Acceptable Levels of Dioxin Contamination in an Office Building Following a Transformer Fire (1988)

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Committee on Toxicology

Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council (U. S.).

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National Research Council
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PREFACE

A fire occurred in a National Aeronautics and Space Administration (NASA) office building in Washington, D.C., approximately 9 years ago. The fire involved a basement transformer that contained polychlorinated biphenyls (PCBs). Fires involving PCB-filled transformers release various highly toxic chemicals, such as dioxins (polychlorinated dibenzo-*p*-dioxins, PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenylenes (PCBPs), and related compounds; some PCBs and chlorinated benzenes might have been pyrolyzed at the time of the fire. The General Services Administration (GSA) requested analytic measurements of dioxin contamination of the building that could have resulted from such pyrolysis. More specifically, GSA wanted advice on acceptable concentrations of PCDDs in the NASA building. The most toxic PCDD congener is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD); it is also the most extensively studied. Therefore, this report emphasizes 2,3,7,8-TCDD, although such fires can yield a range of related chemicals many of which are of toxicologic concern.

NASA and GSA desire that appropriate actions be taken both to protect the health of workers and to avoid unnecessary and misinformed concern. The National Research Council organized the Subcommittee on Dioxin of the Committee on Toxicology in the Board on Environmental Studies and Toxicology, and the Subcommittee forwarded a letter report dated April 8, 1988, on a proposed sampling strategy to Mr. Wilson Gale of GSA.

The current report provides a basis for appropriate cleanup action, as needed, by GSA to reduce PCDD contamination to acceptable levels in the office building. It is not the intent of this report to review exhaustively the toxicity data on PCDDs, but rather to give sufficient information on which to base remedial action. The recommendations regarding acceptable contamination are based on laboratory and epidemiologic data, and they are offered for ambient air and deposition on surfaces.

The Subcommittee on Dioxin wishes to express its sincere gratitude to Linda Miller Poore and Bernidean Williams of the Toxicology Information Center for obtaining and verifying bibliographic references and to Erik Hobbie of the Committee on Toxicology staff for invaluable assistance in manuscript preparation.

John Doull, M.D.
Chairman
Subcommittee on Dioxin
Committee on Toxicology

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INTRODUCTION

Fires involving electric equipment that contains polychlorinated biphenyls (PCBs) can release highly toxic materials. Before a building contaminated with such materials can be reoccupied, it needs to be cleaned to a degree that meets health-related goals. Four states (New York, California, New Mexico, and Louisiana) have established cleanup guidelines after transformer fires in office buildings. The standards have usually been based on consideration of the toxicity of the highly persistent polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs)--combustion byproducts or contaminants of the PCBs in the transformers. Because 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) is the most toxic PCDD congener, as well as the most extensively studied, this report emphasizes 2,3,7,8-TCDD, as has been the practice elsewhere.

PCBs were used extensively in the United States from the late 1930s through the mid-1970s as dielectric and hydraulic fluids and in other applications (National Research Council, 1979). Production and most new uses of the PCBs were restricted by the Toxic Substances Control Act (TSCA) in 1976. However, equipment containing thousands of gallons of PCBs remains in use; its inspection, maintenance, and ultimate disposal are now strictly regulated by several provisions of TSCA. PCB-spill cleanup and disposal are also subject to regulation by states and are proposed in pending legislation to be regulated under the federal hazardous-waste statutes, as amended in 1988.

Because of their persistence and toxicity, PCDDs, PCDFs, and PCBs are of major environmental and public health concern (U.S. EPA, 1985), and a number of regulatory and other actions have been taken by federal and state agencies to reduce human exposure to them. The demonstration that they and their combustion products could be released into the environment, in toxicologically important quantities, in fires involving PCB-containing equipment was the chief basis for issuance by the Environmental Protection Agency (EPA) of the "transformer rule" under TSCA in 1985. That rule requires expedited removal of remaining PCB-containing electric equipment in public buildings, increased inspection and safety precautions to reduce the likelihood of fire, and other measures designed to reduce the hazards associated with combustion products of PCBs and chlorinated benzenes in transformers.

