CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Dimethyl Disulfide

Chemical Code # 5899, **Tolerance #** 52971
SB 950 # NA

Original, July 1, 2010
Revised, 4/19/13

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, study not submitted
Chronic toxicity, dog:	Data gap, study not submitted
Oncogenicity, rat:	Data gap, study not submitted
Oncogenicity, mouse:	Data gap, study not submitted
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 269564 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T130419
Revised by T. Moore, 4/19/13

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

Study not submitted.

CHRONIC TOXICITY, RAT

Study not submitted.

CHRONIC TOXICITY, DOG

Study not submitted.

ONCOGENICITY, RAT

Study not submitted.

ONCOGENICITY, MOUSE

Study not submitted.

REPRODUCTION, RAT

** 52971-0030; 231347; "A Two-Generation Reproductive Toxicity Inhalation Study of Dimethyl Disulfide in Rats"; (M.D. Nemec; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160122; 12/15/06); 30 Sprague-Dawley Crl:CD(SD) rats/sex/group were exposed whole-body to 0, 5, 20 or 80 ppm of Dimethyl Disulfide Technical (lot no. 05.05.05; purity: 99.8%) 6 hours/day, 7 days/week through 2 generations (1 litter/generation). The overall mean analytical concentrations for the F0 and F1 generations were 5.0, 20.4 and 79.9 ppm and 5.0, 20.6 and 80.0 ppm, respectively. Mg/l equivalent exposure concentrations were 0.02, 0.08, and 0.30 mg/l at 5, 20, and 80 ppm, respectively (calculated by the reviewer). Parental animals were exposed for at least 10 weeks prior to mating. The animals were exposed daily during mating through gestation day 20. Exposures were not performed between gestation day 21 and lactation day 4, resuming on day 5 through to weaning. During lactation, the dams were removed from their litters for the 6 hour exposure period. The mean body weights of both sexes in both generations of the 20 and 80 ppm were lower during the 1st week of the premating ($p<0.05$ or 0.01). The mean weights of both sexes in the 20 ppm had recovered by the 10th week of the premating period except for the males in the F1 generation in which the mean body weights for the 5 ppm group and above were less than that of the controls ($p<0.01$). However, the mean pup weight of the 5 ppm group was less than that of the 20 ppm animals throughout the lactation period and at the initiation of the premating period and therefore did not demonstrate an exposure-related response. The mean relative adrenal weights of the 80 ppm females in both generations and the 80 ppm males in the F1 generation were greater than the control values ($p<0.01$). The 80 ppm males in the F0 generation demonstrated a greater incidence of vacuolization in the adrenal cortex than did the control animals (0: 6/30 vs. 80: 12/30). This lesion was not observed in the adrenal cortex of the 80 ppm males of the F1 generation. There were no treatment-related effects on reproductive performance or parturition. Spermatogenic endpoints were not affected by the treatment. The treatment did not adversely affect litter sizes and pup survival and development. **No adverse effect indicated. Parental NOEL:** 5 ppm (0.02 mg/l) (based upon lower mean body weights and food consumption noted for both sexes in both generations at 20 ppm); **Reproductive NOEL:** 80 ppm (0.30 mg/l) (based upon the lack of treatment-related effects on the dams of both generations in the 80 ppm group); **Developmental NOEL:** 80 ppm (0.30 mg/l) (based upon the lack of treatment-related effects on the development of the offspring in the 80 ppm group of both generations); **Study acceptable.** (Moore, 11/21/07)

52971-0032; 231349; "A Lactational Inhalation Phased-Exposure Study of Dimethyl Disulfide in Rats"; (M.D. Nemec; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160126; 12/15/06, revised 1/16/07); Thirty six Crl:CD(SD) female rats with litters/group were exposed whole-body during the lactation period to 0, 5, 20 or 80 ppm of Dimethyl Disulfide

