ECETOC

February, 1983

Joint Assessment of Commodity Chemicals

No. 2

1,4-DIOXANE

CAS : 123-91-1

European Chemical Industry
Ecology & Toxicology Centre

Avenue Louise 250, B. 63
B - 1050 Brussels, Belgium

THE ECETOC SCHEME FOR THE "JOINT ASSESSMENT OF COMMODITY CHEMICALS" (JACC)

This report has been produced as part of a programme for making critical reviews of the toxicology, including ecotoxicology, of selected industrial chemicals.

A number of organisations, world-wide, have produced and are continuing to produce such reviews with the aim of ensuring that, based on an up-to-date knowledge of the toxicological, and other relevant, information regarding existing chemicals they can continue to be produced and used safely. ECETOC is contributing to this activity with its JACC reviews.

In general, commodity chemicals, ie. those produced in large tonnage by several companies and having widespread and multiple uses, are reviewed jointly by experts from a number of the companies concerned. Before it is decided to review a chemical, every effort is made to discover whether an adequate review exists already, in which case no work is necessary.

It should be noted that in a JACC review only the uses of the chemical as such are considered, ie. its occurrence as an impurity in other products is not normally taken into account.

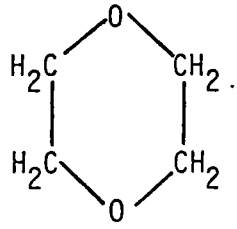
Addendum :

In this document a critical assessment of the toxicology and ecotoxicology of 1,4-dioxane is presented. 1,4-dioxane was chosen as one of four varied chemicals on which trial exercises were carried out to aid in developing the JACC scheme.

TABLE OF CONTENTS

A critical assessment of the toxicology and ecotoxicology of 1,4-dioxane is presented.

A. CHEMICAL IDENTITY AND PHYSICAL-CHEMICAL PROPERTIES.



$C_4H_8O_2$

CAS 123-91-1
EEC No.603-024-00-5
US No.1165

Other names : Dioxane; diethylene ether; 1,4-diethylene dioxide; diethylene oxide; dioxyethylene ether. 1,4-Dioxane will hereafter be referred to as 1,4-D.

1. Physical Properties

1,4-D is a colourless liquid with a mild, not unpleasant, ethereal odour.

Molecular weight		88.11
Density d^{20}_{20}		1.0329
Boiling point (1013 mbar)	°C	101.3
Vapour pressure at 20°C	mbar	41.3
Melting point	°C	11.8
Viscosity at 20°C	mPas	1.31
Refractive index n_d		1.4224
Heat of vaporization (1014 mb)	kJ/kg	404.15
Cryoscopic constant	k mol/kg	4.63
Flash point : open cup	°C	23.3
" " : closed cup	°C	12.2
Solubility	miscible with water, most organic solvents, aromatic hydrocarbons and oils.	

1,4-D forms an azeotrope with water (18,4% water, B.P. 87.8°C), and with ethanol (90.7% ethanol, B.P. 78.1°C).

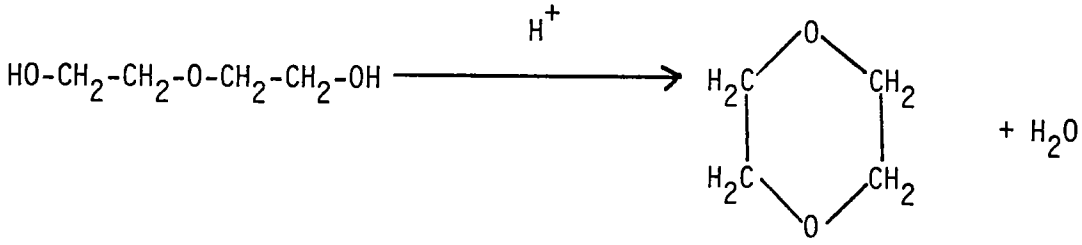
2. Chemical Properties

Technical grade 1,4-D has, typically, a purity of 99.5%, a water content of 0.1%, and a peroxides content of 10 ppm. It is a fairly stable compound with low reactivity. By treatment with strong acids at high

temperatures it is possible to open the ring structure. 1,4-D is easy to chlorinate, and depending on the reaction temperature (40° to 160°C) the products range from 2,5-dichloro-dioxane up to octachlorodioxane. The chlorodioxanes are of no technical importance. On contact with air, 1,4-D may form explosive peroxides whose chemical structure is not known. The addition of suitable stabilizers can prevent this oxidation. Peroxides in 1,4-D can be reduced with $SnCl_2$, $FeCl_2$ or activated aluminium oxide.

