8-12-91

REVIEWER

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 12 1991

AUG 12 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate (Roundup) - EPA Registration No. 524-308 - Environmental Fate of Dioxane and Quantitative Estimate of Cancer Risk to the General Public From Dietary Exposure and to Workers Who are Exposed to Roundup Herbicide Surfactant Containing 1,4-Dioxane

Project No.: 0-1696
Record No.: None
Caswell No.: 661A
MRID No.: None (2 Volumes)

TO: Robert J. Taylor, PM Team #25
Fungicide-Herbicide Branch
Registration Division (H7505C)

FROM: William Dykstra, Ph.D., D.A,B,T.
Review Section I, TB-I, IRS
Health Effects Division (H7509C)
William Dykstra 7/24/91

THRU: Roger Gardner, Section Head
Review Section I, TB-I, IRS
Health Effects Division (H7509C)
Roger Gardner 7-26-91

and

Karl Baetcke, Ph.D., Chief
Toxicology Branch I, IRS
Health Effects Division (H7509C)
Karl D. Baetcke 7/26/91

Requested Action:

Evaluate environmental fate and calculate carcinogenic risk to the general public and workers from Roundup® contaminated with 1,4-Dioxane (inert).

Conclusions and Recommendations:

1,4-Dioxane is a B_2 carcinogen.

Worst-case cancer risks to combined mixer/loader/applicators of ground boom equipment is 7.04×10^{-5}. This assumes 100% dermal absorption. Exposure was estimated without BEAD information by OREB.

Dietary risks are non-existent according to DEB (Chem 1), since no residues of 1,4-Dioxane are present on human food items at harvest.

The environmental fate of 1,4-Dioxane, as stated by OTS, is that 1,4-Dioxane has half-lives of 1 to 6 months in soil and 2-12 months in ground water, respectively.

Background:

Based on previously analyzed data, TB concluded (memorandum of March 18, 1981) that low levels of 1,4-dioxane (less than 0.03%) would not pose an "unreasonable adverse effect" to workers from exposure to Roundup (memorandum attached). This memorandum appeared to have resolved the toxicological significance of the 1,4-dioxane impurity in the herbicide surfactant.

However, oral communication with Mr. William Burnam, Deputy Director of HED, during the week of June 12, 1990 indicated that a quantitative estimate of worker risk from 1,4-dioxane exposure would be desirable. This information would also fulfill a verbal request made by the Agency to Monsanto in 1981 regarding such a risk assessment for dioxane.

Monsanto has now provided a quantitative estimate of risk based on the animal tumor data, risk model, and worker exposure data. The Monsanto data have been evaluated by the Agency and found deficient in certain respects.

HED has adopted the Office of Drinking Water (ODW) calculation of the Q_1^* (1.1×10^{-2}) ($mg/kg/day^{-1}$), and has calculated the worker exposure estimates by OREB. Both of these estimates are significantly different from those provided by Monsanto.

The worker risk, as calculated by HED, is significantly higher than Monsanto's estimate.

Review

1. Toxicology Data

   a. Oncogenicity Studies in Animals - Nasal and liver tumors were reported in multiple strains of rats ingesting 7,000 to 18,000 ppm of 1,4-dioxane in drinking water for 14 to 23 months.

      Liver and gallbladder tumors have been produced in guinea pigs given drinking water containing 1,4-dioxane for 23 months at levels ranging from 5,000

to 20,000 ppm. In studies conducted by the National Cancer Institute, liver tumors were found in rats and mice, while nasal cavity tumors were found in rats only. Therefore, dioxane has produced tumors in three species of animals at multiple sites by the oral route.

b. Genotoxicity Studies - 1,4-Dioxane did induce DNA strand breaks in rat hepatoytes in vitro. Dioxane did not induce sex-linked recessive lethal mutations in Drosphilia. Mutations, such as aneuploidy in yeast, were also not observed.

c. Overall Evaluation by EPA - A weight-of-evidence evaluation by EPA for 1,4-dioxane indicates that there is sufficient evidence of carcinogenicity in animals. Under the guidelines used by the Agency, 1,4-dioxane meets the criteria for group B2, a probable human carcinogen and has been classified as such by CAG (memorandum attached).

2. Linearized Multistage Procedure, Extra Risk

The Q_1* was determined to be 1.1×10^{-2} $(mg/kg/day)^{-1}$ using the EPA IRIS data base derived from the ODW analysis of the cancer data in animals (memorandum attached).