SOURCES OF PCBs, PCDDs, AND PCDFs

Soot from fires involving PCB-filled transformers can have much higher concentrations of PCBs, PCDDs, PCDFs, and other products than "normal" soot; combustion of many substrates might yield PCDDs and PCDFs, and that can confound determinations of the contribution of a specific fire. The materials can be dispersed in soot and vapors during fires, depending on temperature. The dispersion of both soot and vapor occurs by convective transfer and at times by mechanical transfer through an operating heating, ventilation, and air-conditioning system. If soot and vapor enter ventilation systems, they may be dispersed widely throughout a building and to the external environs. Analysis of ventilation systems constitutes an appropriate method of tracking dispersion of contaminants.

Contaminated surfaces and subsurface areas can be sources of airborne PCBs, PCDDs, and PCDFs (attached to interior dusts or volatilized), as shown in longitudinal studies in the state office building in Binghamton, New York.

PCDDs and PCDFs can be generated by combustion sources other than fires, such as internal-combustion engines burning leaded fuel with EDC scavengers, waste incinerators, and manufacturing processes that use chlorinated phenols and chlorinated benzenes, such as the production of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Most recently, PCDDs and PCDFs have been found in effluents and paper pulp produced by chlorine-dependent processes.

BACKGROUND EXPOSURE TO PCDDs

Because of their multiple sources and environmental persistence, these compounds are ubiquitous in our environment at very low concentrations, having been identified in fish, lake sediments, human adipose tissue, and milk (Kimbrough and Houk, 1987).

The rather sparse data available on the concentrations of PCDDs and PCDFs in various food products are not sufficient to allow accurate assessment of the total dietary intake by the general adult population. However, they are sufficient to permit an approximate evaluation of exposure of specific populations by this route, although general estimates have been made (Travis and Hattemer-Frey, 1987; Davies, 1988; Rappe et al., 1987). Food is generally the major source of exposure. In general, exposure via inhalation of air and dusts is probably lower than that through food, and exposure through drinking water is negligible, compared with dietary and inhalation exposure. In some cases, especially in occupational exposure, skin absorption from contaminated surfaces and tools might play an important role (WHO, 1988). The daily intake of 2,3,7,8-TCDD toxic equivalents by a normal consumer is estimated at approximately 1.2 pg/kg bw/d (WHO, 1988). A discussion of toxic equivalents or toxicity equivalence factors (TEFs) is presented later in the report.

CHEMISTRY AND MECHANISM OF ACTION

2,3,7,8-TCDD is considered to be the most toxic of the 75 possible PCDD congeners. Removal or addition of chlorine atoms tends to diminish toxicity of the chemical by altering rates of metabolism and affinity for molecular target sites (Poland et al., 1983; Birnbaum et al., 1987). Halogenation can occur on any or all of the eight available ring positions, and the resulting congeners differ in their physical, chemical, biologic, and toxic properties. The most toxic PCDF congeners are believed to be the pentachlorinated dibenzofurans (Birnbaum et al., 1987; Brewster et al., 1988). The most toxic PCB isomers are those that are approximate stereoisomers of TCDD and are substituted at four to six of the lateral positions (Safe, 1984).

Of the 210 isomers and congeners that make up the chemical classes PCDDs and PCDFs, 2,3,7,8-TCDD has been by far the most extensively studied in experimental animals. The effects of the closely related 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin have been studied in several species and by various routes of administration. Only a few other isomers have been studied.

The available evidence indicates that the biologic effects of the most toxic PCDDs and PCDFs are qualitatively similar (Poland and Knutson, 1982; Neal, 1985; Safe, 1986). Indeed, PCBs, PCDDs, and PCDFs elicit a number of common toxic and biologic responses in various animal species including chloracne and dermal toxicity, thymic atrophy, immunotoxicity, neurotoxicity, teratogenic or developmental toxicity, porphyria, tumor promotion, body-weight loss, and induction of cytochrome P_1-450-dependent monooxygenases (Safe, 1987; UAREP, 1988). The effects of mixtures of the compounds at submaximal doses appear to be additive (Safe, 1987).

