VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In 1945, Cook [106] compiled a list of maximum allowable concentrations of atmospheric industrial contaminants which included dioxane. He cited the Utah state standard for dioxane of 1,000 ppm. In addition to this value he suggested 500 ppm as an accepted and tentative value based on animal studies conducted by Fairley et al [21].

The American Conference of Governmental Industrial Hygienists (ACGIH) adopted a list of "Maximum Allowable Concentrations of Air Contaminants for 1946" [107] that included 500 ppm for dioxane as recommended by Cook [106]. The Maximum Allowable Concentration (MAC) for dioxane was reduced to 100 ppm in 1947 [108] but no explanation of the changes was given. At the 10th Annual Meeting of the American Conference of Governmental Industrial Hygienists [109], the term "Maximum Allowable Concentration" was changed to Threshold Limit Value (TLV). In 1959, Elkins [110] recommended 50 ppm as the MAC for dioxane as "tentative," based on reports from Yant et al [19], Barber [20], and De Navasquez [38] but Elkins [110] did not elaborate. At the 27th Annual Meeting of the ACGIH [111] in 1965, the term "skin" was added to the TLV to denote that dioxane can be absorbed through the skin of man, and that reliance upon the observation of a TLV of 100 ppm alone might not be sufficient to prevent toxicity.

Tables of "Permissible Levels of Toxic Substances in the Working Environment" for many countries were published by the International Labour Office (ILO) in 1970 [112]. The reported dioxane standards are presented in Table VI-1.

TABLE VI-1

LIST OF HYGIENIC STANDARDS
OF DIOXANE FROM VARIOUS COUNTRIES (1970)

	ppm	mg/cu m
Bulgaria	3	10
Finland	100	360
Germany	100	360
Poland	3	10
Rumania	15	50 (skin)
United States	100	360 (skin)
USSR	3	10
Yugoslavia	100	360

Adapted from reference 112

Table VI-1 shows that the MAC for dioxane used by Bulgaria, Poland, Rumania and the USSR is much lower than that of other countries including the US but the basis for these lower limits was not described in the ILO report.

The 1971 Documentation of Threshold Limit Values for Substances in Workroom Air which was updated by the ACGIH in 1974 [113] supported the dioxane TLV of 100 ppm as a time-weighted average based on reports of Yant et al [19], Schrenk et al [48], Fairley et al [21], De Navasquez [38], Smyth [56], Barber [20], and Johnstone [31]. The TLV of 100 ppm as established by the ACGIH was believed to be low enough to prevent systemic poisoning [113].

A tentative TLV of 50 ppm with a "skin" notation for dioxane was published by the ACGIH in a list of intended changes for 1972 [114], and 1973 [115]. The TLV of 50 ppm (180 mg/cu m) (skin) was adopted in 1974 [116].

The Swedish National Board of Occupational Safety and Health [117] gave a limit of 25 ppm (90 mg/cu m) in 1974, noting that dioxane can be absorbed through the skin and that it also has carcinogenic properties.

In the Transactions of the 36th Annual Meeting of the ACGIH [118] in 1974, the committee classified dioxane as an experimental animal carcinogen. However, the following year [119], the experimental carcinogen listing of dioxane was removed, with a note that the issue would be kept under continuing review by the TLV Committee.

The TLV for dioxane remained at 50 ppm (180 mg/cu m) (skin) in 1975 and 1976 [73,120]. In 1976, the term Short-Term Exposure Limit (STEL) was instituted. It represented the maximal concentration to which workers can be exposed for a period up to 15 minutes continuously without suffering from (1) intolerable irritation, (2) chronic or irreversible tissue change, or (3) narcosis of sufficient degree to reduce work efficiency. Not more than four excursions per day were permitted, with at least 60 minutes between exposure periods and the daily TLV-TWA also not being exceeded. The STEL value for dioxane was tentatively set the same as the TLV, ie, 50 ppm [73]. In the guidelines set by the ACGIH for experimental animal carcinogens, dioxane was excluded as a carcinogen since it exceeded the dosage limitations put forth by their committee [73]. They stated that no substance was considered by the Committee as an occupational carcinogen if given to rats at doses greater than 2,000 mg/cu m by the respiratory route, above 3,000 mg/kg by the dermal route, and above 500 mg/kg/day by the oral route for a lifetime, which is equivalent to 100 g total dose for the rat. The hepatocellular and nasal tumors observed when 1% dioxane was given to rats by Argus et al [62] and by Kociba et al [65] was equivalent to 132

