

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### Diphenyl Oxide (CASRN 101-84-8)

The High Production Volume (HPV) Challenge Program<sup>1</sup> was conceived as 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 sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did 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<sup>1,2</sup>) 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 by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, 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. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

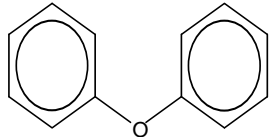
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<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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

<sup>3</sup> U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

These hazard characterizations are technical documents intended to inform 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.

|   |  |
|---|--|
| <p><b>Chemical Abstract Service Registry Number (CASRN)</b></p>   | <p><b>101-84-8</b></p>   |
| <p><b>Chemical Abstract Index Name</b></p>  | <p><b>Benzene, 1,1'-oxybis-</b></p>  |
| <p><b>Structural Formula</b></p>  |  |
| <p style="text-align: center;"><b>Summary</b></p> <p>CASRN 101-84-8, benzene, 1,1'-oxybis-, is a white crystalline solid or colorless liquid with moderate water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization is considered moderate based on the Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. CASRN 101-84-8 is not readily biodegradable and is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).</p> <p>Acute oral toxicity and acute dermal toxicity of CASRN 101-84-8 to rats and rabbits, respectively, is low. No mortality was seen when rats were exposed to the saturated vapor of CASRN 101-84-8 for six hours. Acute inhalation toxicity of Therminol VP-1 (CASRN 101-84-8, 73.5% and biphenyl (CASRN 92-52-4, 26.5%)) to rats is low. Dietary exposure of rats to CASRN 101-84-8 for 90 days resulted in markedly decreased mean body weight and food consumption in high-dose animals, but this was attributed to unpalatability of the test substance. Therefore, there were no treatment-related effects; the NOAELs were approximately 301 mg/kg-bw/day for males and 334 mg/kg-bw/day for females (highest doses tested). Inhalation exposure of rats, rabbits and dogs to CASRN 101-84-8 vapor resulted in portal of entry effects only; no systemic toxicity was observed up to 20 ppm (0.14 mg/L/day). No reproductive toxicity studies are available. However, the 90-day dietary toxicity study in rats showed no adverse treatment-related effects on reproductive organs. A prenatal developmental oral (gavage) toxicity study of Therminol VP-1 in rats revealed maternal toxicity at 200 mg/kg-day and above (mortality and reduced body weight gain) but showed no treatment-related developmental effects. The NOAEL for maternal toxicity was 50 mg/kg-day and for developmental toxicity it was 500 mg/kg-day (highest dose tested). CASRN 101-84-8 did not induce gene mutations in bacterial cells or chromosomal aberrations in mammalian cells <i>in vitro</i>. Therminol VP-1 did not induce gene mutations in bacterial cells <i>in vitro</i> or micronuclei in mice bone marrow <i>in vivo</i>. CASRN 101-84-8 was slightly to severely irritating to rabbit skin and slightly irritating to rabbit eyes.</p> <p>The acute 96-hr LC<sub>50</sub> of CASRN 101-84-8 for fish is 4.2 mg/L (2.06 mg/L - estimated). The acute 48-hr EC<sub>50</sub> value of CASRN 101-84-8 for aquatic invertebrates is 1.7 mg/L (1.58 mg/L – estimated). The 96-hr EC<sub>50</sub> value of CASRN 101-84-8 for algae is 2.5 mg/L (1.82 mg/L – estimated). Since this is a volatile chemical and testing performed with nominal concentrations may underestimate its toxicity, the estimated ecotoxicity values are used in support of this chemical's experimental results.</p> |  |

There are no data gaps identified under the HPV Challenge Program.

The sponsor, Solutia Inc. and The Dow Chemical Company, submitted a Test Plan and Robust Summaries to EPA for diphenyl oxide (CASRN 101-84-8; CA Index name: benzene, 1,1'-oxybis-) on December 20, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on January 22, 2003 (<http://www.epa.gov/chemrtk/pubs/summaries/diphoxid/c14164tc.htm>). EPA comments on the original submission were posted to the website on May 27, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 21, 2003, which were posted to the ChemRTK website on October 29, 2003.