Many aspects of toxicity appear to be related to the ability of an isomer to bind to a specific receptor protein, the Ah receptor (Poland et al., 1976). The binding of the Ah receptor with an appropriate ligand and its translocation to the nucleus induces the expression of several genes (Okey et al., 1983; Whitlock, 1987). The pleiotropic response (induction of a variety of unrelated multiple effects) that ensues includes the induction of cytochrome P_1-450-associated monooxygenases (e.g., aryl hydrocarbon hydroxylase, AHH) and, in specific cells and tissues of sensitive species, both differentiative and proliferative toxic responses (Poland et al., 1983).

The expression of toxicity of 2,3,7,8-TCDD and related compounds--including liver damage, body-weight loss, thymic involution, cleft palate, and chloracne--has been correlated with their binding affinity for the Ah receptor, which parallels their ability to induce several enzymes and

affect other cell receptors, some of which have been linked to the expression of carcinogenicity in several mouse strains (Poland and Knutson, 1982; Bandiera et al., 1984; Madhukar et al., 1984; Poland et al., 1985; Vickers et al., 1985). However, the mechanisms of TCDD toxicity are not completely understood. Cytosolic receptor binding alone might not be the sole determinant of all toxic manifestations (Neal, 1985; Okey and Vella, 1984; Pohjanvirta et al., 1988; Grieg et al., 1984). Interspecies comparisons have shown less than complete correlations between the concentration of intracellular Ah receptor, its ability to bind 2,3,7,8-TCDD, and toxicity (Denison and Wilkinson, 1985; Gasiewicz and Rucci, 1984; Neal, 1985); in the mouse, the development of TCDD-induced liver toxicity cannot be ascribed solely to the presence of the Ah receptor (Greig et al., 1984).

EFFECTS ON ANIMALS

The biologic effects reported in animals exposed to 2,3,7,8-TCDD include lethality, wasting syndrome, carcinogenicity, reproductive and teratogenic effects, immunotoxicity, hepatotoxicity, and enzyme induction. There are striking species differences in the acute lethality of 2,3,7,8-TCDD; e.g., the LD_{50} for the guinea pig is 2 μg/kg and that for the hamster is over 3,000 μg/kg (McConnell et al., 1978). Different strains of mice vary widely in susceptibility to some effects of 2,3,7,8-TCDD. Humans do not appear to be as sensitive and might be less sensitive to some of the toxic effects of TCDD than, for instance, the guinea pig or the subhuman primate (Ayres et al., 1985; Kimbrough, 1988).

Genotoxicity

One step in tumor formation is thought to be an irreversible alteration of the DNA of a cell. Cancer cells are clonal, so it is assumed that a single heritable alteration of a cell can lead to tumor formation. That is the basis of the no-threshold models of carcinogenesis. 2,3,7,8-TCDD has been tested in nearly all available genetic test systems. Wahba et al. (1988) showed clastogenic effects (strand breakage) in rats exposed to 2,3,7,8-TCDD. However, many studies have found no significant genetic or cytogenetic effects (reviewed in IARC, 1982; Kociba, 1984; Brooks et al., 1988; UAREP, 1988; WHO, 1988; Kimbrough and Houk, 1987). Although there is no evidence of direct mutagenic interaction of 2,3,7,8-TCDD with DNA, there is considerable evidence of activity of this chemical at the gene level. 2,3,7,8-TCDD enhances transcription of several genes by binding (in its receptor complex) to specific promoter genes (Whitlock, 1987). Observed clastogenesis might be due to indirect effects. Thus, 2,3,7,8-TCDD is currently viewed as having little or no capability for structurally damaging the genetic material of cells, although it clearly alters the expression of several genes, including proto-oncogenes.

Carcinogenicity

Male and female Sprague-Dawley rats were maintained for 2 yr on diets supplying 2,3,7,8-TCDD at 0.1, 0.01, and 0.001 μg/kg per day (Kociba et al., 1978). Two-year ingestion at 0.001 μg/kg per day produced no toxicologically significant effects. Ingestion at the intermediate dosage of 0.01 μg/kg per day produced moderate toxicity. The main effects observed were increased urinary excretion of porphyrins (in females), liver toxicity (including increased incidence of hepatocellular nodules), and increased incidence of focal alveolar hyperplasia in the lungs. Continuous ingestion of 2,3,7,8-TCDD at 0.1 μg/kg per day for 2 yr produced many toxic effects, including increased mortality, decreased body-weight gain, increased urinary excretion of porphyrins, increased serum gamma-glutamyl transferase (GGT) and serum glutamic-pyruvic transaminase (SGPT), structural changes (primarily of the hepatic, lymphoid, respiratory, and vascular tissues), and increased incidences of hepatocellular carcinomas of the liver (in females) and squamous cell carcinomas of the lung, hard palate, nasal turbinates, and tongue (Kociba et al., 1978). The incidence of sex-hormone-dependent tumors, such as tumors of the breast, was reduced, perhaps because 2,3,7,8-TCDD interferes with estradiol binding sites (Romkes et al., 1987; Romkes and Safe, 1988).

