

Section 8d

**Hoechst Celanese**

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August 3, 1993  
GSK/308/93

Document Control Officer (TS-790)  
Office of Toxic Substances  
EPA, Room 20 East Tower  
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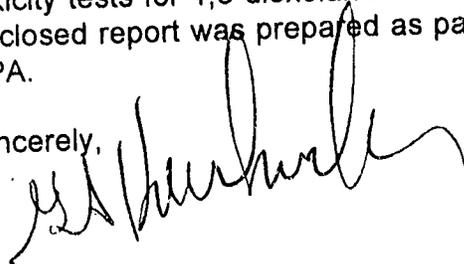
**ATTN: 8(d) HEALTH & SAFETY REPORTING RULE (NOTIFICATION/REPORTING)**

**Re: 1,3-Dioxolane, CAS 646-06-0**

Gentlemen:

As a follow-up to Hoechst Celanese's letter (from M. Sullivan) of 1988, we formed a committee to examine already existing data, including MSDS, literature searches and toxicity tests for 1,3-dioxolane in order to establish an internal exposure level. The enclosed report was prepared as part of this review and thus is being submitted to the EPA.

Sincerely,



G. S. Kirshenbaum  
Manager, Product Stewardship

GSK/rr

Enclosure

Return receipt/certified (P 259 990 538)

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**Hoechst** 

HOECHST CELANESE CORPORATION  
WORKPLACE EXPOSURE LIMIT RATIONALE DOCUMENT  
1,3-DIOXOLANE

A. Chemical and Physical Properties:<sup>(1,2)</sup>

- |                                           |                                                                                   |
|-------------------------------------------|-----------------------------------------------------------------------------------|
| 1. Chemical Name                          | 1,3-dioxolane.                                                                    |
| 2. Chemical Family                        | Cyclic Acetal.                                                                    |
| 3. Synonyms                               | ethylene glycol formal/formal glycol/ethylene glycol methylene ether.             |
| 4. CAS RN                                 | 646-06-0                                                                          |
| 5. Structure                              |  |
| 6. Molecular Formula                      | C <sub>3</sub> H <sub>6</sub> O <sub>2</sub>                                      |
| 7. Molecular Weight                       | 74.09                                                                             |
| 8. Physical State                         | Liquid.                                                                           |
| 9. Appearance                             | Water white liquid with ether odor.                                               |
| 10. Solubility in Water                   | 100%                                                                              |
| 11. Reactivity                            | May form peroxides when exposed to air. Reacts with strong acids.                 |
| 12. Vapor Density (Air=1)                 | 2.6                                                                               |
| 13. Stability                             | Stable under neutral or slightly alkaline conditions.                             |
| 14. Incompatibilities                     | Strong acids and oxidizing agents.                                                |
| 15. Specific Gravity (H <sub>2</sub> O=1) | 1.0666                                                                            |
| 16. Boiling Point (760 mm Hg)             | 168°F (76°C)                                                                      |
| 17. Vapor Pressure                        | 70 mm Hg @ 20°C                                                                   |
| 18. Volatility by Volume                  | 100%                                                                              |
| 19. Evaporation Rate (BUAC=1)             | 6                                                                                 |
| 20. Flammability                          | Flammable Liquid.                                                                 |
| 21. Flash Point (Closed Cup)              | 21°F (-6°C)                                                                       |
| 22. Autoignition Temperature              | 525°F (274°C)                                                                     |
| 23. Flammability Limits                   | ≈2.7% (lower limit in air)                                                        |
| 24. Hazardous Polymerization              | May occur upon contact with Lewis Acids.                                          |

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**B. Manufacture and Uses:**

1,3-Dioxolane is prepared by the condensation of ethylene glycol and formaldehyde in the presence of an acid catalyst<sup>(3)</sup>.

Currently, Hoechst Celanese uses dioxolane as comonomer in the manufacture of Celcon®. A mixture of 1,3-dioxolane and 1,3,5-trioxane is polymerized at the Advanced Materials Group's Bishop, Texas plant. The production employs a closed system which limits workplace exposure.