## 1. Chemical Identity

### 1.1. Identification and Purity

The following description is taken from the 2002 Test Plan and Robust Summary:

Diphenyl oxide is manufactured by two US producers and is sold primarily to industrial customers, both in the U.S. and in the rest of the world, for use either as a heat transfer fluid (blended with biphenyl) or as a chemically reacted intermediate in the production of flame retardants, surfactants, textile dye labeling and in coating applications. Diphenyl oxide's use as a chemical intermediate and as a heat transfer fluid, diphenyl oxide is processed and utilized exclusively in closed systems.

Although not mentioned in the test plan, the robust summaries indicate that the purity of diphenyl oxide was greater than 98%. Therminol VP-1 (heat transfer fluid) is a mixture of 73.5% diphenyl oxide and 26.5% biphenyl and was used in some human health effects testing (acute inhalation, genotoxicity and developmental toxicity).

### 1.2. Physical Chemical Properties

CASRN 108-84-8 is a white crystalline solid or colorless liquid with moderate water solubility and moderate vapor pressure.

The physical-chemical properties of CASRN 101-84-8 are summarized in Table 1.

| <b>Property</b>                          | <b>Value</b>  |
|--|---|
| CASRN                                    | 101-84-8  |
| Molecular Weight                         | 170   |
| Physical State                           | White crystalline solid or colorless liquid                           |
| Melting Point                            | 28°C (measured)   |
| Boiling Point                            | 257–259°C (measured)  |
| Vapor Pressure                           | 0.020 mm Hg at 20°C (measured)  |
| Water Solubility                         | 21 mg/L at 25°C (measured)  |
| Dissociation Constant (pK <sub>a</sub> ) | Not applicable  |
| Henry's Law Constant                     | 2.8×10 <sup>-4</sup> atm·m <sup>3</sup> /mole (measured) <sup>2</sup> |
| Log K <sub>ow</sub>                      | 4.2 (measured)  |

<sup>1</sup> Solutia Inc. and the Dow Chemical Company. September 12, 2003. Final Revised Test Plan and Robust Summary for Diphenyl Oxide. Available from:

<http://www.epa.gov/chemrtk/pubs/summaries/diphoxid/c14164tc.htm> as of December 19, 2009.

<sup>2</sup> SRC. 2009. The Physical Properties Database (PHYSPROP). SRC: Syracuse, NY. Available from: <http://www.srcinc.com/what-we-do/free-demos.aspx> as of December 19, 2009.

## **2. General Information on Exposure**

### **2.1. Production Volume and Use Pattern**

According to the 2006 IUR submissions, CASRN 101-84-8 had aggregated production and/or import volume(s) in the United States between 50 million and 100 million pounds.

Non-confidential industrial processing and uses reported in the 2006 IUR submissions for this chemical include pesticide and other agricultural chemical manufacturing, other basic organic chemical manufacturing, soap and cleaning compound manufacturing, chemical product and preparation manufacturing and food manufacturing. Non-confidential commercial and consumer uses include NRO (Not Readily Obtainable).

### **2.2. Environmental Exposure and Fate**

CASRN 101-84-8 is expected to have moderate mobility in soil. CASRN 101-84-8 was inherently biodegradable using a modified semi-continuous activated sludge (SCAS) test (OECD 302A). Additional screening studies using effluent from a domestic wastewater treatment plant resulted in over 70% degradation within 20 days; however, CASRN 101-84-8 only degraded by 6.3% after 28 days in an OECD TG 301C test. Thus, CASRN 101-84-8 is not readily biodegradable based on these results. Volatilization is considered moderate based on the Henry's Law constant. The rate of hydrolysis is considered negligible. CASRN 101-84-8 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

The environmental fate data are provided in Table 2.