g/rat or 1,015 mg/kg/day. Evidence or arguments supporting these criteria of classification of carcinogens were not presented by the ACGIH Committee.

The current federal standard for dioxane (29 CFR 1910.1000) is 100 ppm, as a TWA, which was adopted from the 1968 ACGIH recommendation [121].

Basis for the Recommended Environmental Standard

(a) Permissible Exposure Limit

Dioxane has been shown to induce tumor formation in experimental animals [43,62-67,70]. There is confirmed evidence of cancer induction in rats given large oral doses of approximately 1% dioxane in drinking water [43,62,64,65,67]. Neoplastic lesions most often described were tumors of the liver and nasal cavity. In the liver, they were described as "incipient" liver tumors, hepatomas, and hepatocellular carcinomas. In the nasal cavity, epithelial carcinomas, olfactory neuroblastomas, and seromucous adenocarcinomas (as well as rhabdomyosarcomas) were described. In two of these studies [43,65], a relationship was reported between the amount of dioxane ingested in drinking water and the incidence of tumors. In one study [65], a statistically significant increase ($P<0.05$) in hepatic tumors of all types, in hepatocellular carcinomas, and in nasal carcinomas was seen in rats given drinking water containing 1% dioxane as compared to the controls (12/66 vs 2/106, 10/66 vs 1/106, and 3/66 vs 0/106, respectively). One hepatocellular carcinoma (statistically not significant) was seen in a rat given drinking water containing 0.1% of dioxane. In the other study [43], the incidence of liver tumors was 14, 28, 53, and 82% in rats given drinking water containing 0.75, 1.0, 1.4, and 1.8% of dioxane, respectively. These tumor percentages apparently included

both "incipient" tumors and hepatomas. In another report of what appears to be the same experiment, these authors [85] reported 1, 1, 2, and 2 squamous cell carcinomas in rats given water containing 0.75, 1.0, 1.4, and 1.8% of dioxane, respectively.

In the Holmes report [67], a dose-response relationship was also apparent with 1/32 of controls, 23/57 of the 0.5% dioxane group, and 23/51 of the 1.0% dioxane group having developed squamous cell carcinomas of the nasal cavity. Two of the 0.5% dioxane group had olfactory neuroblastomas and one had a rhabdomyosarcoma. Seven of the 1% group had olfactory neuroblastomas and two had seromucous adenocarcinomas. The two seromucous adenocarcinomas, 4/4 of the neuroblastomas and 4/46 of the squamous cell carcinomas had metastasized to other sites.

A dose-response relationship also occurred among mice given dioxane in their drinking water [67]. Four of 99 examined controls, 24/94 of the 0.5% dioxane group, and 44/87 of the 1.0% dioxane group had hepatocellular carcinomas.

Two gall bladder carcinomas, three early hepatomas, nine cases of epithelial lung hyperplasia, and one adenoma of the kidney were seen in 22 guinea pigs given 0.5-2.0% dioxane in drinking water [63]. One case of epithelial hyperplasia, four of mononuclear cell accumulation in the lung, and one cartilaginous growth were seen among 10 controls.

There was inconclusive evidence of cancer induction when mice were topically treated with dioxane and of cancer promotion when the topical application was preceded by 1 week with application of DMBA [44,69,70].

As commented in Chapter III, the lack of a significant excess in numbers of tumors in several hundred rats does not give reassurance of lack

of tumor excess in 100,000 humans similarly exposed, because of discrepancies in population sizes and because of lack of evidence on relative sensitivities to tumor induction in the two species.

