSULFATE (FMC NO. 193-1803): SENSORY IRRITATION STUDY
 IN SWISS WEBSTER MICE

PARTICLE SIZE DISTRIBUTIONS

Gravimetric Concentration (mg/l)	Sample Number	Mass Median Aerodynamic Diameter (μ m)	Geometric Standard Deviation(μ m)	D16 (μ)	D84 (μ)
0.26	1	9.0	9.0	1.0	81
0.77	1	7.3	3.0	2.4	22
1.38	1	11.7	2.8	4.2	33
3.22	1	16.0	3.6	4.4	58

**Sodium Persulfate (FMC No. 193-1803): Sensory Irritation Study
in Swiss Webster Mice**

Protocol, Protocol Amendment, and Protocol Deviations

(17 Pages)



BUSHY RUN RESEARCH CENTER

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PROTOCOL

TITLE: Sodium Persulfate: Sensory Irritation Study in Swiss Webster Mice

BRRC PROJECT ID: 93N1343

FMC STUDY NUMBER: 193-1803

SPONSOR: FMC Corporation
Chemical Research
and Development Center
Box 8
Princeton, NJ 08543

TESTING FACILITY: Bushy Run Research Center (BRRC)
Union Carbide Corporation
6702 Mellon Road
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Reviewed and Approved by:

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Sponsor's Representative:

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UNION CARBIDE CORPORATION

OBJECTIVE

The objective of this study will be to evaluate the sensory irritant potential of sodium persulfate dust in mice by determining the concentration that produces a 50% decrease in the respiratory rate (RD50).

Design and Basis for the Study

This protocol is based on the ASTM Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals (ASTM, 1984).

Four groups of animals, each containing 4 male ND4 Swiss Webster mice, will be exposed to the test substance and sacrificed 7 days following the exposure; a control group of 4 animals will be exposed to room air and sacrificed at the same timepoint. The respiratory rate of each animal will be monitored prior to the exposure, during the exposure, and for a short period following the exposure; each animal will serve as its own control. Exposure concentrations will be tested with the goal being to obtain at least one concentration above the RD50 value.

The portions of this study conducted by BRRC will be in compliance with the following guidelines and standards:

ASTM (1984). Standard test method for estimating sensory irritancy of airborne chemicals. Annual Book of ASTM Standards, Designation E981-84. American Society for Testing and Materials, Philadelphia, PA.

U.S. Environmental Protection Agency (EPA), Toxic Substances Control Act (TSCA) Good Laboratory Practice Standards, 40 CFR Part 792.

PERSONNEL

All personnel who participate in the conduct of the study will be documented in the raw data.

PROJECT DATES

<u>Starting Date of Acclimation</u>	November 16, 1993
<u>Proposed Starting Date of Test Substance Administration</u>	November 23, 1993
<u>Proposed Date for Completion of In-Life Phase</u>	December 7, 1993
<u>Proposed Date for Submission of Draft Final Report</u>	February 7, 1994

METHODS

Test Substance

Chemical Name	Sodium persulfate
CAS Registry Number	7775-27-1

Source FMC Corporation, Princeton, NJ

Sponsor Identification Number To be added by amendment.

BRRC Sample Number To be added by amendment.

Description White, crystalline powder (Source-MSDS)

Purity Purity information will be provided by the Sponsor and documented in the raw data and final report.

Stability The test substance is considered to be stable at room temperature for the duration of the study.

Storage Conditions To be added by amendment.

Quantity To be added by amendment.

Reserve Sample A reserve sample of approximately 5 to 10 g will be retained in an amber bottle with a Teflon-lined cap from each container of test substance used during the study. The reserve sample will be stored at ambient temperature for 5 years. Prior to discarding the reserve sample, the Sponsor will be contacted.

Safety A Material Safety Data Sheet (MSDS) supplied by the Sponsor will be reviewed by all relevant personnel before their participation in the study. This review will be documented. Normal precautions for untested substances will be used. These procedures include the use of disposable Tyvek® or plastic coats or jumpsuits, hats, booties or shoe covers, and rubber gloves while in the animal rooms. Eye protection will include the use of safety glasses at all times. Disposable Tyvek® coats or smocks and neoprene gloves will be worn during administration of the test substance. In addition, monogoggles will be used when handling the test substance. A NIOSH/MSHA approved organic vapor and dust respirator will be used whenever there is potential for worker exposure.