| Property                                   | Value   |
|--|---|
| Photodegradation Half-life                 | 1 day (estimated)   |
| Hydrolysis Half-life                       | Stable  |
| Biodegradation                             | 51–94% after 7 days (inherently biodegradable);<br>76% after 20 days (readily biodegradable)<br>6.3% after 28 days OECD TG 301C (not readily biodegradable) <sup>2</sup><br>20% after 75 days (resistant to biological action) <sup>3</sup> |
| Bioconcentration Factor                    | BCF = 196 (measured in trout);<br>BCF = 112–583 (measured in carp) <sup>2</sup> ;<br>BCF = 49–594 (measured in carp) <sup>2</sup>   |
| Bioaccumulation Factor                     | BAF = 286 (estimated) <sup>4</sup>  |
| Log K <sub>oc</sub>                        | 3.2 (estimated) <sup>4</sup>  |
| Fugacity<br>(Level III Model) <sup>3</sup> |   |
| Air (%)                                    | 2.9   |
| Water (%)                                  | 18.3  |
| Soil (%)                                   | 77.7  |
| Sediment (%)                               | 1.1   |
| Persistence <sup>5</sup>                   | P2 (moderate)   |
| Bioaccumulation <sup>5</sup>               | B1 (low)  |

<sup>1</sup> Solutia Inc. and the Dow Chemical Company. September 12, 2003. Final Revised Test Plan and Robust Summary for Diphenyl Oxide. Available from: <http://www.epa.gov/chemrtk/pubs/summaries/diphoxid/c14164tc.htm> as of December 19, 2009.

<sup>2</sup> National Institutes of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available from: [http://www.safe.nite.go.jp/english/kizon/KIZON\\_start\\_hazkizon.html](http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html) as of December 19, 2009.

<sup>3</sup> HSDB. 2008. Hazardous Substances Data Bank. Available from: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> as of February 18, 2010.

<sup>4</sup> U.S. EPA. 2009. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available from: <http://www.epa.gov/opptintr/exposure/pubs/episutedl.htm> as of December 19, 2009.

<sup>5</sup> Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

**Conclusion:** CASRN 101-84-8 is a white crystalline solid or colorless liquid with moderate water solubility and moderate vapor pressure. It is expected to have moderate mobility in soil. Volatilization is considered moderate based on the Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. CASRN 101-84-8 is not readily biodegradable. CASRN 101-84-8 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

### 3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 3.

#### *Acute Oral Toxicity*

Sprague-Dawley rats (2 – 3/sex/dose) were administered diphenyl oxide via gavage at 2000, 2510 or 3160 mg/kg bw and observed for 14 days. Mortalities occurred at  $\geq 2510$  mg/kg bw. Weakness was observed prior to death.

**LD<sub>50</sub> = 2450 mg/kg bw**

#### *Acute Dermal Toxicity*

New Zealand albino rabbits (1/sex/dose) were administered undiluted diphenyl oxide dermally at 3160, 5010, or 7940 mg/kg bw and observed for 14 days. No mortalities occurred. [Monsanto Co.; Toxicity Studies on Diphenyl Oxide with Attachments and Cover Letter Dated 060889, (1977), EPA Doc. No. 86-890000346, Fiche No. OTS0518143]

**LD<sub>50</sub> > 7940 mg/kg bw**

#### *Acute Inhalation Toxicity*

Sprague-Dawley rats (6 males) were exposed to saturated diphenyl oxide vapor (no concentration stated) for 6 hours and observed for 14 days. No mortality was observed. [Monsanto Co.; Toxicity Studies on Diphenyl Oxide with Attachments and Cover Letter Dated 060889, (1977), EPA Doc. No. 86-890000346, Fiche No. OTS0518143]