Technical (lot no. 05.05.05; purity: 99.8%) for 6 hours/day (0. 0.02, 0.08, 0.30 mg/l) (calculated by reviewer). The dams in each group were divided into subsets of 12 animals each. Animals in Subset I were exposed to the test material from lactation day 5 through lactation day 12; animals in Subset II from lactation day 13 through lactation day 20 and animals in Subset III from lactation day 5 through lactation day 20. The mean body weight gains of the dams in the 20 (Subset I and III) and 80 ppm groups (Subset I, II and III) were less than that of the control group during their respective exposure periods (p<0.05 or 0.01). The mean food consumption of the dams in the 80 ppm group (Subset I and II) was less than the control value during their respective exposure periods (p<0.05 or 0.01). There was no treatment-related effect upon pup survival or body weight gain. **No adverse effect indicated. Maternal NOEL:** 5 ppm (0.02 mg/l) (based upon the lower body weight gain noted for the dams in the 20 ppm group); **Developmental NOEL:** 80 ppm (based upon the lack of a treatment-related effect at the highest exposure concentration). **Study supplemental** (non-guideline study). (Moore, 11/27/07)

TERATOLOGY, RAT

** 52971-0028; 231345; " Dimethyl Disulfide (DMDS): Inhalation Teratology Study in the Rat"; (L. Barker; Hazleton UK, Harrogate, North Yorkshire HG3 1PY, England; Report No. 6205-514/9; 12/27/91); Thirty Crl:CD(SD) BR mated female rats/group were exposed whole body to 0 (filtered air), 5, 15 or 50 ppm of Dimethyl Disulfide Technical (batch no. 82551; purity: 99.88%) 6 hours/day from day 6 to day 15 of gestation (0, 0.02, 0.06, 0.20 mg/l, calculated by the reviewer). No maternal deaths resulted from the exposure. The mean body weights of the dams in the 15 and 50 ppm groups were less than that of the controls on days 10 and 15 of gestation (p<0.01 or 0.001). The mean food consumption of the 50 ppm dams between day 6 and day 15 of gestation was less than the control value (p<0.001). The mean body weight of the fetuses in the 50 ppm group was less than that of the controls (p<0.01). No treatment-related malformations or other developmental effects were noted. **No adverse effect indicated. Maternal NOEL:** 5 ppm (0.02 mg/l) (based upon the lower mean body weights of the dams in the 15 ppm group; **Developmental NOEL:** 15 ppm (0.06 mg/l) (based upon the lower mean weight of the fetuses in the 50 ppm group); **Study acceptable.** (Moore, 11/15/07)

** 52971-0031; 231348; "Inhalation Prenatal Developmental Toxicity Study of Dimethyl Disulfide in Rats"; (M.D Nemec; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160128; 12/19/06); Twenty seven mated female Crl:CD® (SD) rats/group were exposed whole body to 0 (filtered air), 5, 20 or 80 ppm of Dimethyl Disulfide Technical (lot no. 05.05.05; purity: 99.18%) 6 hours/day from day 6 through day 19 of gestation (0, 0.2, 0.08, 0.30 mg/l, calculated by reviewer). The mean body weight gain of the dams in the 20 and 80 ppm groups were less than that of the control group through day 12 of gestation (p<0.01 or 0.05). This effect persisted in the 80 ppm group through day 20 of gestation. The mean food consumption of the dams in the 80 ppm group was less than that of the controls throughout the study. The food consumption of the 20 ppm group was less than the control value between days 9 and 12 of gestation (p<0.05). The mean body weight of the fetuses in the 80 ppm group was less than that of the control (p<0.01). The ossification of the sternebra and other bones of the fetuses in the 80 ppm group was delayed. **No adverse effect indicated. Maternal NOEL:** 5 ppm (0.02 mg/l) (based upon the lower body weight gain and food consumption noted for the dams in the 20 ppm group); **Developmental NOEL:** 20 ppm (0.08 mg/l) (based upon the lower mean body weights of the fetuses and the delayed ossification of the fetuses in the 80 ppm group); **Study acceptable.** (Moore, 11/26/07)

52971-0039; 231356; " A Range-Finding Inhalation Developmental Neurotoxicity Study of Dimethyl Disulfide in Rats"; (M.D. Nemec; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160125; 7/21/06, revised 1/16/07); Ten Crl:CD® (SD) female rats with litters/group were exposed whole-body to 0, 2, 20 or 80 ppm of Dimethyl Disulfide Technical (lot no. 05.05.05; purity: 99.18%) 6 hours/day from lactation day 5 through lactation day 20. No deaths resulted from the exposure. No treatment-related effect on the mean body weights were evident during the exposure period. The mean food consumption of the 80 ppm dams with their litters was less than that of the controls over the course of the exposure (p<0.01). There was no treatment-related effect on the survival of the pups over the course of the study. The mean body weights of the pups in the 80 ppm group were less than those of the control animals by the end of

the exposure period (p<0.01). **No adverse effect was indicated. Maternal NOEL:** 20 ppm (based upon the lower food consumption noted for the 80 ppm dams); **Developmental NOEL:** 20 ppm (based upon the lower mean body weights noted for the pups in the 80 ppm exposure group); **Study supplemental.** (Moore, 12/4/07)