B. PRODUCTION AND USES

The most important way of manufacturing 1,4-D is via the dehydration of diethyleneglycol:



Ethyleneglycol is less frequently used as starting material.The reaction is carried out at temperatures around 160°C at a pressure of 250-1100 mbar. Sulphuric acid is the most common catalyst, but phosphoric acid, toluene sulphonic acid, sodium hydrogen sulphate and strongly acidic ion-exchange resins are also used.

1,4-D is not an important solvent in the chemical industry itself, but finds use mainly outside. Compared to other organic solvents, only small quantities of dioxane are produced. It is estimated that in W. Europe there is a total demand of 1500 tonne/yr. The industrial consumption of 1,4-D has been constant over the last few years.

Because of its excellent solvent characteristics, 1,4-D is primarily used as a solvent for cellulosics and a wide range of organic products : lacquers, wetting and dispersing agents in textile processing, dye baths, etc. It is used in the pharmaceutical industry in extraction processes. 1,4-D can protect active aluminium or aluminium-alloy surfaces, and it is an excellent stabilizer for a number of chlorinated solvents.

C. HUMAN EXPOSURE

The normal routes of human exposure to 1,4-D are inhalation and contact with the eyes or skin. It may be absorbed through human skin both from lipoidal or polar vehicles (Bronaugh, 1980). In W. Europe it is estimated that only a few thousand people are exposed to 1,4-D. At production plants only around 10 people are exposed. No accurate figures are available.

Occupational exposure limits in most countries range from 25 ppm (Time Weighted Average) to 100 ppm (Short-Term Exposure Limits). These limits were based on the hepato- and nephro-toxic effects of 1,4-D observed in laboratory animals and in exposed workers at much lower doses than those required for the induction of a carcinogenic effect as seen in animals.

No data are available about the levels of exposure to 1,4-D. Its uses and properties imply that a variable, but low, level of human exposure occurs. Typical occupational exposure levels in degreasing operations are known to be significantly lower than current hygienic standards.

Monitoring. Sampling and analyses in air may be performed by collecting 1,4-D vapours in an adsorption tube followed by desorption with carbon disulphide and gas chromatographic analysis. (IARC,1976; NIOSH, 1977). Biological monitoring, while technically feasible, is not practised.

D. TOXICOLOGICAL DATA

1. Human

   Irritation of the eyes, nose and throat was observed in 12 volunteers exposed to an air-borne concentration of 1080 mg/m^3 (300 ppm) of 1,4-D for 15 minutes (Silverman et al.,1946).

   Over a period of 40 years of industrial production of 1,4-D, six deaths have been attributed to acute intoxication but there are no reports of chronic toxicity. The six deaths followed acute over-exposure, with possible oral absorption in 5 (Barber, 1934), and percutaneous absorption in 1 (Johnstone, 1959) case . Precise details on the degree of exposure are lacking , although for the death resulting from percutaneous absorption an atmospheric exposure of up to 500 ppm for one week was reported.

In all cases the workers dipped their hands into liquid 1,4-D and in some cases they were reported as also putting their heads into the vapour space of a vat containing 1,4-D.

No malignancies related to exposure to 1,4-D were detected in 3 studies performed on workers at a 1,4-D production plant and one study at a plant in which 1,1,1-trichloroethane was mixed with 1,4-D as a stabiliser. In 3 of these studies extensive health screening was also performed but revealed no abnormalities in health parameters (Dernahl,1976; Thiess et al.,1976; Buffer et al.,1978; Kramer et al.,1978).