**C. Regulatory Status**<sup>(3,4,5)</sup>

- |     |                                                                                                                                                  |                                                                                                                                                                                                                                                                       |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1.  | DOT Proper Shipping Name<br>DOT Classification<br>DOT Identification Number                                                                      | Dioxolane<br>Flammable Liquid<br>UN1166                                                                                                                                                                                                                               |
| 2.  | RCRA Hazardous Waste                                                                                                                             | Not listed as a RCRA Hazardous Waste.<br>Characteristic waste: ignitable and reactive.                                                                                                                                                                                |
| 3.  | CERCLA Hazardous Substance                                                                                                                       | Not listed, but reportable to NRC due to ignitability.                                                                                                                                                                                                                |
| 4.  | SARA Section 302<br>SARA Section 311/312<br><br>SARA Section 313                                                                                 | Not listed.<br>Regulated due to potential adverse health effects, irritation and flammability.<br>Not listed.                                                                                                                                                         |
| 5.  | OHSA Hazardous Substance                                                                                                                         | Yes, based on irritancy, adverse health effects and flammability.                                                                                                                                                                                                     |
| 6.  | OSHA PEL                                                                                                                                         | None.                                                                                                                                                                                                                                                                 |
| 7.  | ACGIH PEL                                                                                                                                        | None.                                                                                                                                                                                                                                                                 |
| 8.  | FDA                                                                                                                                              | No Information.                                                                                                                                                                                                                                                       |
| 9.  | TSCA<br>Section 8(a) PAIR<br>Section 8(b)<br>Section 8(d)<br>Section 8(e)<br><br>Section 4<br>Section 5<br>Section 6<br>Section 12<br>Section 13 | Listed.<br>Listed.<br>Listed.<br>Several Substantial Risk Submissions have been made. The most notable of these was made by Hoechst Celanese for findings in a sponsored teratology study.<br>Not listed.<br>Not listed.<br>Not listed.<br>Not listed.<br>Not listed. |
| 10. | Clean Air Act                                                                                                                                    | Regulated under Section 111 of the Clean Air Act.                                                                                                                                                                                                                     |

11.	Right-To-Know NJ PA MA CA Prop. 65	Listed. Listed. Listed. Not listed on California Carcinogen or Reproductive Toxins List.
12.	Canadian WHIMIS	Listed.
13.	Canadian Inventory	Listed on the DSL.
14.	Japanese Inventory (MITI)	Listed.
15.	European Inventory (EINECS)	Listed.
16.	IARC	Not listed.
17.	NTP	Not listed.
18.	EPA Carcinogen	Not listed.

#### D. Animal Toxicology

##### 1. Acute Toxicity

1,3-Dioxolane has a low order of acute toxicity, requiring large doses to produce death in several animal species. Single dose studies in rats and rabbits have approximated the LD50 (LC50) for oral, inhalation and dermal routes of exposure in the range of 5.2 - 5.8g/kg, 68- 87 mg/l and 15 g/kg body weight, respectively <sup>(6,8)</sup>. Doses approximating the LC50 produce a narcotic effect with lung and liver discoloration noted upon necropsy <sup>(6,7,8)</sup>. Administration of single high doses of 1,3-Dioxolane to mice produced cytotoxic effects to the bone marrow <sup>(9)</sup>. This last observation is consistent with the findings of several repeat dose studies in which hematotoxicity has been demonstrated to be the most sensitive toxic endpoint (see below).

1,3-Dioxolane can cause significant eye irritation. When tested in the rabbit eye, the mean of maximum Draize scores (72h) was 26.9, indicating moderate to severe irritation <sup>(10)</sup>. Tests on rabbit skin, however, demonstrated only very slight irritation <sup>(11)</sup>.

##### 2. Genotoxicity

The mutagenicity and clastogenicity of 1,3-Dioxolane have been studied in multiple assay systems by many investigators yielding primarily negative results. Several laboratories have shown that 1,3-Dioxolane fails to induce gene mutation using the Ames assay in the presence or absence of enzymatic activation <sup>(12,13,14)</sup>. 1,3-Dioxolane also was found non-mutagenic in the Mouse Lymphoma Forward Mutation Assay and when tested in Saccharomyces cerevisiae with or without an activation system <sup>(15,16)</sup>. This material has failed to induce chromosome aberrations in Chinese Hamster Ovary cells in tissue culture <sup>(17)</sup> and failed to increase the frequency of dominant lethal mutations in rats <sup>(18)</sup>.

Mixed results were obtained in several other types of genotoxicity evaluations. A study published in 1984<sup>(14)</sup> suggested that 1,3-Dioxolane could produce increases in micronucleated polychromatic erythrocytes in the bone marrow of the mouse. An attempt to repeat this finding using pure test material and a modern protocol produced negative results<sup>(9)</sup>. Of the two *in vitro* cell transformation assays identified in the literature, one was negative, the other weakly positive<sup>(20,21)</sup>. Single doses of 1,3-Dioxolane administered i.p. were shown to produce single-strand breaks in rat hepatocyte DNA by an alkaline elution technique<sup>(22)</sup>. Although some *in vitro* studies have been weakly positive, this material is assumed to have little genotoxic potential based on the greater weight attributed to *in vivo* experiments which yielded negative results<sup>(9,16)</sup>.