TERATOLOGY, RABBIT

** 52971-0029; 231346; "An Inhalation Prenatal Developmental Toxicity Study of Dimethyl Disulfide in Rabbits"; (M.D. Nemec; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160119; 9/2/05); Twenty four mated female New Zealand White rabbits/group were exposed whole body to 0 (filtered air), 15, 45 or 150 ppm of Dimethyl Disulfide Technical (lot no. 03.10.04; purity: 99.73%) 6 hours/day from day 6 through day 28 of gestation in two replicates of 12 animals/group (analytical concentrations, 1st replicate: 0, 15.3, 45.0 and 135.0 ppm; 2nd replicate:15.0, 45.0 and 134.6 ppm) (0, 0.06, 0.18, 0.53 mg/l, calculated by the reviewer). No exposure-related effect was noted on the mean body weights of the study animals. The mean food consumption of the 135 ppm does was less than the controls on the first day of exposure (p<0.05). Thereafter no effect was noted. No exposure-related effect was evident on the fetuses. **No adverse effect indicated. Maternal NOEL:** 45 ppm (0.18 mg/l) (based on the decreased food consumption noted for the does on the 1st day of exposure in the 135 ppm group); **Developmental NOEL:** 135 ppm (0.53 mg/l) (based on the lack of an exposure-related effect on the fetuses in the 135 ppm group); **Study acceptable.** (Moore, 11/16/07)

GENE MUTATION

52971-0033; 231350; "Ames *Salmonella*/Microsome Plate Test (EPA/OECD) Dimethyldisulfide"; (T.R. Barfknecht; Pharmakon Research International, Inc., Waverly, PA; Study No. PH-301-Pw-003-85; 5/31/85); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were treated with Dimethyldisulfide Technical (lot no. 5275-164, purity not reported) at concentrations ranging from 50 to 5000 ug/plate for 48 to 72 hours at 37° C by plate incorporation under conditions of activation and non-activation. One trial was performed with triplicate samples for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study unacceptable**, possibly upgradeable (purity of the test material was not reported). (Moore, 11/28/07)

** 52971-0034; 231351; "*In Vitro* Assay for the Induction of Point Mutations in the HGPRT-locus of Chinese Hamster Ovary Cells by Dimethyldisulfide (DMDS)"; (Ir. A.A.J.J.L. Rutten, W.R. Leeman; TNO-CIVO Toxicology and Nutrition Institute, Department of Toxicology, 3704 HE Zeist, The Netherlands; Report No. V89.257; 5/8/90); Chinese hamster ovary (CHO) cells were exposed to Dimethyl Disulfide Technical (batch no. 6437 (lot no. 82551); purity: 99.88%) at concentrations ranging from 0.46 to 1000 ug/ml for 3 hours at 37° C with and w/o activation in the 1st trial and from 4.12 to 1000 ug/ml in the second trial. A single culture was incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutant frequency of the treated cells. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 11/29/07)

** 52971-0038; 231355; "Bacterial Reverse Mutation Assay"; (V.O. Wagner, M.R. VanDyke; BioReliance, Rockville, MD; Study No. AB40SB.503.BTL; 1/15/07); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 to 72 hours at 37° C with Dimethyl Disulfide Technical (lot no. VS060001; purity: 99.2%) at concentrations ranging from 1.5 to 5000 ug/plate with and w/o activation in the first trial. In the second trial, the range of concentrations was adjusted to 50 to 5000 ug/plate. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S-9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 12/3/07)