2. Experimental

2.1. Acute toxicity

The acute toxicity of 1,4-D has been extensively studied in various animal species, via different routes. The compound had a rather low toxicity after single exposures in any of the species tested by the oral, inhalation, intraperitoneal, intravenous and percutaneous routes. The LD_{50} by the oral route ranges from 2000 mg/kgbw (rabbit) to 5700 mg/kgbw (mouse). The inhalation LC_{50} is 46 g/m³ (12,780 ppm) in the rat and 65 g/m³ (18,000 ppm) in the mouse, for a 2-hour exposure (NIOSH, 1980).

2.2. Subchronic and chronic toxicity

The data available on subchronic toxicity are mostly from papers published in the 1930's (eg. as quoted by ACGIH, 1980; Clayton and Clayton, 1981). Despite the obvious objections as far as protocols are concerned, and some lack of detail, it can be concluded from these papers that for short periods (hours) some toxic effects occur at above 2000 ppm (irritation of eyes, nose and lungs), and that for longer periods (30 days) signs of toxicity occur at 800 ppm and upwards (kidney and liver damage; death in some cases).

More complete and detailed information is available on chronic toxicity from carcinogenicity tests carried out in 1974 (Kociba et al., 1974; Torkelson et al.,1974). 1,4-D administered to male and female Sherman rats in the drinking water, at concentrations of 1% (1015-1599 mg/kgbw/d) and at 0.1% (94-148 mg/kgbw/d) for 2 years, produced higher early mortality and lower body weights in comparison with controls. Degeneration and necrosis of the renal tubular epithelium and liver

cells were observed in varying degrees. No pathological alteration was detectable at 0.01% (9.6-19 mg/kgbw/d). Only small alterations, of doubtful toxic significance, were seen in Wistar rats exposed by inhalation for two years at 111 ppm for 7 hr/d, 5 d/wk. A decrease in blood urea nitrogen and in serum alkaline phosphatase were observed.

2.3. Carcinogenicity

Many studies have been performed on the carcinogenic effects of 1,4-D; two in mice, five in rats and one in guinea-pigs. In 6 of these experiments the route of administration was oral (drinking water), in one the inhalation route was used, and in another the material was applied cutaneously.

One oral study (King et al.,1973) on mice was too short (40-43 weeks) for any conclusions to be drawn. Other long-term studies via the oral route were performed on rats, mice and guinea-pigs (Argus et al.,1965, 1973; Hogh-Ligeti et al.,1970; Kociba et al.,1974; Holmes, 1978). From these oral studies it can be concluded that 1,4-D is carcinogenic in experimental animals at oral daily dose levels of 0.35 g/kgbw or more, and that the main organs affected are the liver (hepatomas and hepatocellular carcinomas) and the nasal cavities (squamous-cell carcinomas and adenocarcinomas). From ingestion studies (Kociba et al.,1974; Holmes,1978) a no effect level of about 0.1 g/kgbw/d is indicated.

The only inhalation study, performed on Wistar rats (96 males/96 females; 111 ppm; 7 hr/d, 5 d/w, 2 years) showed no difference in tumour incidence between the exposed and control animals (Torkelson et al.,1974).
With percutaneous application in Swiss Webster mice (30 males, 30 females; thrice weekly paintings of 0.2 ml of an unspecified concentration of 1,4-D in acetone for 60 wk) no significant increase in skin or other types of tumours was recorded. Under the same experimental conditions, 1,4-D was shown to be a tumour promotor, as demonstrated in a group of mice treated with 1,4-D and dimethylbenzanthracene by skin painting (King et al.,1973).

An anti-tumourigenic effect of 1,4-D was noted by Baykut et al.(1978) when the compound was introduced locally into spindle-cell sarcoma mass in rats. Since the original paper is not available, no definite conclusions can be drawn.

2.4. Metabolism and pharmacokinetics

1,4-D may be absorbed through the human skin (Bronaugh,1980). In volunteers exposed to 50 ppm in air for 6 hours, a total of 5.4 ± 1.1 mg/kgbw was absorbed, the maximum amount in the body at any one time being 1.2 ± 0.2 mg/kgbw (Young, 1977). In vitro studies in excised human skin showed that up to 3.2% of the applied quantity of 1,4-D may penetrate the skin under occlusive conditions, but only up to 0.3% when it is allowed to evaporate (Maibach, 1980). The velocity of skin penetration is independent of the presence of other polar or non-polar components. When a "popular lotion" containing 1,4-D was applied to the skin, 90% of the 1,4-D evaporated within 15 minutes. These findings are consistent with the data from an in vivo study in monkeys, where 2.3% of the 1,4-D content was resorbed from a methanolic preparation and 3.4% from a lotion (Maibach,1980). Here, too, rapid evaporation was observed.