Test Animals

Species and Strain ND4 Swiss Webster mice

Supplier Harlan Sprague Dawley, Inc., Indianapolis, IN

Rationale The Swiss Webster mouse is specified as the strain of choice for sensory irritation studies in ASTM E981-84.

Number and Sex For each exposure group, 4 male mice of appropriate weight will be randomly selected by cage. There will be 4 exposure groups. A control group of 4 male mice will also be exposed to room air only during the conduct of this study.

Age and Weight The animals will be approximately 28 days of age on the scheduled animal receipt date. The animals will weigh between 22 and 28 g on the day of exposure. The body weight range just prior to exposure will be stated in the final report.

Acclimation and Pretest Evaluations Shortly after their arrival at the laboratory, the animals will be transported to the room selected for the study. Once in the room, the animals will be removed from the shipping cartons and examined. Any animals with evidence of disease or physical abnormalities will be discarded. If an unusually large number of animals shows evidence of disease or physical abnormalities, the entire shipment of animals will be rejected for use in the study. All remaining animals will be housed 2 to a cage for an acclimation period of at least 5 days.

Pretest Health Evaluation A pretest health evaluation will be initiated within 3 days after the receipt of the animals. The pretest health evaluation will consist of visual observation by a veterinary pathologist of at least 5 animals selected directly from the shipping cartons or while housed in stainless steel cages on carriers.

Identification Within 3 days of arrival at BRRC, animals will be identified with a tail tattoo indicative of their study assignment. Animals will be uniquely identified prior to exposure by an additional tail marking. The animal numbers will be documented in the study records. Records will be kept documenting the fate of all animals received for the study.

Husbandry

Conditions All animals will be housed 2 to a cage in an appropriate animal room at BRRC from arrival until termination of the in-life phase of the study. Stainless steel cages with wire mesh floors will be used throughout all phases of the study. Cages will be changed and sanitized at least once every 2 weeks. Paperboard kept under each cage will be changed at least 3 times each week. The dimensions of the cages used and the room in which animals are kept will be provided in the raw data.

Temperature and humidity will be recorded using an automatic recorder. Temperature will be maintained at 66-77°F and relative humidity will be maintained at 40-70%. The temperature and humidity will be checked by a technician at each room check and a record will be kept indicating that it was done. Appropriate corrective action will be taken whenever readings outside the specified limits are observed.

The accuracy of the temperature and humidity recording devices will be checked periodically and calibrated when necessary. The verification and calibration data will be recorded. In the event that automatic recording cannot be maintained, the temperature and humidity of the animal room will be manually recorded at each room check.

An automatic timer will be set to provide fluorescent lighting for a 12-hour photoperiod (approximately 0500 to 1700 hours for the light phase). In the animal room, there will be at least 10 air changes each hour.

Diet

Pelleted, certified AGWAY® PROLAB® Animal Diet Rat, Mouse, Hamster 3000 (Agway Inc.) will be available ad libitum (except during exposures). The analyses of chemical composition and possible contaminants of each batch of diet will be performed by Agway Inc. and the results of the analyses will be reviewed by the Study Director.

Water

Tap water (Municipal Authority of Westmoreland County, Greensburg, PA) will be available ad libitum, except during exposures, by water bottles and an automatic watering system with demand control valves mounted on each rack. Water bottles, water pressure and function of the individual cage rack systems will be checked at each room check, and a record will be kept indicating it was done. Drinking water contaminant levels will be measured at approximately 9-month intervals according to the specifications of the EPA Safe Drinking Water Act Regulations and will comply with human drinking water requirements. The results of the analyses will be reviewed by the Study Director.

Administration of Test Substance**Route and
Justification**

The route of test substance administration will be by inhalation. This is considered to be a meaningful way to evaluate sensory irritation of chemicals as specified in ASTM E981-84. The inhalation route is also a potential route of human exposure.

**Preliminary
Exposure**

Two or 3 animals will be exposed to increasing concentrations of the test substance until a sensory irritation pattern is observed. When a sensory irritation pattern is observed, samples of the chamber air will be drawn and analyzed. In addition, these animals will be observed for signs of toxicity and irritation during the exposure (including but not limited to periorcular wetness and perinasal wetness) and findings will be recorded. The exposure will continue at this concentration until a plateau in the respiratory rate depression of the mice is reached. If the plateau or maximal depression is not reached during a 30-minute period during the preliminary exposure, then the length of the exposure period for the study will be increased to ensure that a maximal depression is reached during an exposure.