Sprague-Dawley rats (6/sex) were exposed to THERMINOL VP-1 aerosol—a mixture of diphenyl oxide (73.5%) and biphenyl (26.5%)—for 4 hours via whole-body inhalation at concentrations ranging from 1.0 to 5.3 mg/L and were observed for 14 days. Mortality was seen at 1.1 mg/L and above. LC<sub>50</sub> value for males was 4.45 mg/L. LC<sub>50</sub> value for females was not calculated because of insufficient data for calculation. The combined LC<sub>50</sub> value for both sexes was 2.66 mg L. [Monsanto Co.; Acute Toxicity of Therminol VP-1 Administered by Inhalation to Sprague-Dawley male and Female Rats with Cover Letter Dated 080592, EPA Doc. No. 88-920009870, Fiche No. OTS671522]

**LC<sub>50</sub> = 2.66 mg/L (combined sexes)**

#### *Repeated-Dose Toxicity*

(1) In a 90-day study, Sprague-Dawley rats (10/sex/dose) were administered diphenyl oxide via the diet at 0, 200, 1000 or 5000 ppm. Measured doses were 0, 11.7, 60.7 or 301.1 mg/kg-bw/day for males and 0, 14.5, 73.9 or 334.8 mg/kg-bw/day for females. An additional 10 rats/sex/dose were retained for a 4-week recovery period following the 13-week feeding period. Throughout the treatment period, rats were examined for clinical signs of toxicity, and body weights and food consumption were measured. Ophthalmologic examinations were conducted before and after the treatment period and blood biochemistry, hematology and urinalysis were evaluated at the end of the treatment period. Necropsies were performed on all animals and organ weights (brain,

gonads, heart, kidneys, liver and spleen) were measured. Histopathological examinations were conducted on comprehensive tissues in the control and high-dose groups and on lungs, liver and kidney of all animals. Mean weekly body weight and food consumption were statistically significantly decreased (significance not provided) in high-dose animals and in females at the mid-dose level. Decreased body weight and food consumption were attributed to unpalatability of diphenyl oxide in the diet. No treatment-related findings were observed.

**NOAEL (male) = 301 mg/kg-bw/day** (highest dose tested)

**NOAEL (female) = 334.8 mg/kg-bw/day** (highest dose tested)

(2) Sprague-Dawley rats (20 males), New Zealand albino rabbits (4 males) and beagle dogs (2 males) were exposed to diphenyl oxide vapor via whole-body inhalation at 5 or 10 ppm (approx. 0.03 or (0.07 mg/L, respectively) for 7 hours/day, 5 days/week for a total of 20 exposures in 31 or 33 days. An additional group of Sprague-Dawley rats (10/sex) were exposed to 20 ppm (approx. 0.14 mg/L) diphenyl oxide vapor for 7 hours/day, 5 days/week for a total of 20 exposures in 27 days. The control groups were kept under ambient conditions. Eye and nose irritation were the only treatment-related effects in animals exposed to 10 or 20 ppm. No other treatment-related effects were seen. [Dow Chem.Co.; Repeated Inhalation Toxicity of Diphenyl Oxide (DOP) in Experimental Animals with Attachment. EPA Doc. No. 86-890001214, Fiche No. OTS0520725]

**LOAEL (local) ~ 0.14 mg/L/day**

**NOAEL (local) ~ 0.03 mg/L/day**

**NOAEL (systemic) ~ 0.14 mg/L/day** (highest dose tested)

### ***Reproductive Toxicity***

In the dietary repeated-dose toxicity study described previously, reproductive organs of both genders were weighed and examined macroscopically and histopathologically. No adverse effects related to treatment were observed.

### ***Developmental Toxicity***

Pregnant female Sprague-Dawley rats (24/dose) were administered a mixture of diphenyl oxide (73.5%) and biphenyl (26.5%) via gavage at 0, 50, 200 or 500 mg/kg-day in corn oil on gestational days 6 through 15. Dams were observed for mortality, weight gain, food consumption and clinical signs of toxicity. Fetal resorptions, viability post implantation loss, total implantations and mean litter weight were determined. One-half of fetuses were processed for soft-tissue evaluations and the other half for skeletal evaluations. Two dams at 500 mg/kg-day died. Reduced maternal body weight gain and food consumption were seen at 200 and 500 mg/kg-day. No treatment-related effects on developmental outcomes were observed.