3. Exposure Assessment by OREB (Memorandum Attached)

OREB has calculated an upper bound worst case lifetime average daily exposure estimate for the application of dioxane-contaminated Glyphosate using ground boom equipment. The result of this calculation is:

6.4×10^{-3} mg/kg/day

This value was not adjusted for dermal penetration.

Using the above assumptions, the combined mixer/loader/applicator lifetime average daily exposure is calculated as follows:

Mixer/Loader

290 acres/day X 2 lb ai/acre X 0.93 mg ai/lb ai X 0.03% dioxane/30.41% ai X 1/70 kg X 200 days/yr X 40 yr/70 yr X 1 yr/365 days = 2.4×10^{-3} mg/kg/day.

Applicator

56.7 mg/ai/hr X 2 lb ai/acre X 8 hr/day X 0.03% dioxane/30.41% ai X 1/70 kg X 200 days/yr X 40 yr/70 yr X 1 yr/365 days = 4×10^{-3} mg/kg/day.

Combined

$2.4 \times 10^{-3} + 4 \times 10^{-3} = \underline{6.4 \times 10^{-3}}$ mg/kg/day.

a. Calculation of Risk by TB-I

Risk = Q_1* X exposure

Note: Dermal absorption is assumed to be 100 percent, since dermal penetration data were not available for dioxane.

(1) Mixer/Loader

Risk = 1.1×10^{-2} $(mg/kg/day)^{-1}$ X 2.4×10^{-3} mg/kg/day

$\underline{Risk = 2.64 \times 10^{-5}}$

(2) Applicator

Risk = 1.1×10^{-2} $(mg/kg/day)^{-1}$ X 4×10^{-3} mg/kg/day

$\underline{Risk = 4.4 \times 10^{-5}}$

(3) Combined

Risk = $2.64 \times 10^{-5} + 4.4 \times 10^{-5}$

$\underline{Risk = 7.04 \times 10^{-5}}$

b. Dietary Risk to General Public - No detectable residues of 1,4-dioxane are present in crops treated with Roundup (DEB memorandum attached). Therefore, there are no dietary cancer risks to the consuming public as a result of exposure to food which has been treated with 1,4-dioxane as a component of Roundup.

c. Environmental Fate and Degradation - Based on recent information by OTS (memorandum attached), 1,4-dioxane is not expected to significantly volatize from water or to strongly absorb to soil and sediments. It is expected to leach through soil rapidly, provided degradation is sufficiently slow. 1,4-Dioxane has half-lives of 1 to 6 months in soil and 2 to 12 months in groundwater, respectively. However, OTS staff believe that additional data are needed to further identify the risks from dioxane.

Conclusion:

Based on the results of worker risk (7.04×10^{-5}), TB-I recommends that a more definitive estimate of worker exposure be provided by OREB which would be based on all needed information from BEAD, in the event that the worker risk is deemed unacceptable.

Following the new worker exposure estimate, a revised carcinogenic risk estimate will be determined for workers.

The carcinogenic risks associated with dietary exposure to 1,4-dioxane, as a component of Roundup are non-existent and therefore not considered of toxicological concern.

Detailed conclusions regarding environmental fate require more data but dioxane leaches through the soil and has a half-life in groundwater of 2 to 12 months.

Attachments

cc: Penelope Fenner-Crisp, H7509C
William Burnam, H7509C
Amy Rispin, H7507C
Richard Schmitt, H7509C
Charles Trichilo, H7509C
Bernice Slutsky, H7509C

ROUN-DIO.BD/lca

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dioxane as a contaminant in Roundup (Glyphosate) formulations, DEB# 6895

FROM: A. Rathman, Section Head
Special Registration Section I
Dietary Exposure Branch
Health Effects Division (H7509C)

TO: Roger Gardner, Acting Section Head
TOX 1
Health Effects Division (H7509C)

TOX has requested confirmation of a statement made by Lynn Bradley in 1981 that residues of dioxane from application of Roundup would pose no residue problem. (Dioxane is apparently a contaminant in a surfactant used in Roundup). Based upon the levels of dioxane present (0.03% max) in Roundup, DEB would again conclude that any dioxane from the application of Roundup would pose no residue problem.