The National Toxicology Program conducted a carcinogenesis bioassay of 2,3,7,8-TCDD in Osborne-Mendel rats and B6C3F1 mice (NTP, 1982a). Fifty rats and 50 mice of each sex were given 2,3,7,8-TCDD suspended in a vehicle of corn oil and acetone (at 9:1) 2 d/wk for 104 wk at 0.01, 0.05, and 0.5 μg/kg per week (rats and male mice) or 0.04, 0.2, and 2.0 μg/kg per week (female mice). 2,3,7,8-TCDD was carcinogenic in mice, inducing hepatocellular carcinomas in males and females and follicular-cell thyroid adenomas in females. In male rats, a statistically significant increase in the incidence of hepatocellular carcinomas in the high-dose group was observed (NTP, 1982a). 2,3,7,8-TCDD has also been tested in short-term tumor models as an initiator (DiGiovanni et al., 1977; Cohen et al., 1979; Kouri et al., 1978); the results have been mixed, with 2,3,7,8-TCDD varying from a very weak initiator to an inhibitor of some types of initiation.

The application of 0.005 μg of 2,3,7,8-TCDD 3 d/wk for 99-104 wk to the skin of female Swiss-Webster mice increased the incidence of fibrosarcomas, compared with that in untreated controls (NTP, 1982b). Hexachlorodibenzo-*p*-dioxins have also been found to be carcinogenic in rats. In the Syrian hamster, 2,3,7,8-TCDD was found to be extremely potent as a carcinogen, producing squamous cell carcinomas after subcutaneous or intraperitoneal injection (Rao et al., 1988). That study is of interest in demonstrating that 2,3,7,8-TCDD is a complete carcinogen in a species that is relatively resistant to acute lethality.

Tumor Promotion

There is in vivo evidence that 2,3,7,8-TCDD and 2,3,7,8-TCDF are potent tumor promoters in skin (Poland et al., 1982) and in liver (Pitot et al., 1980) and in vitro evidence that it promotes the malignant transformation of C3H/10T½ mouse cells (Abernethy et al., 1985). Recently, 2,3,4,7,8-pentachlorodibenzofuran and 1,2,3,4,7,8-hexachlorodibenzofuran have been shown to be tumor promoters in rats (Nishizumi and Masuda, 1986). The mechanisms of tumor promotion by these chemicals are not clear, but might involve changes in EGF receptors (Hudson et al., 1986) and altered expression of oncogenes and tumor-promoter genes (Evans, 1988).

Teratogenicity

Courtney and Moore (1971) showed that 2,3,7,8-TCDD, when administered subcutaneously at 3 μg/kg on days 6-15 of gestation, was teratogenic to various strains of mice. It induced cleft palates and kidney malformations. However, no teratogenic effects were observed in CD rats. Cleft palate has not been observed in rats and rabbits. Hydronephrosis is a more sensitive indicator of PCDD exposure in mice than is cleft palate. Studies of 2,4,5-T and 2,3,7,8-TCDD have failed to demonstrate male reproductive toxicity or adverse effects on the offspring of males exposed at doses that are not lethal to test animals (Lamb and Moore, 1984).

Immunotoxic Effects

Immunosuppression is a widely recognized toxic effect after exposure of animals to PCDDs, PCDFs, or PCBs; the potency of various isomers to produce immunotoxicity is directly correlated with their affinity for the Ah receptor (Vecchi et al., 1983; Silkworth and Grabstein, 1982; Kerkvliet et al., 1985b).