**LOAEL (maternal toxicity) = 200 mg/kg-day** (based on reduced maternal body weight gain)

**NOAEL (maternal toxicity) = 50 mg/kg-day**

**NOAEL (developmental toxicity) = 500 mg/kg-day** (highest dose tested)

### *Genetic Toxicity – Gene Mutation*

#### *In vitro*

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to diphenyl oxide in a plate incorporation assay at concentrations of 0, 0.1, 1, 10, 33, 100 and 500 µg/plate in the presence and absence of metabolic activation. A Spot Test was conducted prior to conduct of the plate incorporation assay up to a maximum concentration of 10 mg/plate. At 1 mg/plate severe toxicity was seen with or without metabolic activation; however, no mutagenic activity was seen at maximum concentration of 10 mg/plate in all 4 tester strains. In the Plate Incorporation Assay, toxicity was observed in strains TA98 and TA100 at 500 µg/plate and 33 µg/plate and higher for TA1535 and TA1537. No mutagenic activity was detected towards any of the 4 tester strains, with or without metabolic activation. Positive and negative controls were tested concurrently and responded appropriately.

**Diphenyl oxide was not mutagenic in this assay.**

(2) In an NTP study, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to diphenyl oxide at concentrations of 0, 3.3, 10, 33.3, 100 and 333.3 µg/plate in the presence and absence of metabolic activation. Positive and negative controls were tested concurrently and responded appropriately. Cytotoxicity was seen at 333.3 µg/plate.

**Diphenyl oxide was not mutagenic in this assay.**

(3) *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to Therminol VP-1, a mixture of diphenyl oxide (73.5%) and biphenyl (26.5%), at concentrations of 0.003 to 0.3 mg/plate with metabolic activation or 0.001 to 0.1 mg/plate without metabolic activation. Cytotoxicity was seen at 0.3 mg/plate in the presence and at 0.1 mg/plate in the absence of metabolic activation. All positive and negative controls responded appropriately. The test substance did not increase the frequency of revertant colonies compared to controls. [Monsanto Chem. Co; Ames/Salmonella Mutagenicity Assay of Therminol VP I (Final Report) with Cover Sheet and Letter Dated 021690, (1990), EPA Doc. No. 86-900000101, Fiche No. OTS0522355]

**Therminol VP-1 was not mutagenic in this assay.**

### *Genetic Toxicity – Chromosomal Aberrations*

#### *In vitro*

Chinese hamster ovary (CHO) cells were exposed to diphenyl oxide at concentrations of 10, 50, 100 or 150 µg/mL in the absence of metabolic activation or 5, 30 or 50 µg/mL in the presence of metabolic activation. Concentrations were based upon the results of a preliminary cytotoxicity study. Positive and negative controls were tested concurrently and responded appropriately. Cytotoxicity was reported at 150 µg/mL (in the presence of metabolic activation).

**Diphenyl oxide did not induce chromosomal aberrations in this assay.**

***In vivo***

CD-1 mice (15/sex/dose) were injected (ip) Therminol VP-1, a mixture of diphenyl oxide (73.5%) and biphenyl (26.5%), in corn oil at 0, 100, 500 and 1000 mg/kg bw. A positive control was also included. Bone marrow was harvested at 24, 48 and 2 hours following dosing. There was a statistically significant decrease in body weights. No statistically significant increase in the mean micronucleated PCEs was observed at any of the doses of Therminol VP-1. The positive control responded appropriately. [Monsanto Co; Micronucleus Assay with Therminol VP-1 with Cover Letter. EPA Doc. No. 86-910000014, Fiche No. OTS0530068]