**Target Exposure
Concentration
Selection**

The results from the preliminary exposure will be used to help choose the target concentration for the first exposure. Four exposure concentrations will be tested with the goal being to obtain at least one concentration above the RD₅₀ value. The target exposure concentrations will be selected by the Sponsor and will be added in a protocol amendment. Target concentrations selected should produce at least a 12% decrease in the mean respiratory rate. The control group will be exposed to room air only.

**Exposure Chambers
and Respiratory
Rate Recording
Conditions**

Mice will be placed in individual plethysmographs with their heads protruding through a flexible rubber neck seal into the center of the glass exposure chamber. The temperature of the exposure chamber will be monitored and recorded 3 times during each exposure. The plethysmographs will be closed with rubber stoppers, ensuring that they are well sealed to prevent air leaks.

Each plethysmograph will be connected to a Statham PM 15ETC pressure transducer, Gaeltec 8T-2 pressure transducer, or a Fukuda TY 303 microphone to detect pressure or sound changes created during inspiration and expiration. These respiratory signals will then be amplified and continuously displayed on a Western Graphtec Recorder (Western Graphtec, Irvine, CA).

Respiratory signals will be converted to digital representations at 200 samples/second by a computer. A computer program written for an IBM-AT personal computer will calculate, display, and store every 15 seconds, the respiratory rates for each animal (Burleigh-Flayer *et al.*, 1988). Respiratory rates will be recorded by a computer during the 10-minute preexposure period, the 30-minute exposure, and the 10-minute postexposure period.

**Type and Duration
of Exposure**

Animals will be acclimated to the plethysmograph-exposure chamber apparatus for approximately 10 minutes prior to initiation of the exposure. The preexposure period may be extended if the respiratory rates of the animals are not within a normal range. Animals will be exposed head-only to the test substance during the next 30 minutes (unless the preliminary exposure indicates a longer exposure period is necessary). Animals in the control group will be sham-exposed to air for the same period of time. Animals will remain in the plethysmograph-exposure chamber apparatus for approximately 10 minutes following the exposure.

**Generation of
Dust Atmosphere**

Sodium persulfate dust atmospheres will be generated using an Accurate Dry Material Feeder (Accurate, Whitewater, WI) and Jet-O-Mizer dust generator (Fluid Energy Aljet, Plumsteadville, PA). A complete description of the generation method will be provided in the raw data.

**Chamber
Atmosphere
Sampling**

Chamber concentrations of the test substance will be determined at least 3 times during the exposure by standard gravimetric techniques using 25 mm Gelman glass-fiber filters (Gelman Sciences Inc., Ann Arbor, MI). Chamber probes for sampling will be placed in the breathing zone of the animals. The daily nominal (estimated) chamber concentration will also be determined.

**Test Substance
Analyses**

Prior to initiation of the study, a sample of the test substance will be drawn, and a compositional analysis will be performed by the Sponsor.

The particle size distribution will be measured with a Marple Personal Cascade Impactor (Andersen Instruments, Inc., Atlanta, GA). Particle size determination will be performed at least once during each exposure.

Study Design

**Group
Assignment**

The control and exposure groups will each consist of 4 male mice. Exposure group assignment will be made using a card-based randomization procedure.

Animals not selected for the study will remain housed in the study room until the study begins and may be selected for another exposure group.

In the event the body weight criteria are not met, animals not originally assigned to the study will be randomly selected as replacements. Animals with any abnormal clinical signs will also be replaced prior to exposure.

Animals not assigned to the study will be used for training of BRRC staff or methods development, or they will be humanely sacrificed and discarded.

Experimental Evaluations

Mortality Checks and Clinical Signs

All animals will be observed for mortality and clinical signs of toxicity and/or irritancy (including but not limited to periorcular wetness and perinasal wetness) each day and findings will be recorded. As part of the daily detailed physical examination of the animals, the eyes will be checked for clinical signs. Detailed individual physical examinations will be performed just prior to exposure, shortly following exposure, and once each day (a.m.) during the postexposure period. Additionally, a second mortality check will be conducted each weekday (p.m.). The approximate time of death will be recorded.

Animals will also be observed on a group basis during the exposure.

Sacrifice of Distressed Animals

If any animal shows signs of extreme distress or is moribund, it will be sacrificed for humane reasons before the scheduled date.

Body Weight

Individual body weights will be measured on the morning prior to the exposure and at 7 days following the day of exposure. Individual body weight gains will be computed.

