

**SCREENING-LEVEL HAZARD CHARACTERIZATION
FOR HIGH PRODUCTION VOLUME CHEMICALS**

SPONSORED CHEMICAL

**Dimethyl Sulfoxide (CAS No. 67-68-5)
[9th CI Name: Methane, Sulfinylbis-]**

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Prepared by

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SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program¹ is a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website³.

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to “bin” chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance^{2,4} and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA² and OECD⁵ guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT’s existing chemicals review process. These hazard characterizations are technical documents intended to support subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations^{4,6}. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. HPV Chemicals Hazard Characterization website (<http://www.epa.gov/hpvis/abouthc.html>).

⁴ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

⁵ OECD. Guidance on the Development and Use of Chemical Categories; <http://www.oecd.org/dataoecd/60/47/1947509.pdf>.

⁶ U.S. EPA. Risk Characterization Program; <http://www.epa.gov/osa/spc/2riskchr.htm>.

SCREENING-LEVEL HAZARD CHARACTERIZATION Dimethyl Sulfoxide (CAS No. 67-68-5)

Introduction

The sponsor, Dimethyl Sulfoxide (DMSO) Producers Association, submitted a Test Plan and Robust Summaries to EPA for Dimethyl sulfoxide (Dimethyl sulfoxide, CAS No. 67-68-5; 9th CI name: methane, sulfinylbis-) on August 12, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on October 15, 2003 (<http://www.epa.gov/chemrtk/pubs/summaries/dimthslf/c14721tc.htm>). EPA comments on the original submission were posted to the website on February 19, 2004. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on June 15, 2005 and August 30, 2005, which were posted to the ChemRTK website on July 5, 2005 and September 20, 2005, respectively.

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. In preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Summary-Conclusion

The log K_{ow} value of dimethyl sulfoxide indicates that its potential to bioaccumulate is low. Dimethyl sulfoxide is readily biodegradable, indicating that it does not have the potential to persist in the environment.

The evaluation of available aquatic toxicity data for freshwater fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of dimethyl sulfoxide to aquatic organisms is low.

Acute oral toxicity of dimethyl sulfoxide in rats and mice and acute inhalation toxicity in rats is low. Dimethyl sulfoxide is slightly to non-irritating to skin and eyes. Following repeated inhalation exposure of rats for 13 weeks target organs included the nasal passages and pharynx. Irritation of the nasal passages and pharynx were observed along with red-staining around the nose. Following repeated oral exposure of monkeys for 18 months primary effects included increased mortality, ptyalism and emesis, and decreased body weight at the highest dose level. Following repeated dermal exposure of monkeys for 18 months, primary effects included a non-dose-dependent scaling and flaking of the skin. Examination of the reproductive system during a 13-week inhalation repeated-dose toxicity study in rats revealed no abnormalities on estrus cycle in females, sperm count, motility or morphology in males, or on the reproductive organs of both sexes. In two oral developmental toxicity studies in rats, maternal effects included decreased food consumption and decreased body weight gain. Developmental effects included decreased fetal weights, higher rates of early resorptions per animal, increased total post-implantation loss, dilated renal pelvis, dilated ureters and reduced or delayed ossification of ribs. All of the fetal effects except dilated renal pelvis occurred at levels that demonstrated maternal toxicity. Dimethyl sulfoxide did not show a potential to induce gene mutations in bacterial or yeast cells, and was not mutagenic in *in vivo* studies in *Drosophila*. Dimethyl sulfoxide did not induce micronuclei or sister-chromatid exchange in mice or chromosomal aberrations or sister chromatid exchange in mammalian cells, but did induce an increase in chromosomal aberrations in rats.

The potential health hazard of dimethyl sulfoxide is moderate based on repeated-dose and reproductive/developmental toxicity. Available data suggest dimethyl sulfoxide has the potential to be genotoxic.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical properties and environmental fate data submitted is provided in the Appendix. For the purpose of the screening-level hazard characterization, the review and summary of these data was limited to the octanol-water partition coefficient and biodegradation endpoints as indicators of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

Log K_{ow} : -1.35

Biodegradation:

In a study biodegradation of the test compound was determined by analyzing for dissolved organic carbon (DOC). The test compound had an initial concentration of 162 mg/L and degraded by 99% after 27 days.