**Therminol VP-1 did not induce micronuclei in bone marrow in this assay.**

***Genetic Toxicity – DNA Effects***

***In vitro***

(1) Rat hepatocytes were exposed to diphenyl oxide at 1 and 100 µg/mL in an unscheduled DNA synthesis (UDS) assay. The cytotoxic concentration was 200 µg/mL. Each concentration of diphenyl oxide showed negative net grain counts while the positive control showed a strong positive response. [SRI International; Evaluation of the Potential of Diphenyl Oxide to Induce Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures, (1987), EPA Doc. No. 86-890000342, Fiche No. OTS0518139]

**Diphenyl oxide was not genotoxic in this assay.**

(2) Rat hepatocytes were exposed to Therminol VP-1, a mixture of diphenyl oxide (73.5%) and biphenyl (26.5%) at 1 and 1000 µg/mL in an unscheduled DNA synthesis (UDS) assay. Precipitate was observed at 250, 500 and 1000 µg/mL. Each concentration of Therminol VP-1 showed negative net grain counts while the positive control showed a strong positive response. [SRI International; Evaluation of the Potential of Therminol VP-1 to Induce Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures, (1987), EPA Doc. No. 86-890000350, Fiche No. OTS0518147]

**Therminol VP-1 was not genotoxic in this assay.**

***Additional Information***

***Skin Irritation***

(1) New Zealand albino rabbits (6, sex not stated) were administered 0.5 mL of undiluted diphenyl oxide dermally for 24 hours. Severe edema and erythema were seen in all animals up to 72-hours observation period. Slight defatting effects—skin flaking off, was seen during 7 to 10 days. There was no deep tissue injury. The 24 and 72-hour average irritation score was reported to be 5.5. [Monsanto Co.; Initial Submission: Toxicological Investigations with Diphenyl Oxide in Rats and Rabbits with Cover Letter Dated 0817 and Attachment. EPA Doc. No. 88-920007135, Fiche No. OTS0545474]

**Diphenyl oxide was severely irritating to rabbit skin.**

(2) New Zealand albino rabbits (1 male, 5 females) were administered 0.5 mL of undiluted diphenyl oxide dermally (intact skin) for 4 hours under semi-occlusive conditions. Very slight erythema and little or no edema were seen at 30 minutes observation. Slight erythema was seen at 48 and 72 hours and by day 14, only one animal showed very slight erythema. The average score was 1.6. [Monsanto Co.; Primary Dermal Irritation Study in Rabbits (4-hour Exposure/Semi-occlusive Covering) with Attachment, (1988), EPA Doc. No. 86-890000344, Fiche No. OTS0518141]

**Diphenyl oxide was slightly irritating to rabbit skin.**

### ***Eye Irritation***

New Zealand albino rabbits (6, sex not stated) were administered 0.1 mL of undiluted diphenyl oxide in to the eye for 24 hours. Moderate discomfort was seen immediately after the test substance instillation. Moderate erythema, copious discharge containing whitish exudates and areas of barely perceptible corneal dullness (2 rabbits) were seen up to 24 hours with gradual improvement during 48-72 hours. At 120 hours all irritation was subsided. The 24, 48 and 72-hour average irritation score was reported to be 6.1. [Monsanto Co.; Initial Submission: Toxicological Investigations with Diphenyl Oxide in Rats and Rabbits with Cover Letter Dated 0817 and Attachment. EPA Doc. No. 88-920007135, Fiche No. OTS0545474]