The metabolic fate of 1,4-D in rats and humans is clearly dose-dependent (Young, 1977,1978). In rats, after intravenous injection of 3-10 mg/kgbw, 1,4-D was eliminated according to linear kinetics, with a half-life of 1.1 hours. Higher doses (30, 100, 300, 1000 mg/kgbw) were eliminated more slowly, indicating saturation of an elimination process.

In human subjects exposed for 6 hours to 50 ppm in air, 1,4-D was eliminated according to a one-compartment, open-system model with zero order uptake and first order elimination. The half life was 59 ± 7 min. No accumulation resulted from repeated daily 8 hr. exposures to 50 ppm in air.

1,4-D, in rats and humans, is eliminated mainly in the urine after exposure via various routes (Braun et al.,1977; Young, 1978). Minor quantities of the compound as such are also eliminated with expired breath. Very small amounts are excreted with the faeces. The main urinary metabolite of 1,4-D is β-hydroxyethoxyacetic acid (HEAA), both in humans and rats. Excretion of unchanged 1,4-D increases, while HEAA excretion decreases, with increasing doses (Braun, 1977; Young, 1978). Comparing the dose-dependent toxicokinetic parameters of dioxane clearance (which are similar in rat and man) with the dose response for carcinogenicity in the animal model a clear coincidence is shown

for the saturation of the metabolic clearance pathway and the onset of tumours.

The metabolism studies show a clear similarity between the rat and humans.

Baykut et al.(1978) while performing studies on the anti-tumour effect of 1,4-D in vitro, demonstrated a 1,4-D-haemoglobin interaction. At low concentrations (0.1-0.5%) 1,4-D converted oxyhaemoglobin into metahaemoglobin, whilst at high concentrations (10-20%) a 1,4-D-haemoglobin complex was also formed. At a 40% concentration, protein coagulation occurred.

2.5. Mutagenicity

No mutagenic effect was detected in Salmonella typhymurium studies with metabolic activation made by two USA laboratories under NTP sponsorship (NTP, 1981). No experimental details are available concerning the strains, 1,4-D doses, or number of repetitions of the single doses. A more complete report was published by Stott et al.(1981). 1,4-D was negative in the Ames mutagenicity assay, with or without metabolic activation, over a dose range from 0 to 103 mg/plate in 4 strains of S. typhimurium. In the same paper it was reported that no in vivo DNA alkylation or increase in hepatic DNA repair occurred. 1,4-D was also negative in primary hepatocyte "Unscheduled DNA Synthesis" bioassays.

2.6. Teratology and reproduction.

No reproduction study dealing with pure 1,4-D has been found in the literature. However, Lane (1982) described a multigeneration dominant lethal, teratology study in mice dosed with 1,1,1-trichloroethane stabilized with 3% 1,4-D given in drinking water. The animals received 0, 3, 10, 30 mg/kgbw/d of 1,4-D. None of the treated mice showed abnormalities in their reproduction or development.

E. ECOTOXICOLOGICAL DATA

1. Environmental Distribution

No data on environmental concentrations could be found in the available literature. However, in view of the relatively low tonnage produced, and the volatility and water/solubility of 1,4-D which promote rapid dilution, very low environmental concentrations may be expected.

2. Persistence

2.1. Biodegradation

Unpublished determinations of BOD (Dow, 1981) indicate that less than 30% of 1,4-D biodegrades in 20 days. Although this would indicate that 1,4-D is not easily biodegradable, a definite conclusion about its biodegradability cannot be drawn because of the variability of the data and the limited number of results.

2.2. Phototransformation in air.

Dilling et al.(1976) studied the phototransformation of 1,4-D in air, and correlated their results with published data of tropospheric hydroxyl radical concentrations. They calculated an average tropospheric half-life at 25°C of 14 hours (diurnal time).