Dimethyl sulfoxide is readily biodegradable.

Conclusion: The low log K_{ow} value of dimethyl sulfoxide indicates that its potential to bioaccumulate is low. Dimethyl sulfoxide is readily biodegradable, indicating that it does not have the potential to persist in the environment.

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

(1) Fathead minnows (*Pimephales promelas*; 10/concentration) were exposed to dimethyl sulfoxide at nominal concentrations of 0, 11.4, 22.8, 34.1, 45.5 or 56.9 g/L for 96 hours under flow-through conditions. Average (of measurements at 0, 24, 48, 72 and 96 hours) measured concentrations were 8.91, 20.3, 27.2, 41.9 and 56.6 g/L, respectively. No mortality occurred at 0, 11.4 and 22.8 g/L and 100% mortality occurred at 45.5 and 56.9 g/L groups by 24 hours.

96-h LC_{50} = 34 g/L

(2) Japanese killifish (*Oryzias latipes*; 10/concentration) were exposed to dimethyl sulfoxide under static or semi-static conditions for 48 hours.

48-h LC_{50} = 33 g/L

(3) Rainbow trout (*Oncorhynchus mykiss*; 10/concentration) were exposed to dimethyl sulfoxide for 96 hours under static conditions. No analytical measurements were performed.

96-h LC_{50} = 33-37 g/L

(4) Bluegill sunfish (*Lepomis macrochirus*; 10/concentration) were exposed to dimethyl sulfoxide for 96 hours under static conditions. No analytical measurements were performed.

96-h LC_{50} > 40 g/L

Acute Toxicity to Aquatic Invertebrates

(1) *Daphnia magna* (10/concentration) were exposed to dimethyl sulfoxide for 48 hours under static conditions.

48-h EC_{50} = 24.6 g/L

Toxicity to Aquatic Plants

(1) Green algae (*Chlorella pyrenoidosa*) were exposed to nominal concentrations ranging from 1.0 to 40 g/L for 10-14 days (precise duration not specified).

10-14-d EC_{50} (growth) = 20.1 g/L

Conclusion: The evaluation of available aquatic toxicity data for freshwater fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of dimethyl sulfoxide to aquatic organisms is low.

3. Human Health Effects

Acute Oral Toxicity

(1) Carworth CFN rats (5/sex/group) were administered doses of dimethyl sulfoxide at 10, 20 or 40 g/kg-bw by oral gavage followed by a 14-day observation period. Clinical signs at lethal doses included ataxia, myasthenia, decreased motor activity and bradypnea (slow breathing) shortly after administration. Clinical signs at nonlethal doses included decreased motor activity, polydipsia (drinking large volume of fluids) and polyuria (frequent urination). All deaths, with the exception of one, occurred within 24 hours.

LD₅₀ = 28.3 g/kg-bw

(2) Albino mice (5/sex/group) were administered doses of dimethyl sulfoxide at 10, 20 or 40 g/kg-bw by oral gavage followed by a 14-day observation period. Clinical signs at lethal doses included ataxia, myasthenia, decreased motor activity and bradypnea. Clinical signs at nonlethal doses included decreased motor activity. All deaths, with the exception of one, occurred within 24 hours.