**Diphenyl oxide was slightly irritating to rabbit eyes.**

**Conclusion:** Acute oral toxicity and acute dermal toxicity of CASRN 101-84-8 to rats and rabbits, respectively, is low. No mortality was seen when rats were exposed to the saturated vapor of CASRN 101-84-8 for six hours. Acute inhalation toxicity of Therminol VP-1 (CASRN 101-84-8, 73.5% and biphenyl (CASRN 92-52-4, 26.5%)) to rats is low. Dietary exposure of rats to CASRN 101-84-8 for 90 days resulted in markedly decreased mean body weight and food consumption in high-dose animals, but this was attributed to unpalatability of the test substance. Therefore, there were no treatment-related effects; the NOAELs were approximately 301 mg/kg-bw/day for males and 334 mg/kg-bw/day for females (highest doses tested). Inhalation exposure of rats, rabbits and dogs to CASRN 101-84-8 vapor resulted in portal of entry effects only; no systemic toxicity was observed up to 20 ppm (0.14 mg/L/day). No reproductive toxicity studies are available. However, the 90-day dietary toxicity study in rats showed no adverse treatment-related effects on reproductive organs. A prenatal developmental oral (gavage) toxicity study of Therminol VP-1 in rats revealed maternal toxicity at 200 mg/kg-day and above (mortality and reduced body weight gain) but showed no treatment-related developmental effects. The NOAEL for maternal toxicity was 50 mg/kg-day and for developmental toxicity it was 500 mg/kg-day (highest dose tested). CASRN 101-84-8 did not induce gene mutations in bacterial cells or chromosomal aberrations in mammalian cells *in vitro*. Therminol VP-1 did not induce gene mutations in bacterial cells *in vitro* or micronuclei in mice bone marrow *in vivo*. CASRN 101-84-8 was slightly to severely irritating to rabbit skin and slightly irritating to rabbit eyes.

| <b>Table 3. Summary of the Screening Information Data Set<br/>as Submitted under the U.S. HPV Challenge Program</b>                       |   |
|---|---|
| <b>Endpoints</b>  | <b>SPONSORED CHEMICAL<br/>Diphenyl oxide<br/>(101-84-8)</b>   |
| <b>Summary of Human Health Data</b>   |   |
| <b>Acute Oral Toxicity<br/>LD<sub>50</sub> (mg/kg-bw)</b>   | 2450  |
| <b>Acute Dermal Toxicity<br/>LD<sub>50</sub> (mg/kg-bw)</b>   | > 7940  |
| <b>Acute Inhalation Toxicity<br/>LC<sub>50</sub> (mg/L)</b>   | 2.66 <sup>1</sup> (combined sexes)  |
| <b>Repeated-Dose Toxicity<br/>NOAEL/LOAEL<br/>Oral (mg/kg-bw/day)</b>   | (rat)<br>NOAEL (males) ~ 301 (hdt)<br>NOAEL (females) ~ 334.8 (hdt)   |
| <b>Repeated-Dose Toxicity<br/>NOAEC/LOAEC<br/>Inhalation (mg/L/day)</b>   | (rat)<br>NOAEC = 0.14 (hdt) <sup>1</sup>  |
| <b>Reproductive Toxicity<br/>NOAEL/LOAEL<br/>Oral (mg/kg-bw/day)</b>  | No effects were seen following evaluation of reproductive organs<br>in a 90-day oral repeated-dose toxicity study in rats |
| <b>Developmental Toxicity<br/>NOAEL/LOAL<br/>Oral (mg/kg-bw/day)</b><br><br><b>Maternal Toxicity</b><br><br><b>Developmental Toxicity</b> | <br><br>NOAEL = 50 <sup>1</sup><br>LOAEL = 200 <sup>1</sup><br><br>NOAEL = 500 (hdt) <sup>1</sup>                         |
| <b>Genetic Toxicity – Gene Mutation<br/><i>In vitro</i></b>   | Negative<br>Negative <sup>1</sup>   |
| <b>Genetic Toxicity – Chromosomal<br/>Aberrations<br/><i>In vitro</i></b>   | Negative  |
| <b>Genetic Toxicity – Chromosomal<br/>Aberrations<br/><i>In vivo</i></b>  | Negative <sup>1</sup>   |
| <b>Additional Information<br/>Skin irritation</b>   | Severely irritating (24-h exposure)<br>Slightly irritating (4-h exposure)   |
| <b>Eye irritation</b>   | Slightly irritating   |

hdt = highest dose tested, <sup>1</sup>Test substance is Therminol VP-1 (mixture of 73.5% diphenyl oxide and 26.5% biphenyl)

#### 4. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

This chemical is a volatile and testing performed with nominal concentrations may underestimate its toxicity, the estimated ecotoxicity values are used in support of this chemical's experimental results.