### 3. Subacute and Subchronic Exposures

1,3-Dioxolane has been studied in animals using repeat dosing regimens and these results provide the base from which to extrapolate potential hazard to humans. Hoechst Celanese Corporation contracted Argus labs to perform a state-of-the-art teratogenicity study on 1,3-Dioxolane in 1990<sup>(23)</sup>. A subacute range-finding study was performed in advance of the teratology test<sup>(24)</sup>. Male and female Sprague-Dawley derived rats received 1,3-Dioxolane in corn oil by gavage once daily for 14 days. The doses were 0 (water), 0 (corn oil), 75, 250, 750, and 2000 mg/kg. At the highest dose 3/10 males and 4/10 females died. Surviving animals in this group showed decreases in body weight, organ weight changes and histopathological alterations in liver, kidney, thymus, spleen and testes. Hematotoxicity proved to be the most sensitive toxic endpoint with decreases in platelets, lymphocytes and reticulocytes, in both males and females. This response showed a direct relationship to dose. The No Observed Effect Level (NOEL) for hematotoxic effects was 250 mg/kg for males and 75 mg/kg for females.

There have been two subacute toxicity studies of 1,3-Dioxolane by inhalation. The first of these was contracted by the Celanese Corporation in 1981<sup>(25)</sup>. The study was performed by Bio/dynamics and groups of male and female Sprague-Dawley rats were exposed to 0, 974, or 3250 ppm of 1,3-Dioxolane vapor 6 h/day, 5 days/wk for two weeks. There were no treatment related deaths and few signs of toxicity were noted. The high dose group showed a decrease in leukocyte count which was statistically significant in males only. Based on hematotoxicity the NOEL for this study was 974 ppm for males and 3250 ppm for females. A similar study was performed by Dow Chemical in August 1989 using male and female Fischer 344 rats<sup>(26)</sup>. In this test, concentrations studied were 0, 500, 2000, and 5000 ppm and animals were exposed for 6 h/day for 9 days. At the highest doses of 1,3-Dioxolane, animals showed slight incoordination (mild narcotic effect), decreased body weight and decreases in white blood cell counts. Significant decreases in white blood cell counts were also observed at the 2000 ppm dose level. No pathological changes were observed in histological sections prepared from the peripheral nervous system or the central nervous system, bone marrow, spleen, thymus or lymph nodes. The NOEL for this study was 500 ppm for both male and female rats based on decreases in white blood cell counts. Comparison of the results of these two studies reveals an inconsistency in the Lowest Observed Effect Level (LOEL) for the female rat. In the Dow study, the LOEL for hematotoxic changes was 2000 ppm (male and female) while at Bio/dynamics, no significant effects on WBCs were seen in female rats up to 3250 ppm. Since the entire toxicity database for 1,3-Dioxolane indicates that male and female toxic responses are not different to any pronounced degree, a conservative assumption encompassing the effects seen in both studies, with both sexes, will be utilized. The LOEL for the combined data set is 2000 ppm and the true NOEL must, by definition, be below this concentration. The highest NOEL for the combined data set is 974 ppm. This concentration produced no toxic effects in rodents of either sex at Bio/dynamics and could be utilized to calculate a WEL.

Dow Chemical has also performed a 13 week inhalation toxicity study with Fischer 344 rats<sup>(27)</sup>. Groups of ten rats per sex were exposed to 1,3-Dioxolane for 6 h/day, 5 days/wk for 13 weeks. The concentrations studied were 0, 300, 1000 and 3000 ppm and satellite groups of animals were included for multiple clinical studies and an 8 week recovery group. Findings in the 3000 ppm dose group were consistent with the earlier studies described. Females showed a decrease in body weight and animals of each sex demonstrated decreased white blood cell counts, decreased number of myeloid cells in bone marrow, decreased spleen weights and increased liver weights. Male and female rats exposed to 1000 ppm 1, 3-Dioxolane showed decreased white blood cell counts and decreased spleen weights (females only). Decreases in lymphocytes were the primary determinant to the overall change in white cell count and recovery was demonstrated at 8 weeks post-exposure. The NOEL based on hematotoxicity was 300 ppm.