LD₅₀ = 17.1 – 26.9 g/kg-bw

Acute Inhalation Toxicity

(1) Male Sprague-Dawley rats (three groups of eight animals) were exposed to dimethyl sulfoxide at a concentration of 1.6 mg/L for 4 hours. One group was sacrificed directly after exposure, one group 24 hours after exposure, and one group 14 days after exposure. No mortality or clinical signs of toxicity occurred during or after exposure to the test substance. Organs appeared normal at necropsy and histopathology revealed focal and diffuse collections of clear pneumocytes within the lung alveoli of dimethyl sulfoxide-treated rats

4-h LC₅₀ > 1.6 mg/L

(2) Male Sprague-Dawley rats (eight animals) were exposed to dimethyl sulfoxide at a concentration of 2.9 mg/L for 24 hours and were sacrificed immediately afterward. No mortality or clinical signs of toxicity occurred during or after exposure to the test substance. Organs appeared normal at necropsy and histopathology revealed areas of pulmonary edema in dimethyl sulfoxide-treated rats

24-h LC₅₀ > 2.9 mg/L

(3) Male Sprague-Dawley rats (eight animals) were exposed to dimethyl sulfoxide at a concentration of 2.0 mg/L for 40 hours and were sacrificed immediately afterward. No mortality or clinical signs of toxicity occurred during or after exposure to the test substance. Organs appeared normal at necropsy and histopathology revealed focal and diffuse collections of clear pneumocytes within the lung alveoli and areas of pulmonary edema in dimethyl sulfoxide-treated rats.

40-h LC₅₀ > 2.0 mg/L

Repeated-Dose Toxicity Study

(1) Sprague-Dawley rats (10/sex/concentration) were exposed to dimethylsulfoxide at mean measured exposure concentrations of 0, 0.310, 0.954 or 2.783 mg/L for 6 hours/day 7 days/week. Treatment-related clinical signs consisted of red staining around the nose in the intermediate- and high-concentration groups. Animals exposed to the test substance gained less weight over the 13-week period compared to controls. Differences from control were small and attributed to a low degree of inappetence caused by mild irritation of the test atmosphere. Lung weights of male animals exposed to dimethyl sulfoxide were greater than those in control animals. The differences were not considered attributable to dimethyl sulfoxide exposure because they were small, not dose-related, and not seen in females. Treatment-related changes were found in the nasal passages and pharynx of high-concentration females, but not in the low- or mid-concentration groups. Changes included lesions in the inferior ventral medial meatus and an increased degree of eosinophilic inclusions in the olfactory epithelium. In the pharynx, prominent goblet cells were present in the majority of high-concentration rats.

NOAEL (systemic toxicity) = 2.783 mg/L (highest concentration tested)

LOAEL (local irritation) = 2.783 mg/L (based on histopathological lesions in the respiratory tract)

NOAEL (local irritation) = 0.964 mg/kg-bw

(2) Monkeys (*Macaca mulatta*) were administered dimethyl sulfoxide (in two doses/day in water) via oral gavage at doses of 0, 990, 2970 and 8910 mg/kg-bw twice a day for 18 months. Two monkeys per sex received the low- or mid- dose levels and three per sex received the high dose. Six animals at the high-dose level died during the study, one accidentally and five as a result of treatment with the test substance. Clinical signs observed included ptialism and emesis, which occurred sporadically and was not related to treatment, except in the high-dose group. Anorexia occurred in the high-dose group and erythema occurred sporadically in all treated groups. Marked decreases in body weight occurred in the high-dose group. During physical examinations throughout the study, no treatment-related changes were found for systolic blood pressure, heart or respiratory rate, body temperature, water consumption, neurological reflexes or electrocardiogram. No significant changes were noted for hematological or biochemical parameters, urinalysis, gross necropsy, absolute or relative organ weights or histology.

LOAEL = 8910 mg/kg-bw/day (based on increased mortality, ptialism and emesis and decreased body weight)

NOAEL = 2970 mg/kg-bw/day

(3) Monkeys (*Macaca mulatta*) were administered dimethyl sulfoxide dermally at doses of 0, 990, 2970 and 8910 mg/kg-bw for 18 months. There were two males and one female in the control group, two animals per sex in the low and mid dose levels, and three animals per sex in the high-dose group. Several accidental deaths in control and test groups occurred as a result of attempts to escape the restrained position. This was not attributed to the test substance. All animals treated topically with the test substance exhibited scaling and flaking of skin; however, there did not appear to be any differences among the treatment levels. Erythema occurred sporadically in all treatment groups. No statistically significant changes in body weight, hematological or biochemical parameters, gross necropsy or histology were noted during the study.