Lymphoid tissue depletion of the thymus, bone marrow, lymph nodes, and spleen is produced by these chemicals over a wide range of doses in various species. However, functional immunosuppression occurs at doses lower than those required for cellular depletion of any lymphoid organ, including the thymus (Silkworth and Antrim, 1985; Tucker et al., 1986; Kerkvliet and Brauner, 1987).

Prenatal exposure to 2,3,7,8-TCDD is preferentially suppressive for the T-cell-mediated component of the immune response (Vos and Moore, 1974; Faith and Moore, 1977). In contrast, with the exception of one report (Clark et al., 1981), the antibody-mediated immune response appears to be most affected when mature animals are exposed to PCDDs (Vecchi et al., 1980; Kerkvliet et al.,

1985a; Tucker et al., 1986). Suppression of the antibody response might result from PCDD effects on both T cells (Kerkvliet and Brauner, 1987) and B cells (Tucker et al., 1986). Mitogen-induced blastogenic responses of lymphocytes from adult animals are not altered at doses of 2,3,7,8-TCDD that significantly suppress antibody production (Vecchi et al., 1980; Tucker et al., 1986). Recent results also suggest that changes in lymphocyte subset distributions are not evident in adult mice treated with a known immunotoxic dose of 2,3,7,8-TCDD (Brauner and Kerkvliet, 1988). These negative findings in animal studies suggest that lymphocyte phenotyping and mitogen-induced blastogenesis may be inappropriate assays to detect potential immunotoxicity in humans exposed to PCDDs.

EFFECTS ON HUMANS

Published medical reports have described chloracne, immune dysfunction, asthenia, neurotoxicity, and hepatotoxicity in humans exposed to PCDDs and PCDFs. Inadequate exposure assessment and small sample size diminish the value of many of the studies. Many have studied possible carcinogenic effects of PCDDs in humans; their results are discussed later in this report.

Dermal Effects

Chloracne is a well-known human effect of exposure to PCDDs, PCDFs, and related halogenated aromatic compounds. The evidence that chloracne can be induced by relatively high-dose exposure to PCDDs and PCDFs is convincing. Chloracne has been reported in association with chronic workplace exposure, with industrial accidents involving the release of 2,3,7,8-TCDD, with general population exposure after the industrial accident in Seveso, Italy, and with PCDF and PCB exposure in the Yusho and Yu-Cheng episodes involving contaminated rice oil (Caramaschi et al., 1981; Reggiani, 1983; Suskind, 1985; Dunagin, 1984). The association between chloracne and exposure to PCDDs and PCDFs is strong: chloracne has been consistently observed soon after heavy human exposure and in some industrial accidents involving the release of 2,3,7,8-TCDD; the heavier the exposure, the more severe the chloracne; there is a positive dose-response relation; the occurrence of chloracne is consistent from study to study; and it is biologically plausible on the basis of animal experimentation (UAREP, 1988).

Porphyrinopathy

TCDD and several other halogenated hydrocarbons affect the biochemical pathway of heme synthesis (Silbergeld and Fowler, 1987). In some cases, this biochemical alteration has been diagnosed as consistent with the clinical disease porphyria cutanea tarda (PCT), an acquired disorder of heme synthesis characterized by significant alterations in the pattern of urinary porphyrins and enzyme alterations. Accompanying clinical signs can include skin discoloration, increased fragility of the skin, and hepatotoxicity. The association between chemical-induced porphyrinopathy and PCT might be too simple, and improved genetic and biochemical criteria for diagnosis suggest that "toxic porphyria" or "porphyrinopathy" could be a more appropriate category. Doss et al. (1984) reported that 13 of 60 human subjects from an area contaminated by 2,3,7,8-TCDD in Seveso, Italy, had abnormal urinary porphyrin excretion patterns a year after exposure. However, studies of several other populations that were exposed to 2,3,7,8-TCDD, including the Ranch Hand cohort (Lathrop et al., 1984) and a cohort in Missouri (Webb et al., 1984), showed no abnormality of urinary porphyrin excretion.

Several studies of workers who were accidentally exposed to complex mixtures containing 2,3,7,8-TCDD in Czechoslovakia (Jirasek et al., 1973, 1974), New Jersey (Bleiberg et al., 1964), and Nitro, West Virginia (Suskind, 1983) reported PCT in some of the workers. Hobson (1984) reviewed those studies and concluded that PCT observed in the workers was attributable to exposure to hexachlorobenzene. PCT has not been a finding in studies of other human populations that were

exposed to 2,3,7,8-TCDD in the absence of hexachlorobenzene and trichlorophenol (UAREP, 1988). Altered heme synthesis is more consistently found in exposed persons (Rogan et al., 1988).