##### *Acute Toxicity to Fish*

(1) Rainbow trout (*Oncorhynchus mykiss*) were exposed to diphenyl oxide at nominal concentrations of 0, 1, 1.8, 3.2, 5.6 or 10 mg/L under static conditions for 96 hours. Mean measured concentrations were not determined. All fish exposed to 5.6 and 10 mg/L died within 96 hours. No mortality was observed at 1, 1.8 and 3.2 mg/L. ECOSAR (v 1.00a) estimated value is used to support these data.

**96-h LC<sub>50</sub> = 4.2 mg/L (nominal)**

**96-h LC<sub>50</sub> = 2.06 mg/L (estimated)**

##### *Acute Toxicity to Aquatic Invertebrates*

Water fleas (*Daphnia magna*) were exposed to diphenyl oxide at nominal concentrations of 0, 1, 1.8, 3.2, 5.6 or 10 mg/L under static conditions for 48 hours. Mean measured concentrations were not determined. All water fleas exposed to 5.6 and 10 mg/L died within 48 hours. Mortality rates at 48 hours were 0, 0, 70 and 95% for the 0, 1, 1.8 and 3.2 mg/L concentrations, respectively. ECOSAR (v 1.00a) estimated value is used to support these data.

**48-h EC<sub>50</sub> = 1.7 mg/L (nominal)**

**48-h EC<sub>50</sub> = 1.58 mg/L (estimated)**

##### *Toxicity to Aquatic Plants*

Green algae (*Pseudokirchneriella subcapitata*) were exposed to diphenyl oxide at nominal concentrations of 0, 0.6, 1.2, 2.5, 5 or 10 mg/L under static conditions for 96 hours. Information on decreases in the numbers of cells at each concentration was not provided. ECOSAR (v 1.00a) estimated value is used to support these data.

**96-h EC<sub>50</sub> (growth rate) = 2.5 mg/L (nominal)**

**96-h EC<sub>50</sub> = 1.82 (estimated)**

**Conclusion:** The acute 96-hr LC<sub>50</sub> of CASRN 101-84-8 for fish is 4.2 mg/L (2.06 mg/L - estimated). The acute 48-hr EC<sub>50</sub> value of CASRN 101-84-8 for aquatic invertebrates is 1.7 mg/L (1.58 mg/L – estimated). The 96-hr EC<sub>50</sub> value of CASRN 101-84-8 for algae is 2.5 mg/L (1.82 mg/L – estimated).

Since this is a volatile chemical and testing performed with nominal concentrations may underestimate its toxicity, the estimated ecotoxicity values are used in support of this chemical's experimental results.

| <b>Table 4. Summary of the Screening Information Data Set<br/>as Submitted under the U.S. HPV Challenge Program</b> |   |
|---|---|
| <b>Endpoints</b>  | <b>SPONSORED CHEMICAL<br/>Diphenyl oxide<br/>(101-84-8)</b> |
| <b>Summary of Environmental Effects – Aquatic Toxicity Data</b>   |   |
| <b>Fish<br/>96-h LC<sub>50</sub> (mg/L)</b>   | <b>4.2<sup>1</sup></b><br>2.06 (e)                          |
| <b>Aquatic Invertebrates<br/>48-h EC<sub>50</sub> (mg/L)</b>  | <b>1.7<sup>1</sup></b><br>1.58 (e)                          |
| <b>Aquatic Plants<br/>72-h EC<sub>50</sub> (mg/L)<br/>(growth rate)</b>   | <b>2.5 (96-h)<sup>1</sup></b><br>1.82 (e)                   |

<sup>1</sup>Nominal concentration; (e) = estimated value using ECOSAR (v1.00a)