LOAEL > 8910 mg/kg-bw/day (highest dose tested)

NOAEL = 8910 mg/kg-bw/day

Reproductive Toxicity

A reproductive toxicity test was not submitted to address the reproductive toxicity endpoint. Evaluation of reproductive organs in repeated-dose toxicity study was used to address the reproductive endpoints for the purposes of the HPV Challenge Program. Therefore, NOAEL/LOAELs for fertility and/or reproductive toxicity cannot be determined for this endpoint.

In the 13-week repeated-dose inhalation toxicity study conducted in rats discussed previously, the reproductive system was evaluated. The estrus cycle in female rats was monitored, male rats were subject to sperm investigations (count, motility and morphology) and the reproductive organs of both sexes were examined histologically. No treatment-related effects were observed at any dose level.

Developmental Toxicity

(1) Pregnant Sprague-Dawley rats were exposed to dimethyl sulfoxide at doses of 0, 200, 1000 or 5000 mg/kg-bw/day on days 6-15 of gestation. There were no clinical signs of maternal toxicity in any treatment or control group. No maternal deaths or abortions occurred. Decreased food consumption was noted in high-dose females and body weight gain was slightly depressed. No macroscopic findings were noted in dams at necropsy. Pre- and post-implantation losses were similar in all treatment and control groups. No treatment-related effects on number of fetuses or sex-ratio were noted. In the high-dose group, fetal body weights were slightly decreased. No external malformations or abnormalities were noted. Increased incidences of two soft tissue malformations were observed: dilated renal pelvis in all treated groups and increased incidence of dilated ureters at the high-dose level. There were no treatment-related skeletal malformations. An increase of reduced or delayed ossification of ribs was observed in fetuses at the high-dose level. No treatment-related microscopic changes were noted in the kidneys of fetuses with dilated renal pelvis.

LOAEL (maternal toxicity) = 5000 mg/kg-bw/day (based on decreased food consumption and body weight gain)

NOAEL (maternal toxicity) = 1000 mg/kg-bw/day

LOAEL (developmental toxicity) = 200 mg/kg-bw/day (based on dilated renal pelvis at lowest dose tested)

NOAEL (developmental toxicity) < 200 mg/kg-bw/day

(2) Pregnant Sprague-Dawley rats were exposed to dimethyl sulfoxide at doses of 0, 1000, 5000 or 10,000 mg/kg-bw/day on days 6-15 of gestation. There were no clinical signs of maternal toxicity in any treatment or control group. No maternal deaths or abortions occurred. Decreased food consumption was noted in mid- and high-dose females and body weight gain was depressed. No macroscopic findings were noted in dams at necropsy. The mean number of corpora lutea and implantation sites per animal showed some variations between treatment and control groups, but the variations were not dose-dependent and could not be ascribed to treatment. No late resorptions or dead fetuses were noted in any group. Higher rates of early resorptions per animal, and higher total post implantation loss were observed in the mid- and high-dose levels. A treatment-related decrease in the rate of live fetuses was slightly lower in the 5000 and 10,000 mg/kg-bw groups. Slight to moderately lower fetal body weights were noted in the 5000 and 1000 mg/kg-bw groups. The sex ratio was similar in control and treated groups. No external abnormalities or malformations were observed in fetuses from any group.

LOAEL (maternal/developmental toxicity) = 5000 mg/kg-bw/day (based on decreased food consumption and body weight gain and on decreased fetal weight, higher rates of early resorptions per animal, higher total post-implantation loss)

NOAEL (maternal toxicity) = 1000 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

(1) Dimethyl sulfoxide was investigated in several *in vitro* reverse mutation studies in *Salmonella typhimurium*. The first study used concentrations of 100, 333, 1000, 3333 or 10,000 µg/plate and employed several strains (TA97, TA98, TA100, TA102, TA104, TA1535, TA 1537 and TA 1538) in the presence and absence of metabolic activation. A second study used concentrations up to 500 mg per plate and employed several strains (TA 98, TA 100, TA 1535, TA 1537 and TA 1538) in the presence and absence of metabolic activation. A third study tested concentrations up to 1.4 mM per plate and employed several strains (TA 98, TA 100, TA 1535, TA 1537 and TA 1538) in the presence and absence of metabolic activation. A fourth study used concentrations between 100 and 300 mg/plate and employed strains TA 97, TA 98 and TA 100 with and without metabolic activation. Positive and negative control were explicitly employed in several of the studies and responded accordingly. Cytotoxic concentrations were not identified in any of the studies.