In the epidemiologic studies reported by Dernehl (written communication, April 1976), Thiess and coworkers [34], and Buffler and associates [35], no significant differences were seen between the observed and expected numbers of cancer deaths in the worker populations at risk.

In one study [34], two cancer deaths, a lamellar epithelial carcinoma of the left lumbar region and a myelofibrotic leukemia were reported among 12 deaths in a group of 74 workers who had been exposed to dioxane in the workroom air. Concentrations of airborne dioxane were reported to range from 0.01 to 13.28 ppm. In the second study [35], two of seven deaths that occurred among 100 exposed workers were attributed to cancer (carcinoma of the stomach and an alveolar cell carcinoma). Workroom concentrations of dioxane measured in 1968, 1973, and 1974 ranged from less than 0.01 to 16.0 ppm. The person who died from carcinoma of the stomach had also been exposed to hydrogen chloride, carbon tetrachloride, perchloroethylene, and trichloroethylene. The other worker had been exposed to vinyl chloride for about 11 years and to methylene chloride for 1.5 years. In the third study (written communication, CU Dernehl, April 1976), four cancer deaths were reported. They were attributed to cancer of the colon, lymphosarcoma, lung carcinoma, and glioblastoma. In all, 80 workers had been exposed to dioxane during the 42-year period the company had been producing dioxane. Analysis of workroom air in 1974 and again in 1975 showed dioxane to range in concentrations from 0.05 to 51 ppm.

Although no statistically significant increase was seen between the total number of observed and expected cancer deaths in the reports of Dernehl (written communication, April 1976), Thiess et al [34], or Buffler and coworkers [35], these results cannot be accepted as conclusive evidence that the reported air concentrations of dioxane represented safe worker exposure levels. The populations at risk were very small, 74, 165, and 80 workers, respectively. Therefore, the statistical tests would not have been able to detect other than major increases in cancer death rates. In addition, only general mortality rates were compared although specific types of cancer can have mortality rates of magnitude less than the total cancer mortality rate. Expected cancer deaths based on the total expected cancer mortality rate are, therefore, misleading and cannot be considered conclusive evidence that humans occupationally exposed to dioxane do not have a greater risk of cancer induction than humans not exposed to the chemical.

The pharmacokinetic study conducted by Young and Gehring [30] showed that the fate of dioxane in rats was markedly dose-dependent due to an apparent limited capacity to metabolize dioxane to HEAA. A more rapid excretion of HEAA was noted when multiple daily doses of 1,000 mg/kg dioxane were given but not with equivalent single doses or with multiple daily doses of 10 mg/kg. This indicates that, at high daily doses, dioxane induced its own metabolism. The differences in metabolism at high doses as compared with those in lower doses may have been quantitative rather than qualitative; some unchanged dioxane was excreted even at the lower doses, if dioxane at less than 1% of the total urinary metabolites is significant. In any case, it remains to be demonstrated whether tumors from dioxane are

from the unchanged chemical or from the metabolite of the chemical. It seems probable that the nasal tumors arose from local contact with unmetabolized dioxane. It may be that the liver tumors arose from unmetabolized dioxane or, conceivably, from a metabolic product, either intermediate or end product. While this is speculative, it is also speculative to interpret that complete metabolism of dioxane will prevent the development of tumors.

An additional argument to consider in the interpretation of the studies of experimental carcinogenicity also concerns the question of the occurrence of tumors in experimental animals only at high doses and not at lower doses. Tumor incidence is proportional to dose and a dose-response relationship was seen in the ingestion studies [65]. Even if dioxane is a weak carcinogen, an incidence of 1-10 cases of cancer in a population of 100,000 would not be unexpected. Such an incidence in experimental animals would probably not be detected in a population of 1,000 animals; yet, in none of the experiments reviewed here has that large a population been used in any one treatment group. If these animals were much more sensitive than man to cancer induction by dioxane, the smaller number of experimental animals might give adequate negative evidence of carcinogenicity. At present there are too few data to be sure of the relative sensitivity of the several species including man in induction of cancer by dioxane. This last statement presumes that dioxane can induce cancer in man; the statement is, of course, unproved, but seems reasonable inasmuch as it can induce cancer in some other mammalian species tested.