CHROMOSOME EFFECTS

**** 52971-0035; 231352**; "Chromosome Analysis of Cultured Human Lymphocytes following *In Vitro* Treatment with DMDS"; (N. de Vogel, J.W.G.M. Wilmer; TNO-CIVO Toxicology and Nutrition Institute, Department of Toxicology, 3704 HE Zeist, The Netherlands; Report No. V89.045; 3/1/90);
Primary human lymphocyte cultures, procured from the whole blood of male volunteers (stimulated with PHA for 48 hours), were treated with Dimethyl Disulfide Technical (batch no. 6437; purity: 99.98%) for 2 hours, followed by an additional 22 hours of incubation after removal of the test material under conditions of activation and for 24 hours under conditions of non-activation. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases per replicate (200 cells/treatment level) were examined for structural aberrations. A treatment-related increase in chromosomal aberrations was evident under conditions of both activation and non-activation. The positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 11/30/07)

** 52971-0037; 231354; "Mammalian Erythrocyte Micronucleus Assay of DMDS in Rats"; (J.T. Weinberg; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160129; 1/18/07); Five Crl:CD® (SD) rats/sex/group were exposed whole-body to 0, 212, 425 or 850 ppm of Dimethyl Disulfide Technical (lot no. VS060001; purity: 99.2%) for 4 hours and euthanized 24 hours post-exposure. An additional 5 animals/sex/group were exposed to 0 or 850 ppm of the test material for 4 hours and euthanized 48 hours post-exposure. A positive control group of 5 animals/sex were injected ip with 40 mg/kg of cyclophosphamide and euthanized at 24 hours post-dose. The bone marrow from each study animals was assessed for the numbers of micronucleated polychromatic erythrocytes (PCE) and the ratio of PCEs to the total number of erythrocytes. Two thousand PCEs/animal were evaluated for the presence of micronuclei. There was no treatment-related increase in the percentage of micronucleated PCEs. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 12/3/07)

DNA DAMAGE

** 52971-0036; 231353; "Dimethyldisulfide: *In Vitro* DNA Repair Test on Rat Hepatocytes in Primary Culture"; (N. Bichet; Sanofi Recherche, Service Commun de Toxicologie, F34082-Montpllier, France; Study No. CEL388A/B; 2/22/90); Primary rat hepatocyte cultures were exposed to Dimethyl Disulfide Technical (batch no. 82551; purity: 99.88%) at concentrations ranging from 1 to 200 ug/ml for 18 to 20 hours at 37° C in the first assay and from 1 to 300 ug/ml under the same conditions in the second assay. Three replicates/treatment level were performed. Twenty cells per replicate were scored (60 nuclei/treatment level). Precipitation was noted at $\geq$ 100 ug/ml in both trials. There was no treatment-related increase in unscheduled DNA synthesis. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 11/30/07)

** 52971-0040; 231357; "Examination of Dimethyl Disulfide in the Micronucleus Test"; (M.I. Willems, P.G.J. Reuzel, H.R. Immel; TNO-CIVO Institutes, 3704 HE Zeist, The Netherlands; Report No. V 89.366; 10/5/89); Five CD-1 mice/sex/group were exposed to 0, 250 or 500 ppm of Dimethyl disulfide technical (batch no. 6437 (lot no. 82551), purity: 99.88%) 6 hours/day for 4 days. An additional 5 animals/sex was included in the 500 ppm group. A positive control group of five animals/sex were treated by ip injection with 1.5 mg/kg of Mitomycin C. Seven males and 5 females in the 500 ppm group died prior to the 3rd exposure. Therefore, the surviving animals in the 500 ppm group only received 3 exposures to the test material. The numbers of polychromatic erythrocytes (PCEs) and normochromatic erythrocytes (NCEs) in a population of at least 2000 erythrocytes/animal were recorded. At least one thousand PCEs/animal were evaluated for the presence of micronuclei. Likewise, the percentage of micronucleated normochromatic erythrocytes (NCEs) in the population of NCE's was determined. There was no treatment-related increase in the percentage of micronucleated PCEs. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 12/4/07)