Dimethyl sulfoxide was not mutagenic in these assays.

(2) Dimethyl sulfoxide did not induce gene mutations in yeast in tests in *Saccharomyces cerevisiae* D4 and D5 at concentrations up to 1400 mM in the absence of metabolic activation and *Schizosaccharomyces pombe* up to 5% (v/v) in the presence and absence of metabolic activation.

Dimethyl sulfoxide was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Dimethyl sulfoxide was tested in a cytogenetic assay in Chinese hamster ovary (CHO) cells. Cells were exposed to concentrations up to 4990 µg/mL in the presence and absence of metabolic activation. In a second study, dimethyl sulfoxide was evaluated in a sister chromatid assay in CHO cells at concentrations up to 5000 µg/mL in the presence and absence of metabolic activation. Positive controls were tested, but responses to the controls were not indicated.

Dimethyl sulfoxide was not mutagenic in this assay.

In vivo

(1) Dimethyl sulfoxide was tested in a micronucleus assay in which male B6C3F1 mice were exposed to doses of 5 mL/kg-bw by the intraperitoneal route and sacrificed at 24, 48 or 72 hours after exposure. In a second experiment, female ICR mice were exposed to doses of 2.5, 5.0, 10.0 or 20.0 mL/kg-bw by the intraperitoneal route and sacrificed 24 hours after dosing to determine if the test substance induced sister chromatid exchange.

Dimethyl sulfoxide was not mutagenic in this assay.

(2) In an *in vivo* cytogenetic assay, male Spague-Dawley rats (10/dose level) were dosed with 0, 0.05, 0.5, 2.5 or 5 mL/kg-bw by intraperitoneal administration daily for 5 days. Twenty-four hours after the last dose, the animals were sacrificed. Three animals in the high-dose group died prior to termination of the study. All groups treated with the test substance showed a statistically significant increase in the number of chromosomal aberrations compared to the negative control group. The level of chromatid breaks was significantly higher in all test groups except 0.5 mL/kg, while the incidence of markers was significantly higher in all test groups compared to the negative control. The number of severely damaged cells at the highest dose level was significantly greater than the other dose groups.

Dimethyl sulfoxide demonstrated the potential to induce chromosomal aberrations in this assay.

Genetic Toxicity – Other Effects

In vivo

Dimethyl sulfoxide did not induce sex-linked recessive lethal mutations in an assay in *Drosophila melanogaster* after intra-abdominal injection of 0.2 µL of 0.1, 1.0 and 5.0% (v/v). Two somatic mutation assays in *D. melanogaster* were negative for the induction of mutations. One study tested dimethyl sulfoxide at 1% in oral feed for exposure periods of 2, 8 and 24 hours. The second evaluated the test substance at dose levels of 12.8 or 128 mM in feed during an exposure period of 3 days.

Dimethyl sulfoxide was not mutagenic in these assays.

Additional Information

Skin Irritation

(1) Rabbits were exposed to the test substance under occlusive dressing for 24 hours. No effects were observed except for a slight erythema, which faded quickly after patch removal.

Dimethyl sulfoxide was not irritating to skin.

(2) Guinea pigs were exposed to the test substance under occlusive dressing for 4 hours. The primary dermal irritation index (PDII) was 1.2.

Dimethyl sulfoxide was slightly irritating to skin.

(3) Five male mice were exposed to the test substance on open skin twice a week for 30 weeks. No discernable effect on the skin was observed.

Dimethyl sulfoxide was not irritating to skin.