#### 4. Reproductive and Developmental Toxicity

Baranski et al (1984)<sup>(18)</sup> studied the effects of 1,3-Dioxolane on fertility and the frequency of dominant lethal mutations in the rat. These researchers administered 1,3-Dioxolane orally to male rats at doses of 580 and 1160 mg/kg five days per week for 8 weeks. Every male rat on study was mated with two females each week. 1,3-Dioxolane did not alter the reproductive performance of the treated males and no increase in the number of preimplantation losses, dead implants or resorbed fetuses per female was noted. It is significant to note that although no adverse changes in fertility were observed overall, focal testicular necrosis was observed in some treated males. Testicular degeneration was also found in the high dose group of the two week gavage study described earlier<sup>(24)</sup>. Taken together, these studies indicate that extremely high levels of exposure to 1,3-Dioxolane can produce deleterious effects to the rat testes. In the 13 week inhalation study run by Dow, however, no concentration-associated increase in testicular pathology was observed<sup>(27)</sup>. Therefore, a workplace exposure level based on the NOEL from the 13 week Dow inhalation study is considered to be protective of the testes (300 ppm).

Histopathologic examination of female reproductive organs, including ovaries, oviducts, uterus and vagina was conducted in the Dow 13 week inhalation study<sup>(27)</sup>. Increases in cystic dilatation of the ovaries was noted in the high dose group; no deviation from normal histology was found for the oviducts, uterus or vagina of treated females. The female reproductive tract does not appear to be a target of this material.

The Hoechst Celanese Corporation contracted Argus Laboratories to study the developmental toxicity of 1,3-Dioxolane in the rat<sup>(23)</sup>. Pregnant rats were administered oral doses of 1,3-Dioxolane in corn oil from day 6 to 15 of gestation. Dosage levels were 0, 125, 250, 500, and 1000 mg/kg/day. Pregnant rats receiving the highest dosage produced fetuses with decreased body weight and tail, vertebral and cardiac malformations. A clear NOEL for embryo-fetal effects was demonstrated at 500 mg/kg/day. Slight maternal toxicity was observed at 500 mg/kg/day making 250 mg/kg/day the maternal NOEL. Since maternal toxicity was observed at a lower dose than embryo-fetal effects, 1,3-Dioxolane would not be considered a specific developmental toxicant. Despite this, it is important to add that the effects produced by 1,3-Dioxolane appear to be chemically related, rather than simply due to indirect effects on the mother. This conclusion is supported by the nature of malformations seen in the fetuses in this study. Septal lesions in the heart, as an example, are seldom due to indirect toxicity (i.e., maternal stress).

#### E. Toxicology Summary and Rationale for Setting the Workplace Exposure Limit

Estimation of a Workplace Exposure Level (WEL) from animal data relies on the identification of exposure levels which produce no significant toxic effects to test animals (safe levels) and then extrapolating these to humans to estimate an exposure level which should not pose a health risk. The safe level in an animal study is termed, the No Observed Effect Level (NOEL). This technique assumes that the response to an administered toxicant is similar in humans and animals. While this is generally a good assumption, exceptions do exist. To compensate for this uncertainty and assure that a safe level for human exposure is adopted, a safety factor is generally applied to this NOEL. A modifying factor may also be used to account for residual uncertainty related to data quality, length of exposure, or known differences in the toxicokinetics between humans and animals.

The best animal toxicity study to use as a basis for a WEL is generally the study of the longest duration by the most relevant route. Before selecting the single best data set, the full spectrum of studies in which adverse effects have been produced needs to be evaluated to ensure that the material does not present a "special" hazard such as high sensitization potential or teratogenicity. In the case of 1,3-Dioxolane, the WEL will be derived by extrapolating to a safe human exposure level from the NOEL in the 13-week inhalation study. This study was judged to be the most useful of all the repeated dose animal exposures due to its clear NOEL, duration and the relevance of the inhalation route to workplace exposures.

A standard safety factor approach will be utilized to calculate the WEL directly from the results of the subchronic inhalation study. This is the most direct approach to obtain a WEL from the animal data and requires a minimum of assumptions. The WEL can also be derived from the same animal data set by calculating the estimated systemic exposure levels. This approach is biologically appropriate, since the bone marrow is the critical target organ for 1,3-Dioxolane and since rats and humans exposed to similar airborne concentrations of toxicant would receive different systemic doses. The WEL calculation described above can be adjusted for differences in systemic delivery between rodents and man by applying a scaling factor based on their respective breathing volumes and body weights. The exposure level estimated by this second method will be compared to the first and, if different, the more conservative of the two will be recommended. Confirming results will strengthen the biological basis of the WEL estimation. Finally, a third calculation will be performed using data from the developmental toxicity study. Although the pharmacokinetics of gavage dosing produces higher blood levels and is therefore less relevant to a workplace exposure scenario, this calculation is deemed necessary due to the "special" hazard presented by a developmental toxicant.