3. Aquatic Toxicity

The acute toxicity of 1,4-D to fresh- and salt-water fish seems very low (Dawson, 1975), as demonstrated by its LC_{50} (96 h) of 10,000 ppm and 6,700 ppm respectively. These high values indicate a virtual absence of acute toxicity to fish at any likely environmental concentrations.

4. Bioaccumulation

The high water-solubility of 1,4-D would seem to exclude the possibility of bioaccumulation.

F. SUMMARY AND CONCLUSIONS

High air-borne concentrations (around 300 ppm) cause eye, nose and throat irritation in man, and acute over-exposure can cause death. The acute toxicity to animals is low. 1,4-D is not mutagenic and there is some evidence that it has no effects on reproduction in mice.

The toxicological profile of 1,4-D is sufficiently defined in respect of experimental acute and chronic toxicity, mutagenicity, and animal carcinogenicity. The animal carcinogenicity studies are considered to be adequate because relevant dosages, and various routes of administration and animal species were used.

Many of these studies were performed on the rat, which is a good model for comparison with man because 1,4-D has the same metabolic pattern and toxicokinetics in both species. Therefore the existence of a no-observed-effect level, which could be derived from animal studies, short-term tests and investigations on metabolism, may also be postulated for humans.

The absence of a mutagenic effect, the recurrent cytotoxicity in the liver as the single target organ and the lack of interaction with DNA indicate that the observed tumourigenic effect of 1,4-D in experimental animals operates via a non-genotoxic mechanism, which implies that a no-effect level exists for the carcinogenic effect.

The data from epidemiological studies are sufficient for evaluating the systemic health effects of 1,4-D, but a clear-cut conclusion cannot be reached regarding carcinogenic risk to humans since the studies are based on insufficiently defined parameters (number of subjects, level of exposure, duration of exposure). It would be helpful to have more extensive epidemiological data but it would be difficult, if not impossible, to find adequate cohorts with respect to number of exposed subjects, exposure level and duration of exposure.

Although there is an almost total absence of data on the environmental fate of 1,4-D, its high water solubility and volatility suggest that it will eventually migrate into water and air. Considering the small volume of production and the rapid photochemical elimination from the atmosphere, further toxicological and ecotoxicological studies are not considered to be of high priority.

G. BIBLIOGRAPHY

- ACGIH (1980). Documentation of the threshold limit values, IV Ed., 154.

- Argus, M.F., Arcos, J.C. and Hoch-Ligeti,C.(1965). Studies on the carcinogenic activity of protein-denaturating agents : hepatocarcinogenicity of dioxane. J. Nat. Cancer Inst.,35, 949.

- Argus, M.F., Sohal, R.S., Bryant, G.M., Hoch-Ligeti, C. and Arcos, J.C.(1973). Dose-response and ultrastructural alterations in dioxane carcinogenesis. Influence of methylcholanthrene on acute toxicity. Europ. J. Cancer, 9, 237.

- Barber, H.(1934). Haemorrhagic nephritis and necrosis of the liver from dioxane poisoning. Guy's Hospital Rep., 84, 267.

- Baykut,F.,Sengün,A.,Üren, A. and Enginün, M.(1978). 1,4-Dioxane-haemoglobin interaction. Chimica Acta Turcica, 6, 161.

- Braun, W.H. and Young, J.D.(1977). Identification of -hydroxyethoxy-acetic acid as the major urinary metabolite of 1,4-dioxane in the rat. Tox. Appl. Pharmacol., 39, 33.

- Bronaugh, R.L., Congdon, E.R., Stadtmauer, E.A. and Scheuplein, R.J. (1980). Percutaneous absorption of 1,4-dioxane through excised human skin. Abstract 145, 19th Soc. Toxicology, Annual Meeting - Washington.

- Buffler, P.A., Wood, S.M., Suarez, L. and Kilian, D.J.(1978). Mortality follow-up of workers exposed to 1,4-dioxane. J. Occ. Med., 20 (4), 255.

- Clayton,G.D. and Clayton,F.E.(1978,1981). Dioxane. In: Industrial Hygiene and Toxicology. Vol.2. Ed. Frank A. Patty.

- Dawson, G.W.(1975-77). The acute toxicity of 47 industrial chemicals to fresh and saltwater fish. J. Haz. Mat.,1, 303.