TOX should be aware that, as was the case in 1981, dioxane is cleared for use as an inert ingredient and under 180.1001(d) for use as a solvent or co-solvent in formulation applied to growing crops. The residues from the use of dioxane as a solvent are expected to be significantly higher than would occur from the presence of dioxane as impurity in a surfactant used in glyphosate formulations.

cc: K. Baetkey TOXI, RF, Circ, Rathman, Schmitt
H7509C: DEB: A. Rathman: sc: CM#2: Rm 810: X557-7324: 08/09/90
RDI: R. Schmitt 8/8/90

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C 20460

MAR 18 1981

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Response to Further Information Concerning Dioxane as an Impurity of ROUNDUP Herbicide (Glyphosate), Sec. 6(a)(2) Data, Tox. Chem. #561A

FROM: Gary J. Burin, Toxicologist
Toxicology Branch, HED (TS-769)

TO: Robert J. Taylor
Registration Division (TS-767)

THRU: William Burnam, Acting Chief
Toxicology Branch, HED (TS-769)

Background Information: On November 17, 1980, Monsanto Company informed the EPA that the present surfactant used in ROUNDUP herbicide contained as a trace impurity low levels of dioxane. This reviewer requested the following further information:

1. Name of the surfactant containing dioxane
2. Level of dioxane found in the surfactant
3. Whether not use of the surfactant will continue, or, as implied in the 6(a)(2) letter, the surfactant will be changed in the future.

Discussion and Recommendation: Monsanto Co. has supplied the requested information. Based on data presented by Monsanto, ROUNDUP would contain less than 0.03% dioxane. Given the use pattern for ROUNDUP, a worse case scenario would lead to average air concentrations of less than .1 ppm of dioxane. This level of dioxane is not expected to pose a hazard with respect to applicator exposure as the TLV for work place exposure set by the American Conference of Government Industrial Hygienists is 25 ppm (See N.I. Sax, Dangerous Properties of Industrial Materials, 3rd Edition, Van Nostrand Reinnold, page 703).

Residues of dioxane in rac's are also not expected to pose a problem, given the levels of dioxane found in the ROUNDUP formulation (personal conversation, Lynn Bradley, RCB, February 27, 1981).

In summary, it is the conclusion of this reviewer that "an unreasonable adverse effect" is unlikely to result from dioxane as a contaminant of this formulation at the reported levels. It is also noted that dioxane is "cleared" as an inert ingredient under 180.1001(d) for use as a solvent or co-solvent.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

AUG - 7 1990

MEMORANDUM

SUBJECT: Environmental Fate of 1,4-Dioxane

FROM: Robert Boethling, Chief
Environmental Fate Section RSB
Exposure Assessment Branch
Exposure Evaluation Division (TS-798)

TO: William Dykstra
Toxicology Branch I
Insecticide and Rodenticide Support
Health Effects Division (H7509 C)

THRU: Thomas Murray, Chief LO for T.M.
Exposure Assessment Branch
Exposure Evaluation Division (TS-798)

Bernice Slutsky requested that I send you a brief note giving my views on the biodegradability of 1,4-dioxane (syn. p-dioxane).

The ethers in general are a very poorly studied group of chemicals. The only extant data on biodegradability of 1,4-dioxane are a few screening tests based on the BOD principle: oxygen uptake over a test period generally less than 28 days. These data apparently are consistent in showing that little degradation occurred, but they have substantial limitations. What we need are data on biodegradability in soil and natural water.

Chuck Trichilo has already received a copy of the attached document on SARA 313 chemicals. Both the attached and his copy are older drafts I found in my files, but they are adequate for present purposes. Please read the narrative on 1,4-dioxane that precedes the "data" summary on that chemical. It is generally accurate. But note also that all of the conclusions regarding biodegradability of dioxane are extrapolated from the few screening test data just mentioned.

I would characterize this chemical as probably rather slow to biodegrade in soil, and I would guess that a half-life around one month is reasonable. Six months seems too pessimistic, but I could be wrong. We need data! In any case, 1,4-dioxane is not 2,3,7,8-TCDD ("dioxin"). I fully expect the latter to be in another league in terms of persistence in soil and water. Expect 2,3,7,8-TCDD to persist in soil for years, not weeks or months.

Finally, whatever 1,4-dioxane is deposited on soil should do one of two things rather quickly: (1) run off to streams; (2) leach through the soil column. That is, it <u>will not</u> remain on the surface.

Also attached is a report I wrote in 1985 on ethers. There is a considerable amount of data - most of it obtained via <u>estimation</u> techniques, however - on 12 ethers, one of which is 1,4-dioxane.

attachments

cc: Bernice Slutsky H7509C

1,4-Dioxane (Dioxane)

Physical Properties: Based upon its physical properties, 1,4-Dioxane is not expected to significantly volatilize from water or to strongly adsorb to soil or sediments. It is expected to leach through soil rapidly provided degradation is sufficiently slow.

Abiotic Degradation

Hydrolysis: No data available; not expected to be significant under normal environmental conditions.