Eye Irritation

In four separate eye irritation tests, rabbits were exposed to 0.1 mL of dimethyl sulfoxide for 24 hours. In one study, slight conjunctivitis was noted at the 24-hour observation period, but dissipated by the 48 hour observation. In another study, slight erythema of the conjunctiva was noted over the first 3 days and a low level of chemosis, iritis and corneal opacity was noted.

Dimethyl sulfoxide was slightly irritating to eyes.

Sensitization

(1) In several sensitization tests with dimethyl sulfoxide were conducted in guinea pigs and mice.

Dimethyl sulfoxide was not a sensitizer in these assays.

(2) A murine local lymph node assay, mice (3/group) were exposed to undiluted test substance in an open epicutaneous manner. A small increase (approximately 2-fold) in LNC proliferation occurred compared with the water-solution treated group

No conclusion was provided about whether the results are interpreted as sensitizing or non-sensitizing.

Conclusion: Acute oral toxicity of dimethyl sulfoxide in rats and mice and acute inhalation toxicity in rats is low. Dimethyl sulfoxide is slightly to non-irritating to skin and eyes. Following repeated inhalation exposure of rats for 13 weeks target organs included the nasal passages and pharynx. Irritation of the nasal passages and pharynx were observed along with red-staining around the nose. Following repeated oral exposure of monkeys for 18 months primary effects included increased mortality, ptyalism and emesis, and decreased body weight at the highest dose level. Following repeated dermal exposure of monkeys for 18 months, primary effects included a non-dose-dependent scaling and flaking of the skin. Examination of the reproductive system during a 13-week inhalation repeated-dose toxicity study in rats revealed no abnormalities on estrus cycle in females, sperm count, motility or morphology in males, or on the reproductive organs of both sexes. In two oral developmental toxicity studies in rats, maternal effects included decreased food consumption and decreased body weight gain. Developmental effects included decreased fetal weights, higher rates of early resorptions per animal, increased total post-implantation loss, dilated renal pelvis, dilated ureters and reduced or delayed ossification of ribs. All of the fetal effects except dilated renal pelvis occurred at levels that demonstrated maternal toxicity. Dimethyl sulfoxide did not show a potential to induce gene mutations in bacterial or yeast cells, and was not mutagenic in *in vivo* studies in *Drosophila*. Dimethyl sulfoxide did not induce micronuclei or sister-chromatid exchange in mice or chromosomal aberrations or sister chromatid exchange in mammalian cells, but did induce an increase in chromosomal aberrations in rats.

The potential health hazard of dimethyl sulfoxide is moderate based on repeated-dose and reproductive/developmental toxicity. Available data suggest dimethyl sulfoxide has the potential to be genotoxic.

4. Hazard Characterization

The low log K_{ow} value of dimethyl sulfoxide indicates that its potential to bioaccumulate is low. Dimethyl sulfoxide is readily biodegradable, indicating that it does not have the potential to persist in the environment.

The evaluation of available aquatic toxicity data for freshwater fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of dimethyl sulfoxide to aquatic organisms is low.

Acute oral toxicity of dimethyl sulfoxide in rats and mice and acute inhalation toxicity in rats is low. Dimethyl sulfoxide is slightly to non-irritating to skin and eyes. Following repeated inhalation exposure of rats for 13 weeks target organs included the nasal passages and pharynx. Irritation of the nasal passages and pharynx were observed along with red-staining around the nose. Following repeated oral exposure of monkeys for 18 months primary effects included increased mortality, ptyalism and emesis, and decreased body weight at the highest dose level. Following repeated dermal exposure of monkeys for 18 months, primary effects included a non-dose-dependent scaling and flaking of the skin. Examination of the reproductive system during a 13-week inhalation repeated-dose toxicity study in rats revealed no abnormalities on estrus cycle in females, sperm count, motility or morphology in males, or on the reproductive organs of both sexes. In two oral developmental toxicity studies in rats, maternal

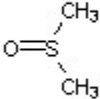
effects included decreased food consumption and decreased body weight gain. Developmental effects included decreased fetal weights, higher rates of early resorptions per animal, increased total post-implantation loss, dilated renal pelvis, dilated ureters and reduced or delayed ossification of ribs. All of the fetal effects except dilated renal pelvis occurred at levels that demonstrated maternal toxicity. Dimethyl sulfoxide did not show a potential to induce gene mutations in bacterial or yeast cells, and was not mutagenic in *in vivo* studies in *Drosophila*. Dimethyl sulfoxide did not induce micronuclei or sister-chromatid exchange in mice or chromosomal aberrations or sister chromatid exchange in mammalian cells, but did induce an increase in chromosomal aberrations in rats.