NEUROTOXICITY

Rat Acute Neurotoxicity Study

52971-0041; 231358; "An Acute Neurotoxicity Study of Dimethyl Disulfide in Rats"; (M.D. Nemec; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160118; 9/2/05); Twelve Crl:CD® (SD)IGS BR rats/sex/group were exposed whole-body to 0, 100, 200 or 750 ppm of Dimethyl Disulfide Technical (lot no. 03.10.04; purity: 99.8%) for 6 hours. One female in the 750 ppm group died on the 1st day of the study. The mean body weight of the males in the 750 ppm group was less than that of the control during the study (p<0.01 or 0.05). In the FOB observations, the numbers of animals of both sexes in the 750 ppm group exhibiting half closed eyelids in the period immediately after the exposure were 6 and 4 out of 12 males and 11 females, respectively (p<0.05). This response was not noted for the control animals. Also, during the period immediately after the exposure, both sexes in the 750 ppm group demonstrated increased grooming behavior and urination (p<0.05). The mean body temperatures of both sexes in the 750 ppm group were less than the control values at the time of peak effect (NS, p<0.05). The total motor and locomotor activities were lower for both sexes in the 750 ppm group and for the females in the 200 ppm group (NS, p<0.05 or 0.01). No treatment-related lesions were apparent in the nervous tissues. **No adverse effect indicated. Rat Acute Neurotoxicity NOEL: (M)** 200 ppm (based upon the effects on the mean body weight, clinical signs, body temperature and motor activity of the males in the 750 ppm group); **(F)** 100 ppm (based upon the effect on motor activity noted for the females in the 200 ppm group). **Study acceptable.** (Moore, 12/5/07)

Rat Subchronic Inhalation Neurotoxicity Study

52971-0042; 231359; "A Subchronic Inhalation Neurotoxicity Study of Dimethyl Disulfide in Rats"; (M. Nemec; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160123; 6/21/06); Twelve Crl:CD® (SD) rats/sex/group were exposed whole-body to 0, 5, 20 or 80 ppm of Dimethyl Disulfide Technical (lot no. 05.05.05, purity: 99.8%) 6 hours/day, 7 days/week for 13 weeks (0, 0.02, 0.08, 0.31 mg/l under ambient conditions, calculated by reviewer). No deaths resulted from the exposure. The mean body weight, body weight gain and food consumption of the males in the 80 ppm group were less than the control values throughout the study (<0.01). The mean body weight and food consumption of the females in the 80 ppm group were less than the control values during the first week of the study (p<0.05). Thereafter, no exposure-related effect was apparent. No apparent treatment-related effects were noted in the Functional Observational Battery. In the motor activity assessment, the 80 ppm males demonstrated lower total motor activity during the 12th week of the study in comparison to the control value (p<0.05). However, the fact that the effect on the ambulatory activity at this time point was not as apparent for these animals, that there was no apparent effect on these animals at other time points during the study and that the females did not demonstrate a similar effect precluded this response as being treatment-related. Although the brain length of the males in the 80 ppm group was less than that of the controls (p<0.05), the mean relative brain weight of this group was greater than that of the control (p<0.01). The histopathological evaluation of the nervous tissue did not reveal any treatment-related lesions. Microscopic examination of the nasal turbinates revealed degeneration of olfactory epithelium in both sexes of the 20 and 80 ppm groups in an exposure-related manner. **No neurological adverse effect was evident. Possible adverse effect:** degeneration of the olfactory epithelium in the nasal turbinates. **Rat subchronic neurotoxicity NOEL:** (M/F) 80 ppm (0.31 mg/l) (based upon the lack of neurotoxic-related effects for both sexes in the 80 ppm group); **Rat subchronic inhalation NOEL:** (M/F) 5 ppm (based upon the degeneration of the olfactory epithelium in the nasal turbinates of both sexes in the 20 ppm group); **Study acceptable.** (Moore, 1/11/08)

METABOLISM

52971-0119; 269563; "Dimethyl Disulfide (DMDS): *In Vitro* Metabolism in Hepatocytes from Rats"; (P. Kilford; Covance Laboratories Ltd., North Yorkshire HG3 1PY, United Kingdom; Study No. 8260134; 8/8/12); Primary cultures of rat hepatocytes were incubated in the presence of 10

umol/l (nominal) of dimethyl disulfide (DMDS) (batch no. D58107; purity: 99.8%) in the head space for 4 hours at 37° C. The analyzed concentrations of DMDS in the medium at the initiation of the two incubations were 588 and 171 nmol/l. Two metabolites were observed in the incubation medium over the course of the 4-hour incubation, dimethyl sulfide (DMS) and methyl mercaptan as well as DMDS. There was no correlation in the study data regarding the concentration of the respective metabolite in the medium and the time of incubation. In addition, interpretation of the data was further complicated by the presence of these materials in the incubation medium when the hepatocytes were incubated in the absence of DMDS. The information provided in the report possibly identified two likely metabolites of DMDS. However, very little additional information could be derived from the data. **Study supplemental.** (Moore, 4/15/13)