Reduction: No data available; not expected to be significant under normal environmental conditions.

Photolysis: No data available; not expected to be significant under normal environmental conditions.

Photooxidation - Water: Based upon experimental rate data, photooxidation with alkylperoxyl radicals ($RO_2\cdot$) is slow (low $t_{\frac{1}{2}} \approx$ 18 years at an estimated high concentration of $5X10^{-10}$ M $RO_2\cdot$), relative to reaction with hydroxyl radicals ($\cdot OH$) (high $t_{\frac{1}{2}} \approx 9.1$ years at an estimated low concentration of $5X10^{-19}$ M $\cdot OH$).

Photooxidation - Air: Based upon estimated rate data, reaction with ozone (O_3) is very slow (low $t_{\frac{1}{2}} \approx 4.3$ years at an experimental high concentration of $3X10^{12}$ O_3/cm^3) relative to reaction with $\cdot OH$ (high $t_{\frac{1}{2}} \approx 3.4$ days based upon measured rate constant for reaction of 1,3,5-trioxane with $\cdot OH$ and an experimental low concentration of $3X10^5$ $\cdot OH/cm^3$).

(Photooxidation - Polluted Air: 50% degradation reported in 3.4 hours in air with 5 ppm NO, irradiated by sunlamps).

Biodegradation: The data located indicate that dioxane is resistant to biodegradation. The only grab sample experiments utilized trench leachate samples from a shallow-land waste burial site, but the study did not report incubation times for the experiments involving dioxane. Under aerobic conditions, 0% and 10% degradation were observed with and without an added N source, respectively; under anaerobic conditions, 4% and 13% degradation were observed, respectively.

Screening tests indicate little or no biodegradation of dioxane by sewage seed and activated sludge. Acclimation appears to have little effect on degradation rates. The MITI test confirms dioxane either is not degraded or is degraded slowly.

Selection of Data/Determination of Rates and Half-lives:

Half-lives:

Soil: No data concerning degradation in soil were located. Since hydrolysis is probably insignificant, biodegradation was selected as the most significant degradation mechanism. Based upon experiments in aqueous systems, biodegradation in soil is expected to be slow. An estimated range of half-lives of 1 to 6 months for dioxane in soil appears to be reasonable based upon scientific judgement.

Air: Photooxidation by $\cdot OH$ appears to be the most rapid degradation process in the atmosphere. High and low half-lives

were calculated using estimations of high and low concentrations of ·OH expected in relatively polluted and pristine air, respectively. These ·OH concentrations were based upon reported experimental data.

Surface Water: The t½ in surface water is based upon the estimated biodegradation rates because the rates for other degradation processes are either very slow (photooxidation) or are expected to be zero or negligible (direct photolysis, hydrolysis, and reduction).

Groundwater: The t½ in groundwater is based upon the estimated aerobic biodegradation rates (and assumed to be two times longer) because the rate of hydrolysis is negligible.

CHEMICAL NAME: 1,4-Dioxane CAS #: 123-91-1

HALF-LIVES:

SOIL: High: 4320 hours (6 months)
$t_{\frac{1}{2}}$ Low: 720 hours (1 month)
COMMENT: Scientific judgement based upon estimated unacclimated aqueous aerobic biodegradation half-life.

AIR: High: 81 hours (3.4 days)
$t_{\frac{1}{2}}$ Low: 8.1 hours (0.34 days)
COMMENT: Based upon photocxidation half-life in air.

SURFACE WATER: High: 4320 hours (6 months)
$t_{\frac{1}{2}}$ Low: 720 hours (1 month)
COMMENT: Based upon estimated unacclimated aqueous aerobic biodegradation half-life.

GROUND WATER: High: 8640 hours (12 months)
$t_{\frac{1}{2}}$ Low: 1440 hours (2 months)
COMMENT: Scientific judgement based upon estimated unacclimated aqueous aerobic biodegradation half-life.

AQUEOUS BIODEGRADATION (<u>unacclimated</u>):

Aerobic half-life: High: 4320 hours (6 months)
($t_{\frac{1}{2}}$, hr) Low 720 hours (1 month)
COMMENT: Scientific judgement based upon unacclimated aerobic aqueous screening test data which confirmed resistance to biodegradation (Kawasaki, M (1980); Sasaki, S (1978)).

Anaerobic half-life: High: 17280 hours (24 months)
($t_{\frac{1}{2}}$, hr) Low: 2880 hours (4 months)
COMMENT: Scientific judgement based upon estimated aerobic biodegradation half-life.