The potential health hazard of dimethyl sulfoxide is moderate based on repeated-dose and reproductive/developmental toxicity. Available data suggest dimethyl sulfoxide has the potential to be genotoxic.

5. Data Gaps

No data gaps were identified under the HPV Challenge Program.

APPENDIX

Summary Table of the Screening Information Data Set as submitted under the U.S. HPV Challenge Program									
Endpoints	SPONSORED CHEMICAL Dimethyl sulfoxide (67-68-5)								
Structure									
Summary of Physical-Chemical Properties and Environmental Fate Data									
Melting Point (°C)	18.5								
Boiling Point (°C)	189								
Vapor Pressure (hPa at 25°C)	0.81								
Log K_{ow}	-1.35								
Water Solubility (mg/L at 25°C)	1×10 ⁶								
Direct Photodegradation	Does not contain chromophores that will absorb light at wavelengths > 290 nm								
Indirect (OH) Photodegradation Half-Life (t_{1/2})	3 h (estimated)								
Stability in Water (Hydrolysis) Half-Life (t_{1/2})	Stable to hydrolysis in water								
Biodegradation at 28 days (%)	99 Readily biodegradable								
Fugacity (Level III Model)	<table border="0"> <tr> <td align="right">Air (%)</td> <td align="center"><1</td> </tr> <tr> <td align="right">Water (%)</td> <td align="center">45.9</td> </tr> <tr> <td align="right">Soil (%)</td> <td align="center">53.9</td> </tr> <tr> <td align="right">Sediment (%)</td> <td align="center"><1</td> </tr> </table>	Air (%)	<1	Water (%)	45.9	Soil (%)	53.9	Sediment (%)	<1
Air (%)	<1								
Water (%)	45.9								
Soil (%)	53.9								
Sediment (%)	<1								
Summary of Environmental Effects – Aquatic Toxicity Data									
Fish 96-hr LC₅₀ (mg/L)	34,000								
Aquatic Invertebrates 48-hr EC₅₀ (mg/L)	24,800								
Aquatic Plants 96-hr EC₅₀ (mg/L)	20,100 (10 – 14-d)								
(growth) (biomass)									
Summary of Human Health Data									
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	17.1								
Acute Inhalation Toxicity LC₅₀ (mg/L)	> 1.6								

Endpoints	SPONSORED CHEMICAL Dimethyl sulfoxide (67-68-5)
Repeated-Dose Toxicity in Rats NOAEL/LOAEL Oral (mg/kg-bw/day)	LOAEL = 8900 (18-month, monkey)
Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L; 6-h/day/day)	LOAEL (local irritation) = 2.783 LOAEL (systemic toxicity) > 2.783
Reproductive Toxicity	Evaluation of reproductive organs from the repeated-dose study showed no effects.
Developmental Toxicity (mg/kg-bw/day) <div style="text-align: right;">Maternal Toxicity</div> <div style="text-align: right;">Developmental Toxicity</div>	NOAEL = 1000 LOAEL = 500 NAOEL < 200 LAOEL = 200
Genetic Toxicity - Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity - Gene Mutation <i>In vivo</i>	—
Genetic Toxicity - Chromosomal aberrations <i>In vitro</i>	Positive
Genetic Toxicity - Chromosomal aberrations <i>In vivo</i>	Negative
Additional Information - Eye irritation Skin irritation Sensitization	Slightly irritating (rabbits) Slightly irritating (rabbits) Not a sensitizer