52971-0119; 269564; "(^{14}C)-Dimethyl Disulfide: A Study of Absorption, Metabolism, and Excretion Following Inhalation, Oral, and Intravenous Administration to the Rat"; (H. Cotton; Covance Laboratories Ltd., North Yorkshire HG3 1PY, United Kingdom; Study No. 2532-001; 5/14/12); Four cohorts of 1 rat/sex were dosed with (^{14}C)-Dimethyl Disulfide (batch no. and radio-characteristics of the material were not provided) according to the following regimens. (A) The animals were dosed with 5 mg/kg of the test material by iv injection and the concentration of the radiolabel in the blood was assayed up to 30 minutes post-dose. (B) The animals were dosed with 5 mg/kg of the test material by iv injection and excretion samples were recovered up to 24 hours post-dose. (C) The animals were dosed orally by gavage with 5 mg/kg and tissue concentrations were assayed at 1 hour post-dose. (D) (otherwise referred to as Group 0 in the text), the animals were dosed by iv injection with the test material and a mass balance determination was performed at 24 hours post-dose. Recovery of radiolabel from the blood of the A cohort revealed an apparent peak level at or prior to 7.5 minutes post-dose with a decline in the concentration at the two succeeding sampling points. In the excretion balance analysis, exhalation of the radiolabel during the 1st 24-hours post dose was the primary route of recovery. Thirty nine and 26% of the administered dose from the male and female, respectively, were recovered in the traps (note: another 34 and 29% of the radiolabel was recovered from the carcass of the male and female, respectively, at 24 hours post-dose as determined in the (D) cohort). In the (C) cohort, the primary site of tissue distribution at 1 hour post-dose was in the liver. For the (D) cohort, only two carbon traps were employed to recover the volatile components being excreted. These traps were washed with an organic solvent and the solvent and any residual material were analyzed for the presence of the radiolabel. This procedure captured only 2.4 and 3.8% of the administered radiolabel from the male and female, respectively, up to 24 hours post-dose in comparison to the higher recovery demonstrated for cohort (A) using carbon dioxide, cold methanol and ethoxy/ethanolamine traps. These preliminary studies demonstrated the high degree of volatility of the test material and any metabolites and the difficulties in recovering a high percentage of the administered dose over the course of a specified recovery interval. **Study supplemental.** (Moore, 4/16/13)

SUBCHRONIC TOXICITY STUDIES

Rat Subchronic Inhalation Toxicity Study

52971-0026; 231343; "DMDS: 90 Day Inhalation Toxicity Study in the Rat with a 4 Week Recovery Period"; (C.J. Collins; Hazleton UK, Harrogate, North Yorkshire HG3 1PY, England; Report No. 6491-514/7; 1/14/92); Twenty Sprague-Dawley rats/sex/group were exposed whole body to 0 (filtered air), 10, 50, 150, or 250 ppm (0, 0.04, 0.20 and 0.98 mg/l at ambient conditions, calculated by reviewer) for 6 hour/day, 5 days/week for 13 weeks. Ten of the animals/sex/group were euthanized at the conclusion of the exposure period. The remaining animals were maintained for an additional recovery period of 4 weeks. An additional group of 20 animals/sex was exposed to 150 ppm (0.59 mg/l) for 6 weeks. Ten of these animals were maintained for a recovery period of two weeks after the termination of the exposures. No deaths resulted from the exposures. The mean body weight gain of both sexes in the 10 ppm group and above during the first 6 weeks of the study was less than the control values (NS, $p<0.05$, 0.01 or 0.001). The