Removal/secondary treatment: High: No data
(%) Low:
COMMENT:

PHOTOLYSIS:

Atmos photol half-life: High: Will not directly photolyze
($t_{\frac{1}{2}}$, hr) Low:
COMMENT:

Max light absorption (nm): No data
COMMENT:

Aq photol half-life: High:
($t_{\frac{1}{2}}$, hr) Low:
COMMENT:

PHOTOOXIDATION half-life:
Water ($t_{\frac{1}{2}}$, hr): High: $8X10^4$ hours (9.1 years)
Low: 1608 hours (67 days)
COMMENT: Based upon measured rates for reaction with hydroxyl radicals in water (Dorfman, LM and Adams, GE (1973); Anbar, M and Neta, P (1967)).

Air ($t_{\frac{1}{2}}$, hr): High: 81 hours (3.4 days)
Low: 8.1 hours (0.34 days)
COMMENT: Based upon measured rate constant for reaction of 1,3,5-tricxane with hydroxyl radicals in air (Atkinson, R (1987A)).

REDUCTION half-life: High: No reducible groups.
($t_{\frac{1}{2}}$, hr) Low:
COMMENT:

HYDROLYSIS:
First-order hydr half-life ($t_{\frac{1}{2}}$, hr):
COMMENT:

Acid rate const $(M(H+)-hr)^{-1}$: No hydrolyzable groups.
COMMENT:

Base rate const $(M(OH-)-hr)^{-1}$:
COMMENT:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 30 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Evaluation of Monsanto Agricultural Products Co. Exposure Assessment for 1,4 Dioxane in Glyphosate Formulations (INTRA 0052).

TO: Roger Gardner, Section Head
Toxicology Branch I - IRS
Health Effects Division (H7509C)

FROM: Steven M. Knott, Chemist
Environmental Chemistry Review Section
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

THRU: Michael P. Firestone, Ph.D., Section Head
Environmental Chemistry Review Section
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

Charles L. Trichilo, Ph.D., Chief
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

INTRODUCTION

Roger Gardner (Toxicology Branch I - IRS) has requested that the Non-Dietary Exposure Branch (NDEB) do an initial screen of "Cancer Risk Assessment for Agricultural and Roadside Applications of Herbicide Surfactant Containing 1,4 Dioxane" and "Cancer Risk Assessment for Agricultural and Forestry Applications of Herbicide Surfactants Containing 1,4 Dioxane". The Agency has classified 1,4 Dioxane (figure 1) as a B_2 carcinogen with a $Q_1^* = 1.1 \times 10^{-2}$ $(mg/kg/day)^{-1}$. It is believed that exposure to this chemical may result from the use of various formulations of Glyphosate manufactured by Monsanto Agricultural Products Co.. Recent concerns over exposure from this use have prompted Monsanto to submit the subject risk assessments. The following is NDEB's review of the exposure estimates used by Monsanto.

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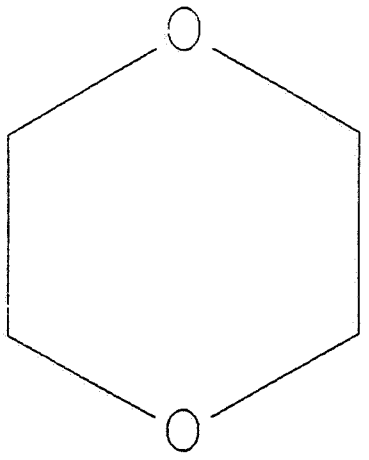

Figure 1: 1,4 Dioxane

CONCLUSION

NDEB has reviewed the subject risk assessments to determine the acceptability of the exposure estimates. It has been determined that the exposure estimates presented by Monsanto are unacceptable for the following reasons:

1) The estimates for ground boom application to agricultural sites were derived from the joint EPA/Health and Welfare Canada/NACA Pesticide Handler Exposure Database. This database is currently under development and is not sufficiently complete to allow generation of scientifically valid estimates of exposure.

2) The estimates for truck-mounted spray guns for roadside workers and backpack and aerial (mixer/loaders) applications for forestry workers were derived from surrogate data that NDEB has not reviewed, or does not have access to. These data should have been submitted with Monsanto's assessments.

NDEB has calculated an **upper bound worst case** lifetime average daily exposure estimate for the application of Dioxane contaminated Glyphosate using ground boom equipment. The result of this calculation is:

6.4×10^{-3} mg/kg/day

This value has not been adjusted for dermal penetration. NDEB defers to Toxicology Branch I - IRS for the adjustment of exposure values for dermal penetration. NDEB also defers to BEAD for the evaluation of the use information used in this

assessment. If a more realistic estimate of exposure is necessary, BEAD must provide NDEB with a Comprehensive Use Assessment Software Package.