Changes in Blood Lipids and Liver Function Tests

Abnormalities in blood lipids and liver function tests have been observed in several studies of TCDD-exposed workers. Differences in serum cholesterol and triglyceride concentrations in workers with and without chloracne have been reported (reviewed in UAREP, 1988). Moses et al. (1984), in a study of 206 workers employed in an American trichlorophenol plant, found triglycerides in workers with chloracne to be 16% higher than in workers without chloracne; the serum gamma-glutamyl transferase concentrations were 50% higher in those with chloracne and serum glutamic-oxaloacetic transaminase concentrations were 15% higher in those with chloracne than in those without chloracne. Suskind and Hertzberg (1984), in a separate study of a large number of workers from the same plant, reported no difference in either total cholesterol or triglycerides between exposed and nonexposed workers.

Neurotoxicity

Filippini et al. (1981), in a study of 470 people exposed to 2,3,7,8-TCDD, noted that the prevalence of peripheral neuropathy was approximately 3 times higher among 55 subjects with chloracne or abnormal serum hepatic enzyme levels than among subjects without. Pazderova-Vejlupkova et al. (1981) reported polyneuropathy of the lower extremities after industrial exposure to 2,3,7,8-TCDD in Czechoslovakia. Moses et al. (1984) studied the health status of 226 workers who had been exposed to 2,3,7,8-TCDD from the manufacturing of 2,4,5-T. Chloracne was found in 52% of the workers. Neurologic examination showed a statistically significant higher prevalence of abnormal sensory findings in workers with chloracne. Ninety-four subjects volunteered for more extensive neurologic evaluation; the examination showed decreased sensation to pinprick in 11 of the 60 subjects with current or past chloracne and in none of the 34 subjects who never had chloracne.

Klawans (1987) studied 47 railroad workers who were exposed to polychlorinated phenols containing 2,3,7,8-TCDD. The initial neurologic complaints included a sense of fatigue and muscle ache. Later examination of these workers showed that about 50% had dystonic writer's cramp or other action dystonia of the hands; about 80% of the workers also manifested tremor; and nearly all were found to have peripheral neuropathies. However, some other studies have found minimal or no neurotoxicologic effects in 2,3,7,8-TCDD-exposed subjects (Suskind, 1985; Hoffman et al., 1986).

Immune System Effects

Few studies have been conducted to determine the immune status of humans exposed to 2,3,7,8-TCDD. Reggiani (1978) reported studies on the immune status of 44 children residing in the 2,3,7,8-TCDD-contaminated area of Seveso, Italy; 20 of them had chloracne. No abnormalities were found in serum immunoglobulin concentrations, concentrations of circulating complement, and lymphoproliferative responses to T- and B-cell mitogens. However, those indicators of immune function are resistant to modulation by 2,3,7,8-TCDD, even in rodents that are sensitive to 2,3,7,8-TCDD immunotoxicity. Thus, the importance of appropriate selection of tests in human immunotoxicity assessment must be emphasized.

Recently, Hoffman et al. (1986) reported that residents of Quail Run, Missouri--a population possibly exposed to 2,3,7,8-TCDD via contaminated soil--had a higher frequency of anergy and relative anergy in skin tests for delayed hypersensitivity than did a control group. However, those results have been questioned by some on the grounds that discrepancies between the two groups resulted in the exclusion of half the data and that anergy was not uniformly present in the same people in followup studies conducted 6 mo later. A recent re-evaluation of this population failed to find effects (Evans et al., 1988). Other indicators of immunocompetence that were not significantly altered were T-cell subset phenotyping, in vitro lymphoproliferative response to mitogens or tetanus

toxoid, and T-cell cytotoxicity generated in mixed-lymphocyte culture. Exposure of people at Quail Run was not confirmed by analysis of 2,3,7,8-TCDD residue in tissues.