Dioxane has been shown to penetrate the skin of animals [21,50] and man [31] causing liver and kidney damage. Therefore, prevention of skin

contact by use of appropriate work practices is very important.

Cancer in workers is the primary health concern in the development of this recommended standard for exposure to dioxane. In addition, liver and kidney damage are potential effects. The permissible limit recommended for occupational exposures to dioxane is based on the belief that dioxane can cause tumors in exposed workers and on the belief that information allowing the derivation of a safe exposure limit is not now available. Thus, a limit that is the lowest concentration reliably measureable over a short sampling period is recommended. This limit is 1 ppm, based on 30-minute sampling at a sampling rate of 1 liter/minute. The reasons for concluding that this is the lowest measureable limit are described in Section (c), Sampling and Analysis.

(b) Medical Surveillance and Recordkeeping

Several human [20,31] and animal studies [21,38-40,43,44,46-51,63-66,69,70] demonstrated that exposure to dioxane produced systemic damage in the kidney and liver. A medical surveillance program should include preplacement and periodic medical examinations that give attention to the kidneys and liver. Appropriate examination to detect possible tumors should be performed; liver function tests are probably significant in this examination, as is examination of the upper respiratory tract, especially the nose. Because dioxane is believed capable of inducing cancer, NIOSH recommends that all medical and environmental records involving dioxane exposure be kept for 30 years after termination of employment. This is also consistent with the requirements of the Toxic Substances Control Act.

(c) Sampling and Analysis

Dioxane in air samples should be collected with activated coconut charcoal, desorbed with carbon disulfide, and analyzed by gas chromatography. The basis for this is discussed in Chapter IV, and detailed directions are provided in Appendices I and II. These methods have been chosen because of their availability and specificity.

The lower limit of the sampling and analytical methods has not been determined. The combined sampling and analytical method has been tested and found by NIOSH to be sufficiently accurate and precise for the determination of the amount of dioxane collected by sampling 10 liters of air containing 6.25 ppm. The amount of dioxane collected on the charcoal under these conditions averaged 0.20 mg when the nominal amount sampled was 0.23 mg. The desorption efficiency was determined with approximately 4 mg added to the charcoal. If the desorption efficieny had been determined at 0.20 mg/100 g of charcoal, the accuracy might have improved. It is recommended that desorption efficiency be determined with various amounts of added dioxane that are representative of the concentrations likely to exist and sampling times required by these concentrations. The method is described in Appendix II.

Although the method has not been tested by sampling atmospheres containing less than 6.25 ppm, or by collecting less than a nominal amount of 0.23 mg of dioxane, it is reasonable to expect that the method will be sufficiently accurate and precise at lower concentrations in the air with smaller amounts collected on the charcoal. For example, sampling an atmosphere containing dioxane at 1 ppm for 4 hours at 200 ml/minute would result in collection of 0.17 mg of dioxane, an amount that would likely be

measured with acceptable accuracy and precision for monitoring exposures of this magnitude. As another example, sampling an atmosphere containing 1 ppm of dioxane at 1 liter/minute for 30 minutes would result in collection of about 0.11 mg of dioxane which the data indicate could be satisfactorily measured.

As is evident from this discussion, the definitive data to allow derivation of the lowest amount of dioxane reliably detectable are not complete. The conclusions reached reflect concern about the amount of dioxane that can be retained by the charcoal in the presence of competing substances, such as water or 1,1,1-trichlorcethane. For this reason, the total amount of sample obtained at a sampling rate of 1 liter/minute is proposed to be limited to 30 liters. (While it is felt that 60 liters may tax the retention ability of the charcoal in the tube, data to prove this are not available). The resultant amount of dioxane adsorbed from air containing 1 ppm is below the amount detectable with a precision of 5-10% relative standard deviation. What the precision will be is not known, but it is believed to be about 15-20%. Better precision would obviously be preferred, but alternatives (risk of incomplete adsorption, other sampling means for which equipment has not been proved, higher permissible limit) seem less acceptable.