mean food consumption of both sexes in the 50 ppm group and above was less than that of the control animals throughout the study (NS, p<0.05, 0.01 or 0.001). Shallow rapid and/or shallow labored breathing was noted for both sexes in the 10 ppm group and above during the 1st and/or 4th week of the study. During the 13th week, only the 250 ppm males demonstrated shallow rapid breathing. Salivation was noted for both sexes in the 250 ppm group during the 13th week of the study. Piloerection was evident for both sexes in the 50 ppm group and above throughout the study. Although some of the hematology parameters were lower for the 250 ppm females after 12 weeks of exposure, the apparent effect was not considered to be physiologically significant. In the clinical chemistry evaluation, the total bilirubin concentration was elevated above the control values at 6 weeks for both sexes in the 150 ppm group (NS, p<0.01) and at 6 and 12 weeks for both sexes in the 250 ppm group (NS, p<0.05, 0.01, or 0.001). The serum alkaline phosphatase activity was increased for both sexes in the 250 ppm group at 6 and 12 weeks of exposure (p<0.05). The mean kidney weight (adjusted for the mean body weights) of the males in the 250 ppm group was greater than that of the control after 13 weeks of exposure (p<0.05). The mean lung weights of both sexes in the 250 ppm group were greater than the control values (p<0.05). However, the histopathological examination did not reveal any treatment-related lesions in these organs. Squamous cell metaplasia was noted in the nasal cavity of both sexes in the 10 ppm group and above after 13 weeks of exposure. The metaplasia was still evident in both sexes of the 50 and 250 ppm groups after the 4-week recovery period. Atrophy/microcavitation of the olfactory epithelium was evident in the nasal cavities of both sexes in the 50 and 250 ppm groups after both the 13-week exposure and the 4-week recovery periods. **Possible adverse effect:** atrophy and microcavitation of the olfactory epithelium. **Rat Subchronic Inhalation Toxicity NOEL:** (M/F) < 10 ppm (0.04 mg/l) (based upon lesions in the nasal cavity and clinical signs noted for the 10 ppm group); **Study acceptable.** (Moore, 11/9/07)

Rat Subchronic Immunotoxicity Study

52971-0027; 231344; "DMDS: 90-Day Inhalation Immunotoxicity Study in the Rat with a 4 Week Recovery Period"; (C.J. Collins; Hazleton UK, Harrogate, North Yorkshire HG3 1PY, England; Report No. 6630-514/11; 5/26/94); The male rats exposed in the subchronic inhalatation toxicity study: DMDS: 90 Day Inhalation Toxicity Study in the Rat with a 4 Week Recovery Period (C.J. Collins; Hazleton UK, Harrogate, North Yorkshire HG3 1PY, England; Report No. 6491-514/7; 1/14/92) were retained for a immunotoxicity evaluation as well. Blood was collected by retro-orbital puncture from the main study animals in the control, 10, 150 and 250 ppm groups in week 12 and from the animals in the recovery groups in week 17. The blood was evaluated for total white blood cell count, total lymphocyte count, pan B-cells, pan T-cells, T-helper cells (CD4+), and T-suppressor cells (CD8+). At the time of necropsy, the blood from the main study males was recovered and analyzed by single radial immunodiffusion for IgG and IgM titers. Bone marrow was recovered from the femoral bone of each male and a myelogram was prepared in which erythropoiesis and granulopoiesis was evaluated and a general examination of the marrow cell population was undertaken. The myeloid/erythroid ratio was determined. The weights of the popliteal lymph node, the submandibular lymph node, the mesenteric lymph node and the thymus of each main study male were recorded and the lymph nodes, mid-colon lymphoid tissue, spleen and thymus were examined microscopically. Characterization of the lymphocyte population revealed a depression in the absolute numbers of CD8+ cells in the 10 and 50 ppm males at 12 and 17 weeks and a depression in the percentage of CD8+ cells of these groups at 12 weeks (p<0.05). The absolute number and percentage of CD8+ cells in the 250 ppm group was depressed at 17 weeks (p<0.01 and 0.05, respectively). Otherwise, no treatment-related effects on the white blood cell population was evident. There was no treatment-related effect upon the IgG or IgM serum concentrations of the males in the main study. In the bone marrow myelogram, there was an exposure-related trend in the decreased percentage of lymphocytes in the marrow at the 250 ppm exposure level (p<0.05). No other effect on erythropoiesis, granulopoiesis or the various cell populations was noted. The mean absolute and relative weights of the popliteal lymph node, the submandibular lymph node, the mesenteric lymph node and the thymus were not affected by the treatment. In the histopathological examination, sinus histocytosis and/or medullary plasmacytosis was noted in the various lymph nodes which were examined. However, no exposure-related effect was evident in the response. Atrophy of the peri-arterial lymphoid sheath (PALS) was noted in the spleen of the