Sacrifice

At 7 days following the day of exposure, all surviving animals will be euthanized with CO₂. Any animal showing signs of severe debility, particularly if death appears imminent, will be sacrificed early. No necropsy or histopathologic evaluation will be performed on sacrificed animals or animals found dead during the postexposure period.

Statistical Evaluations

Each animal will serve as its own control. The control respiratory rate will be calculated by averaging intervals during the preexposure period. For each animal, respiratory rates will be calculated every 15 seconds of the 30-minute exposure period and during the 10-minute postexposure period. The percent decrease in respiratory rate from control will also be calculated for each animal.

For calculating the RD50 value, the irritant effect of the test substance will be treated statistically as a dose-response regression, with the common logarithm of the exposure concentration as the independent variable, and the mean percent decrease in respiratory rate (per exposure group) from control as the dependent variable. The regression line, the RD50 value, and its 95% confidence limit will be determined by the method of least squares (Draper and Smith, 1966).

ALTERATION OF PROTOCOL

Alterations to this protocol may be made as the study progresses. No changes in the protocol will be made without the specific written request or consent of the Sponsor. In the event that the Sponsor authorizes a protocol change verbally, such change will be honored. However, it then becomes the responsibility of the Sponsor to follow such verbal change with a written verification. BRRC reserves the right to revise the protocol or deviate therefrom solely at the discretion of the Study Director if prior approval of the Sponsor cannot be obtained and the integrity of the study is considered in jeopardy. In this event, the Sponsor will be notified of the alteration as soon as possible, and documentation of the change will be the responsibility of the Study Director.

RETENTION OF RECORDS

All raw data, documentation, the protocol and any amendments, specimens, and a copy of the final report generated as a result of this study will be retained in the BRRC Archives for at least 5 years. A reserve sample of test substance from each container used during the study will also be stored in the BRRC Archives.

Following the retention period specified above, the Sponsor will be contacted and given the option of taking receipt, destroying, or arranging for other storage of the data and materials. All data and materials mentioned above will remain the sole property of the Sponsor and can be removed from BRRC at the Sponsor's discretion.

REPORTS

Draft Final Report

The draft final report will be audited by the BRRC Quality Assurance Unit prior to submission to the Sponsor. The draft final report will be submitted to the Quality Assurance Unit approximately 2 months after the completion of the terminal sacrifice. The Quality Assurance Unit will submit the draft final report to the Sponsor one month following receiving it from the Study Director. This report will be a comprehensive report which will include all information necessary to provide a complete and accurate description and evaluation of the test procedures and results. It will include: a summary; appropriate text discussions of the experimental design, materials and methods, and results and interpretations of the results; and summary graphs

and tables of data. In addition, it will contain appendices with individual animal data and other pertinent information.

Final Report

The draft final report will be reviewed by the Sponsor, and comments on the report will be provided to BRRC within 8 weeks from the date of submission of the draft version. BRRC will consider these comments in preparing the final report. Assuming the Sponsor's comments are received at the specified time and no major revisions are required, BRRC will submit a final report within 12 weeks of issuance of the draft report.

The final report will be audited by the Quality Assurance Unit and contain a signed quality assurance statement. It will conform to the formatting specifications of EPA PR notice 86-5.

ANIMAL USE POLICY

It is the goal of BRRC, through the establishment and activities of the Institutional Animal Care and Use Committee, to comply with the U.S. Animal Welfare Act and the subsequent rules promulgated by the U.S. Department of Agriculture and in effect on the date of this protocol. It has been determined that the work described herein minimizes the number of animals used, is necessary, and uses the most appropriate species and strain in order to provide meaningful results and the most useful information for comparative purposes relative to previous studies. Furthermore, this study will be conducted humanely, and to the best of our knowledge, neither unnecessarily duplicates any previous work, nor can it be accomplished using currently available, validated nonanimal models.

GOOD LABORATORY PRACTICE COMPLIANCE

BRRC, through the administration of a quality assurance program by the Good Laboratory Practice Committee and Quality Assurance Unit, assures compliance of all phases of studies conducted by BRRC with existing regulations and generally accepted good laboratory practices.

The study will be subjected to periodic inspections, and at least one in-life phase of the study will be audited by the BRRC Quality Assurance Unit. The final report will be reviewed by the BRRC Quality Assurance Unit.

REFERENCES

- ASTM (1984). Standard test method for estimating sensory irritancy of airborne chemicals. Annual Book of ASTM Standards, Designation E981-84. American Society for Testing and Materials, Philadelphia, PA.
- Burleigh-Flayer, H. Schaper, M., Thompson, R., and Alarie, Y. (1988). Computerization of pulmonary function studies in laboratory animals. *The Toxicologist* 8, 142.