On this basis, a permissible exposure limit of 1 ppm based on a 30-minute sampling period at 1 liter/minute is recommended for occupational exposures to dioxane.

(d) Personal Protective Equipment and Protective Clothing

Dioxane has been shown to penetrate the skin of man [31] and animal readily [21,50,66,69,70]. Therefore, care must be exercised to ensure

adequate protection against contact with dioxane. Proper protective devices such as full face-shields, neoprene-coated gloves, boots, and bib-type aprons that cover boot tops should be used while working with dioxane to prevent contact and consequent absorption of dioxane through the skin.

(e) Informing Employees of Hazards from Dioxane Exposure

A continuing education program is an important part of a preventive hygiene program for employees occupationally exposed to hazardous materials such as dioxane. Properly trained persons should periodically apprise employees of possible sources of dioxane exposure, the adverse health effects associated with such exposure to dioxane, the engineering and work practice controls in use and being planned to limit exposure, and the environmental and medical monitoring procedures used to check on the exposure and health status of employees. Personnel occupationally exposed to dioxane must be warned and advised of the adverse effects of accidental exposure and must be informed of the signs and symptoms of dioxane exposure.

(f) Work Practices

Absorption of dioxane can be minimized by adherence to the work practices recommended in Chapter I and discussed in Chapter V. The basis for these practices is the avoidance of contact with dioxane by confinement of the material and by personal protection of the worker. Engineering controls must be used whenever needed to control concentrations of airborne dioxane within the recommended environmental limit. Wherever dioxane is present, a closed system of control should be used. During the time required to install adequate controls and equipment, to make process changes, to perform routine maintenance operations, or to make emergency

repairs, exposure to dioxane can be minimized by the use of respirators, protective equipment, and protective clothing. However, respirators should not be used as a substitute for proper engineering controls during normal operations.

Since dioxane can penetrate skin readily to cause systemic toxicity and can also cause local skin effects or eye damage, drench-type safety showers and eye wash fountains must be nearby wherever liquid splashes may occur.

VII. RESEARCH NEEDS

The only teratogenic study conducted was on chick embryos [60], and this poses problems in extrapolation to mammalian systems, as discussed earlier in Chapter III. Studies of the possible teratogenic and other reproductive effects of dioxane should be conducted in animals in order to evaluate the need for protecting female workers of childbearing age and their offspring.

There is no information available on possible mutagenic effects of dioxane. This is another area where research is needed.

The pathways of metabolic transformation, distribution, and elimination of dioxane as a function of the dose, rate, and route of administration, have not been adequately investigated in animals and in man. One important factor is to determine whether it is unchanged dioxane or any of its metabolites that induces cancer.

Those studies most indicative of dioxane as a carcinogen have involved administration of dioxane to experimental animals in drinking water. The drinking water may have been chlorinated community water, in which case chemical reactions between components of the water and dioxane are conceivable. If such reactions occur, it seems that chlorinated derivatives of dioxane would be the most likely products. One derivative, dichlorodioxane, has been suggested to be a tumorigen, albeit on the basis of development of sarcomas at the sites of injection [122]. While chlorination of dioxane or its breakdown products is not expected to be a significant factor, in part because of the low concentrations of chlorine in water supplies, the possibilities should not be overlooked. Research to

investigate such reactions and, if significant, their toxicologic consequences should be conducted.

Workers in one dioxane-manufacturing concern [35] are exposed to various other chemicals such as trichloroethylene, perchloroethylene, carbon tetrachloride, methylene chloride, and vinyl chloride. Both experimental and epidemiologic studies, involving exposure to other chemicals in conjunction with dioxane, should be conducted to determine the possible additive, synergistic, or inhibitory effects of exposure to other substances and to dioxane on workers. It is noted that there is suggestive evidence of interactive toxicity in one epidemiologic study [34].

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