#### F. Calculation of the Workplace Exposure Limit

- First Approach: WEL based on the 13-Week Inhalation Study using Standard Safety Factors

The NOEL from the 13-week inhalation data set is the starting point. This value is then divided by the appropriate safety factors. The calculation is as follows:

1. NOEL = 300 ppm (From the Dow 13-wk inhalation study)

2. Safety Factors: 10 Standard occupational safety factor to provide a defined margin of safety for humans above the rat NOEL
  - 3 Modifying factor added in this case to compensate for residual uncertainty regarding unknown differences in the progress of bone marrow toxicity between subchronic and chronic exposure.
3. Calculation:

$$\text{WEL} = (300\text{ppm}) (1/10) (1/3) = 10.0 \text{ ppm}$$

■ Second Approach: WEL based on the 13-Week Inhalation Data using Safety Factors and a Scaling Factor

This approach is similar to the first except a scaling factor is applied to compensate for differences in the systemic dose received by rats and humans due to their respective size and physiology.

1. NOEL = 300 ppm (From the Dow 13-wk inhalation study)
  2. Safety Factors: 10 Standard occupational safety factor to provide a defined margin of safety for humans above the rat NOEL
  - 3 Modifying factor added in this case to compensate for residual uncertainty regarding unknown differences in the progress of bone marrow toxicity between subchronic and chronic exposure.
3. Scaling factor: 1.5 To account for the difference in systemic dose between rats and humans (See Appendix I).
4. Calculation:

$$\text{WEL} = (300 \text{ ppm}) (1/10) (1/3) (1.5) = 15.0 \text{ ppm}$$

■ Third Approach: WEL Based on the Gavage Teratology Study

A WEL based on the gavage teratogenicity data set can also be calculated. For this calculation, a larger safety factor is used due to the seriousness and irreversibility of the toxic effect.

1. Animal NOEL = 500 mg/kg/day (Argus Gavage Study)
2. Safety Factor = 100
3. Scaling Factors:
  - Average body weight of a female worker = 50 kg
  - Volume of air breathed in one 8h workshift = 7m<sup>3</sup>
  - Estimated absorption of 1,3-Dioxolane through the lung = 69%<sup>(28)</sup>

4. Calculation:

$$\text{WEL} = (500 \text{ mg/kg/day}) (1/100) (50 \text{ kg}) (1/7 \text{ m}^3) (1/0.69) = 51.8 \text{ mg/m}^3$$

(conversion to ppm)

$$\text{WEL} = 17.1 \text{ ppm}$$

The WEL estimated from the developmental toxicity study should be protective for potential developmental toxicity in humans. Since it is higher than either of the two WELs derived from the 13 week inhalation data, these WELs would be expected to provide protection against developmental toxicity. It should be added that the developmental toxicity study was conducted by oral-gavage dosing and not by inhalation. Based on dioxolane's absorption pharmacokinetics, one would expect the gavage route of administration to be more harmful to the conceptus than inhalation administration of an equivalent dose. The WEL based on developmental toxicity, thus, is considered to have an extra margin of safety because of the route of exposure used in the animal developmental toxicity study.

Either of the first two approaches may be used to derive an acceptable WEL from the 13-week inhalation data set. The standard safety factor approach relies on fewer assumptions and provides a more conservative value. Therefore, the Advanced Materials Group's Hazard Review Committee recommended a WEL of 10 ppm for 1,3-Dioxolane based on bone marrow effects in a subchronic study. A calculation was made to demonstrate that this WEL would also provide protection against potential developmental toxicity. Short term studies available do not suggest that there is any need for a Short Term Exposure Limit or ceiling value for dioxolane.

**E. HCC Human Experience/Industrial Hygiene**

Monitoring done at the Bishop facility has indicated that there is some potential exposure. However, the detection levels were, in general, below 1 ppm during normal processing.

The most significant route of exposure would be through inhalation due to its high vapor pressure and its ability to be taken up by the lung. Although this material can be absorbed through the skin, there is little opportunity for skin contact.

APPENDIX I

A scaling factor for rat to human conversion of inhalation doses can be calculated based on their respective breathing volumes and body weights.

Rat 65 liters / 0.3 kg = 216.7 l/kg

Human 10,000 liters / 70 kg = 142.9 l/kg

Therefore, the ratio would be 216.7 / 142.9 = 1.52

The rat is receiving roughly 1.5 times more toxicant on a l/kg basis.

REFERENCES

Literature Searches have been performed on the following databases: Chemical Abstracts, Chemlist, Chemline, HSDB, RTECS, CCRIS, Toxline, ARIEL, SANSS.

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DIOXOLANE HRC DOCUMENT

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**Contains No CBI**