250 ppm group (0: 2/10 vs. 250: 8/10). **Possible adverse effect:** decrease in the population of T-suppressor cells (CD8+) in the blood and atrophy of peri-arterial lymphoid sheath in the spleen. **Rat Subchronic Immunotoxicity NOEL:** (M)< 10 ppm (based upon the reduced population of the CD8+ cells in the blood of the 10 ppm animals). **Study supplemental.** (Moore, 11/14/07)

Rabbit 28-Day Repeated Dosing Dermal Toxicity Study

52971-0025; 231342; "Repeated-dose (28-Day) Dermal Toxicity Study with Dimethyl Disulfide (DMDS) in Rabbits"; (M.K. Prinsen, H.E. Falke, H.C. dreef-van der Meulen; TNO-CIVO Toxicology and Nutrition Institute, Department of Toxicology, 3704 HE Zeist, The Netherlands; Report No. V 89.371/280554; 2/2/90); The skin of ten New Zealand White rabbits/sex/group was exposed to 0 or 1063 mg/kg/day of Dimethyl Disulfide Technical (batch no. 6437; purity: 99.88%) for 6 hours/day, 5 days per week for 4 weeks under an occlusive wrap. The skin of another 5 animals/sex/group was exposed to 10.63 or 106.3 mg/kg/day of the same test material according to the same regimen. The treatment of the 1063 mg/kg group was discontinued after study day 16 due to the severe response the animals demonstrated to the test material. The surviving animals in this group were maintained on the study without further treatment until the termination. Five males and four females in the 1063 mg/kg group were found dead prior to the discontinuation of their treatment. The mean body weights of both sexes in the 1063 mg/kg group were less than those of the control group during the 1st two weeks of the study. The mean food consumption of the males in the 1063 mg/kg group was less than that of the control over the 1st two weeks of the study. In the hematology evaluation, the mean red blood count, hemoglobin concentration and the mean corpuscular hemoglobin concentration of the 1063 mg/kg males were less than that of the control ($p<0.01$). No treatment-related effects were noted in the clinical chemistry evaluation. In the necropsy examination, no treatment-related effect on absolute or relative organ weights were evident. Myocardial degeneration was noted in the hearts of the 1063 mg/kg females (0: 0/10 vs. 1063: 4/10). Myocarditis was likewise evident in the hearts of these females (0: 0/10 vs. 8/10 ($p<0.001$)). Slight to moderate acanthosis was noted at the site of application for all of animals in the 10.63 mg/kg group. Parakeratosis was also evident at the site of application for animals in the 10.63 mg/kg group and above. Subcutaneous edema was reported for animals in all of the treatment groups as well. **Possible adverse effect:** myocardial degeneration in the heart. **Rabbit Repeated Dosing 28-Day Dermal Toxicity NOEL:** (M/F) 10.63 mg/kg/day (based upon the signs of lethargy exhibited by both sexes in the 106.3 mg/kg group), **Dermal Irritation NOEL:** (M/F) < 10.63 mg/kg/day (based upon the signs of irritation at the site of application). **Study acceptable.** (Moore, 11/6/07)

Rat Acute 24-Hour Inhalation Exposure Study

52971-0110; 252156; "A Single Exposure Inhalation Toxicity Study of Dimethyl Disulfide (DMDS) in Albino Rats with Microscopic Examination of the Upper Respiratory Tract"; (D.T. Kirkpatrick; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-160135; 6/17/09); Ten male Sprague-Dawley rats were exposed whole-body to 0, 5.0, 8.9, 12.6, and 18.4 ppm (analytical) of Dimethyldisulfide (batch no. 5100DMDS09; purity: 99.5%) for 24 hours (0, 0.02, 0.036, 0.050, 0.074 mg/l under ambient conditions, calculated by reviewer). No treatment-related clinical signs or effect on body weight were noted. No treatment-related lesions were noted in the necropsy. Microscopic examination of the nasal turbinates revealed an exposure-related incidence in olfactory epithelial cell degeneration both in terms of the numbers of animals affected and in the severity of the response (particularly levels III, IV and V). An increased incidence of inflammation was noted in the olfactory and respiratory epithelium of the 18.4 ppm group as well. **Possible adverse effect:** epithelial cell degeneration in the nasal turbinates; **Rat Acute Inhalation NOEL (24-hour exposure):** 5 ppm (based upon an increased incidence in olfactory epithelial cell degeneration in the 8.9 ppm exposure group); **Study supplemental** (non-guideline study). (Moore, 6/16/10)