- Dernahl(1976). Written communication, quoted in 1,4-Dioxane, NIOSH Criteria Document, DHEW Publication, no.77, 226, p.43,(1977).

- Dilling, W.L., Bredeweg, C.J. and Fefertiller, N.B.(1976). Organic photochemistry : simulated photodecomposition rates of methylene chloride, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and other compounds. Environm. Sci. & Technol. 10(4),351.

- Dow (1981). Unpublished data. Biochemical Oxygen Demand of 1,4-dioxane, ES-DR-0000-9529-2, April 20.

- Hoch-Ligeti, C., Argus, M.F. and Arcos, J.C.(1970). Induction of carcinomas in the nasal cavity of rats by dioxane. Brit. J. Cancer, 24, 164.

- Holmes, P.(1978). Bioassay of 1,4-dioxane for possible carcinogenicity. NCI Tech. Rep. Ser. No.80, DHEW Pub. No.(NIH) 78, 1330.

- IARC (1976). Monographs on the evaluation of the carcinogenic risk of chemicals to man, Vol.11, 247.

- Johnstone, R.T.(1959). Death due to dioxane ? AMA Arch. Industr. Hlth, 20, 445.

- King, M.E., Shefner, A.M. and Bates, R.R.(1973). Carcinogenesis bioassay of chlorinated dibenzodioxins and related chemicals. Environm. Hlth. Persp.,5, 163.

- Kramer, C.G., Ott, M.G., Fulkerson, J.E., Hicks, N. and Imbus, H.R.,-(1977). Health of workers exposed to 1,1,1-trichloroethane. A matched-pair study. Arch. Environ. Health, 33, 331.

- Kociba, R.J., McCollister, S.B., Park, C., Torkelson, T.R. and Gehring, P.J.(1974). 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. Toxicol. Appl. Pharmacol., 30, 275.

- Lane, R.W., Riddle, B.L. and Borzelleca, J.F.(1982). Effect of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. Toxicol. Appl. Pharmacol., 63, 409.

- Maibach, H.(1980). Evaporation of dioxane from monkey skin (from a commercially available "Moisturizer"). Submitted to FDA, USA .

- NIOSH (1977). Manual of analytical methods, Vol. III, DHHS (NIOSH) Publication No. 77-157 C.

- NIOSH (1980). Registry of toxic effects of chemical substances. DHHS (NIOSH) Publication No. 81-116.

- NTP (1981). Technical Bulletin No.4.

- Silverman, L., Schulte, H.F. and First, W.W.(1946). Further studies on sensory response to certain industrial solvent vapours. J. Industr. Hyg.,28, 262.

- Stott, W.T., Quast, J.F. and Watanabe, P.G.(1981). Differentiation of the mechanisms of oncogenicity of 1,4-dioxane and 1,3-hexachlorobutadiene in the rat. Toxicol. Appl. Pharmacol.,60, 287.

- Thiess, A.M., Tress, E. and Fleig, I.(1976). Arbeitsmedizinische Untersuchungsergebnisse von Dioxan-exponierten Mitarbeiter. Arbeitsmedizin-Sozialmedizin-Präventivmedizin, 11, 36.

- Torkelson, T.R., Leong, B.K.J., Kociba, R.J., Richter, W.A. and Gehring, P.J.(1974). 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicol. Appl. Pharmacol.,30, 287.

- Young, J.D., Braun, W.H. and Rampy, L.W.(1977). Pharmacokinetics of 1,4-dioxane in humans. J. Tox. Env. Health, 3, 507.

- Young, J.D., Braun, W.H. and Gehring, P.J.(1978). Dose-dependent fate of 1,4-dioxane in rats. J. Tox. Env. Health, 4, 700.

H. MEMBERS OF THE WORKING GROUP

Dr. G. Baldratti (Chairwoman)	Dept. for Occupational Health, Safety, Industrial Toxicology, MONTEDISON (Milano).
Dr. K. Beutel	Technical Center, DOW CHEMICAL EUROPE (Horgen).
Dr. R. Jaeckh	Industrial Hygiene and Toxicology Division, BASF (Ludwigshafen).