DETAILED CONSIDERATIONS

Monsanto Agricultural Products Co. has submitted an exposure/risk assessment for 1,4 Dioxane in formulations of Glyphosate. In this assessment, 4 methods of application were examined.

1) Ground boom application for agricultural uses.

2) Truck-mounted spray guns for road side workers.

3) Aerial application (mixer/loader only) for forestry workers.

4) Backpack sprayers for forestry workers.

The exposure assessments for each of the above scenarios are unacceptable for the following reasons:

1) The ground boom exposure estimates were determined using the EPA's Pesticide Handler Exposure Database (formerly the Pesticide User Exposure Database, see page 2).

2) Currently, NDEB does not have access to studies which evaluate exposure resulting from the use of truck-mounted spray guns. Monsanto should have provided their cited studies (Libich et al. and Monsanto's unpublished data) with their submission.

3) Exposure to aerial mixer/loaders was estimated using surrogate studies which the agency has not reviewed (Nash et al. and Franklin et al.). Copies of these studies should have been included in Monsanto's submission.

4) Exposure to backpack sprayers was estimated using an unpublished study conducted by the Georgia Tech Research Institute. Once again, these data should have been submitted with the subject risk assessment.

Despite this unacceptable derivation of the exposure values, Monsanto's estimates appear to be reasonable. For comparison, NDEB has calculated ground boom exposure using commonly accepted surrogate exposure data and some of the assumptions used by Monsanto. NDEB believes that this is an upper bound worst case estimate of exposure and that actual exposure, from this and other application techniques, will be much lower.

The assumptions used in NDEB's assessment are as follows:

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1) Mixing/Loading is done by open pour loading (unit exposure = 0.93 mg/lb ai as determined from 18 replicates in the Abbott study, "Worker Exposure to a Herbicide Applied with Ground Sprayers in the United Kingdom", Am. Ind. Hyg. Assoc. J., 48 (2): 167-175).

2) Application is conducted from an open cab tractor (unit exposure = 56.7 mg/hr as determined from 18 replicates in the Abbott study, cited above, and 21 replicates in the Wojeck study, "Worker Exposure to Paraquat and Diquat", Arch. Environ. Contam. Toxicol., 12:65-70).

3) Applicators are wearing long pants and long sleeve shirts and mixer/loaders are wearing the above plus chemical resistant gloves.

4) The Glyphosate formulation contains 300 ppm 1,4 Dioxane (at final dilution).

5) The Glyphosate formulation contains 30.41% ai.

6) In an 8-hr day, 290 acres will be treated (based on a tractor speed of 5 mph and a boom width of 60 ft.).

7) The application rate will be 2 lb ai/acre (based on 2 quarts/acre and 4 lb ai/gallon).

8) The applicator will work 200 days/year.

9) The applicator will work 40 years in a 70 year lifetime.

NDEB believes that these assumptions will result in a worst case exposure assessment for the following reasons.

1) Monsanto claims to have a requirement that the surfactant used in their Glyphosate formulations cannot contain more than [redacted]

2) Five miles per hour is the maximum tractor speed recommended for application of these products (Crop Protection Chemical Reference, 1985). Covering 290 acres in an 8-hour day would not allow for work breaks, ferrying time or tank refills.

3) The application rate of 2 lb ai/acre is only recommended for certain weed pressures. A more commonly used rate is 1.5 lb ai /acre (Crop Protection Chemical Reference, 1985).

4) Assuming that a pesticide applicator will apply Glyphosate for 200 days out of the year is unreasonable if

Commercial/financial information and Quality control procedure information not include

weather conditions, weed pressures and other factors are taken into consideration.

NDEB defers to BEAD for the evaluation of the use assumptions. If a more realistic exposure evaluation is needed, BEAD should provide NDEB with a Comprehensive Use Assessment Software Package for the Glyphosate formulations of concern.

NDEB also defers to Toxicology Branch I - IRS for the adjustment of exposure values for dermal penetration rates.