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FMC No. I93-1803

Appendix 2

Page 12

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Page 11

Draper, W. R. and Smith, H. (1966). Applied Regression Analysis. John Wiley & Sons, New York, NY.

Environmental Protection Agency (EPA) (1989). EPA Toxic Substances Control Act (TSCA); Good Laboratory Practice Standards; Final Rule. 40 CFR Part 792.

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PROTOCOL AMENDMENT 1

TITLE: Sodium Persulfate: Sensory Irritation Study in Swiss Webster Mice

BRRC PROJECT ID: 93N1343

FMC STUDY NUMBER: 193-1803

SPONSOR: FMC Corporation
Chemical Research
and Development Center
Box 8
Princeton, NJ 08543

TESTING FACILITY: Bushy Run Research Center (BRRC)
Union Carbide Corporation
6702 Mellon Road
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Reviewed and Approved by:

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John P. Van Miller, Ph.D., DABT Date
Director

Sponsor's Representative:

John Signoria 3/18/94
John Signoria, B.S. Date

UNION CARBIDE CORPORATION

The protocol is amended as follows:

Item 1

Location of Protocol Change	Page 2, Project Dates
Description of Protocol Change	Starting Date of Test Substance Administration - December 9, 1993
	Date for Completion of In-Life Phase - January 4, 1994
	Date of Submission of Draft Final Report - March 1, 1994
Rationale	The exact dates were added by protocol amendment.

Item 2

Location of Protocol Addition	Page 3, Test Substance, Sponsor Identification Number
Description of Protocol Addition	E8317-70-030915 (BRRC No. 56-417) E8317-71-12293 (BRRC No. 56-434)
Rationale	This information was to be added by protocol amendment.

Item 3

Location of Protocol Addition	Page 3, BRRC Sample Number
Description of Protocol Addition	56-417 56-434
Rationale	This information was to be added by protocol amendment.

Item 4

Location of Protocol Addition	Page 3, Storage Conditions
Description of Protocol Addition	The test substance was stored in the fume hood in Room 147 at ambient temperature.
Rationale	This information was to be added by protocol amendment.

Item 5

Location of Protocol Addition Page 3, Quantity

Description of Protocol Addition 569 g and 557 g (56-417)
2.816 kg (gross weight, 56-434)

Rationale This information was to be added by protocol amendment.

Item 6

Location of Protocol Addition Page 6, Target Exposure Concentration Selection

Description of Protocol Addition The protocol states that target exposure concentrations would be selected by the Sponsor and would be added in a protocol amendment. However, exposure concentrations were selected by the Study Director based upon the results of 2 preliminary exposures, and were included in an interim report requested by the Sponsor and will be included in the draft final report rather than added by amendment.

Rationale The Study Director chose exposure concentrations based upon the results of preliminary exposures.

Item 7

Location of Protocol Change Page 3, Test Substance Description

Description of Protocol Change The protocol states that the MSDS describes the test material as a white, crystalline powder. Actually, this is the description provided on the chemical receipt form contained in the raw data. The MSDS describes the test material as "white crystals".

Rationale The test material should be accurately described in the protocol.

Item 8

Location of Protocol Change Page 7, Generation of Dust Atmosphere

Description of Protocol Change The protocol states that a Jet-O-Mizer dust generator (Fluid Energy Aljet, Plumsteadville, PA) would be used in the generation of the test material. However, a generation apparatus of our own design as described in the raw data was used instead.

Rationale

The airflow through the Jet-O-Mizer was too high for use in this study.

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Sodium Persulfate (FMC No. I93-1803): Sensory Irritation Study
in Swiss Webster Mice

BRRC Project ID 93N1343

Protocol Deviations

1. According to the study protocol, all animals assigned to the study were to be observed for mortality and clinical signs of overt toxicity twice each day, 7 days each week. However, on a few occasions, AM or PM mortality checks were not performed.
2. During the week starting on 11-10-93, there were occasional temperature excursions which resulted in the animal room temperature reaching temperatures slightly below 66°C. The protocol specifies 66°C as the lower limit for the room temperature.
3. According to the study protocol, a control group would be included during the study. However, a control group was not utilized as this is not required in the ASTM E981-84 method.

It is the Study Director's belief that these protocol deviations did not affect the outcome of the study.