Using the above assumptions, the combined mixer/loader/ applicator lifetime average daily exposure is calculated as follows:

MIXER/LOADER

290 Acres/day x 2 lb ai/Acre x 0.93 mg ai/lb ai x 0.03% Dioxane/30.41% ai x 1/70 kg x 200 days/yr x 40 yr/70 yr x 1 yr/365 days = **2.4×10^{-3}** mg/kg/day

APPLICATOR

56.7 mg ai/hr x 2 lb ai/acre x 8 hr/day x 0.03% Dioxane/30.41% ai x 1/70 kg x 200 days/yr x 40 yr/70 yr x 1 yr/365 days = **4×10^{-3}** mg/kg/day

COMBINED

$$2.4 \times 10^{-3} + 4 \times 10^{-3} = \mathbf{6.4 \times 10^{-3}} \text{ mg/kg/day}$$

cc: Robert Taylor (H7505C)
Circulation
Correspondence
Chemical File
SACB
BEAD

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1,4-Dioxane; CASRN 123-91-1 (02/01/90)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR 1,4-Dioxane

File On-Line 08/22/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	06/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- 1,4-Dioxane
CASRN -- 123-91-1

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

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Substance Name -- 1,4-Dioxane
CASRN -- 123-91-1
Last Revised -- 06/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< 1,4-Dioxane >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen.

Basis -- Induction of nasal cavity and liver carcinomas in multiple strains of rats, liver carcinomas in mice, and gall bladder carcinomas in guinea pigs.

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Three epidemiologic studies on workers exposed to 1,4-dioxane are available. Theiss et al. (1976) reported 12 deaths among 74 workers exposed to dioxane. Two of the deaths were due to cancer, one lamellar epithelial carcinoma in a 66-year-old man and one myelofibrotic leukemia in a 71-year-old man. No statistically significant increase was noted based on these few cases of cancer. Among 165 production and processing workers exposed to dioxane (as well as vinyl chloride, perchloroethylene, methylene chloride, trichloroethylene and carbon tetrachloride), 12 deaths were reported (Buffler et al., 1976, cited in U.S. EPA, 1986b). Three of these deaths were due to cancer: one stomach cancer, one alveolar carcinoma, and one mediastinal malignancy. These deaths were not different from the expected numbers. In an unpublished report to NIOSH by Dernehl (1976, cited in U.S. EPA, 1986b), four cancers were reported among 80 dioxane workers. The cancers included a colonic cancer, a pulmonary cancer, a lymphosarcoma, and a glioblastoma. Again, the observed number of cancer cases was not different from the expected cancer deaths.

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II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. The NCI (1978) administered 1,4-dioxane (greater than or equal to 99.9% pure) in the drinking water to Osborne-Mendel rats (35 rats/sex/dose) and mice (50 mice/sex/dose) for a significant portion of their lifespan (110 weeks, rats; 90 weeks, mice). Male and female rats were given 530, 240, or 0 mg/kg/day and 640, 350, or 0 mg/kg/day, respectively. High-dose and matched control male rats were placed in the study 1 year after the study began to replace two original groups of male rats that had died

during an air-conditioning failure. Male and female treated rats had a statistically significant elevated incidence of nasal cavity squamous cell carcinomas and treated female rats had a statistically significant elevated incidence of liver adenomas, both dose-related. Male and female mice treated with 830, 720 or 0 mg/kg/day and 860, 380 or 0 mg/kg/day, respectively, developed a statistically significant elevated incidence of liver carcinomas and liver carcinomas or adenomas, both dose-related. Survival rate of treated rats and female mice was decreased by comparison to controls, but the NCI concluded that sufficient numbers of animals were at risk of developing tumors.

Kociba et al. (1974) administered 1%, 0.1%, 0.01% or 0% 1,4-dioxane in the drinking water to male and female Sherman rats for up to 716 days (60 rats/sex/treatment group). The incidences of hepatocellular carcinomas, liver cholangiomas and nasal cavity squamous cell carcinomas showed a significant increase in the high-dose rats of both sexes. Similar administration of 0.5% to 2% 1,4-dioxane to male guinea pigs for 23 months induced gall bladder carcinomas (2/22) and liver hepatomas (3/22) (Hoch-Ligeti and Argus, 1970). Hoch-Ligeti et al. (1970) and Argus et al. (1973) treated male Sprague-Dawley rats with 1.8, 1.4, 1.0, 0.75 or 0% 1,4-dioxane in the drinking water for 13 months, followed by a 3-month observation period. Treatment-related hepatocellular carcinomas and nasal cavity carcinomas were observed at 1.8% and 1.4% 1,4-dioxane, and treatment-related nasal cavity carcinomas were observed at 1.0% and 0.75% 1,4-dioxane. Liver tumors (7/26) were induced in male Wistar rats after oral administration of 1% 1,4-dioxane in the drinking water for 63 weeks (Argus et al., 1965). One kidney transitional cell carcinoma and one myeloid leukemia were also observed in the treated animals. A lymphoid tissue lymphosarcoma was observed in 1 of 9 control rats.

In a 2-year inhalation study (Torkelson et al., 1974), male and female Wistar rats were exposed to 111 ppm or 0 ppm 1,4-dioxane vapor. Three replicate groups of 288 rats/sex served as the treated and control groups. Comprehensive gross and microscopic examination of the major organs and tissues revealed no treatment-related lesions.

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___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

1,4-Dioxane was found to be a promoter in a two-stage skin carcinogenesis study in mice (King et al., 1973). A single dermal application of 50 ug of 7,12-dimethylbenzoanthracene (DMBA) was followed 1 week later by thrice-weekly paintings of 1,4-dioxane (unspecified concentration in acetone) for 60 weeks. Similar applications of 1,4-dioxane without DMBA initiation did not result in a significantly increased incidence of subcutaneous carcinomas.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE
<<< 1,4-Dioxane >>>

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 1.1E-2/mg/kg/day

Drinking Water Unit Risk -- 3.1E-7/ug/L

Extrapolation Method -- Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	3E+2 ug/L
E-5 (1 in 100,000)	3E+1 ug/L
E-6 (1 in 1,000,000)	3 ug/L

<<< 1,4-Dioxane >>>

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- squamous cell carcinoma of the nasal turbinates
Test Animals -- rat/Osborne-Mendel, male
Route -- oral, drinking water
Reference -- NCI, 1978

Dose		Human Equivalent (mg/kg/day)	Tumor Incidence
Administered %	mg/kg/day		
0	0	0	0/33
0.5	240	48	12/25
1.0	530	106	16/33

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___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

Transformed doses in mg/kg/day were provided by the study author. NCI (1978) determined average daily doses from the mean consumption of dioxane solution per week at intervals during the second year of treatment. The length of exposure, experiment and lifespan was 110 weeks for treated and control animals. The weight of the animals was assumed to be 0.55 kg from the study. The human weight was assumed to be 70 kg.

The unit risk should not be used if the water concentration exceeds 3E+4 ug/L, since above this concentration the slope factor may differ from that stated.

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___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

The compound was administered at multiple dose levels by a relevant route of exposure. The animals were exposed for a significant portion of their lifespan, and comprehensive histologic examinations were performed. Although survival was affected by treatment, adequate numbers of rats were at risk for development of late-appearing tumors.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

<<< 1,4-Dioxane >>>

II.D.1. EPA DOCUMENTATION

U.S. EPA. 1986a. Reportable Quantities Document for 1,4-Dioxane (review draft). Prepared by the Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington, D.C. for the Office of Emergency and Remedial Response and Office of Solid Waste and Emergency Response, Cincinnati, OH.

U.S. EPA. 1986b. Evaluation of the Potential Carcinogenicity of 1,4-Dioxane (123-91-1) (review draft). Prepared by the Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington DC for the Office of Emergency and Remedial Response and Office of Solid Waste and Emergency Response, Cincinnati, OH. OHEA-C-073-97.

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1986 Reportable Quantities Document for 1,4-dioxane have received limited Agency review.

Agency Work Group Review: 05/13/87, 02/03/88

Verification Date: 02/03/88

II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Jim Holder / ORD -- (202)382-5721 / FTS 382-5721

Charles Ris / ORD -- (202)382-5898 / FTS 382-5898

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III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- 1,4-Dioxane
CASRN -- 123-91-1

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Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- 1,4-Dioxane
CASRN -- 123-91-1

Not available at this time

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_V. SUPPLEMENTARY DATA

Substance Name -- 1,4-Dioxane
CASRN -- 123-91-1

Not available at this time

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_VI. BIBLIOGRAPHY

Substance Name -- 1,4-Dioxane
CASRN -- 123-91-1
Last Revised -- 02/01/90

__VI.A. ORAL RfD REFERENCES

None

------<<< 1,4-Dioxane >>>------

__VI.B. INHALATION RfD REFERENCES

None

------<<< 1,4-Dioxane >>>------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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U.S. EPA. 1986b. Evaluation of the Potential Carcinogenicity of 1,4-Dioxane (123-91-1) (review draft). Prepared by the Carcinogen Assessment Group, Office of Health and Environmental Assessment, Washington DC for the Office of Emergency and Remedial Response and Office of Solid Waste and Emergency Response, Cincinnati, OH. OHEA-C-073-97.

None

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SYNONYMS

123-91-1
diethylene dioxide
diethylene oxide
1,4-Dioxane
Dioxane, 1,4-
p-dioxane