Reproductive Studies

A few studies of miscarriages and birth defects have considered male-mediated effects by examining pregnancy outcomes among the wives of exposed men (reviewed in Silbergeld and Mattison, 1987). The studies of Vietnam-era veterans had uncertain exposure data and considerable time lapse between last exposure and conception. One study found no excess birth defects among the offspring of the veterans (Donovan et al., 1983). In two studies, excesses of some birth defects were noted--neural tube defects and cleft lip (Erickson et al., 1984; Lathrop et al., 1984). Those excesses might have been associated with probable Agent Orange exposure or might have been chance findings that resulted because many statistical tests were performed. The reproductive studies among the wives of occupationally exposed men showed no excess of adverse reproductive outcomes (Smith et al., 1982; Townsend et al., 1982). Those studies had the potential for simultaneous occurrence of exposure and conception. However, the power of the studies was low, and exposure assessments were inadequate.

In assessing human health effects of PCDDs, one must not only look at contamination with PCDDs, but consider known poisonings with several other related chemicals. For example, two rice-oil contamination incidents in Japan and Taiwan--in Yushu and Yu-Cheng--resulted in exposure of several thousand people to PCDFs and PCBs. Those people and their offspring have been and are being thoroughly studied.

In 1979, a mass poisoning occurred in Taiwan from cooking oil contaminated with thermally degraded PCBs that were contaminated by PCDFs (Rogan et al., 1988). Those chemicals persist in human tissue, so children born to poisoned women after the outbreak were exposed in utero. In 1985, 117 children born to affected women and 108 children born to nonexposed controls were examined and evaluated. The exposed children were shorter and weighed less than controls; and they had abnormalities of gingiva, skin, nails, teeth, and lungs more frequently than did controls. The syndrome is one of very few documented to result from transplacental exposure to pollutant chemicals (Rogan et al., 1988).

Carcinogenicity Studies

Fingerhut et al. (1987), Universities Associated for Research and Education in Pathology (UAREP) (1988), and Kimbrough and Houk (1987) have reviewed human exposures to PCDDs, and in particular TCDDs, and their relationship to human neoplasia. Exposed populations have included production workers, herbicide sprayers, persons exposed to Agent Orange, residents of Times Beach, Missouri, and Seveso, Italy, and workers involved in the manufacture of phenoxy herbicides in Nitro, West Virginia.

Cohort Studies

Several cohort studies have been conducted of chemical workers and herbicide sprayers. In general, the studies have not demonstrated a definitive relationship between mortality from any malignant or nonmalignant condition and exposure to PCDD-contaminated chlorophenols or phenoxy herbicides. However, all the studies were of low statistical power, because of the small numbers of persons followed. A statistically significant increase in mortality from stomach cancer was observed in German workers exposed to trichlorophenol (Thiess et al., 1982). Male Danish workers exposed to phenoxy herbicides showed a statistically significant excess of lung cancer (Lynge, 1985). Interpretation of those results is severely hampered by the limited exposure assessment.

Ott et al. (1987) studied the mortality experience of 2,192 workers employed at the Dow Chemical Company who produced or formulated higher chlorinated phenols or derivative products. As a result of their employment, they shared the potential for exposure to PCDDs. The results of the

study showed no excess of total malignant neoplasms or specific malignancies of particular interest--stomach cancer, liver cancer, connective-tissue and other soft-tissue cancer, lymphomas, or nasal and nasopharyngeal cancer.

Zack and Suskind (1980) studied 121 workers who developed chloracne after exposure to 2,3,7,8-TCDD in an accident at the Monsanto Company plant in Nitro, West Virginia. No excess in total mortality or in deaths from malignant neoplasms was observed in the employees, who were followed over a period of nearly 30 yr.

Stomach-cancer mortality was significantly increased in one small Swedish study of railroad workers who were exposed to various herbicides, mainly amitrol and phenoxy acids (Axelson et al., 1980). No specific malignancies were found in excess in two other studies (Hogstedt and Westerlung, 1980; Riihimaki et al., 1982). All had low statistical power and limited exposure assessment. The researchers had insufficient information about the types of phenoxy herbicides to which the workers were exposed and little information about the intensity and duration of the exposures. It was not known whether the phenoxy herbicides contained 2,3,7,8-TCDD. Corroborating results from other studies and additional observations obtained through further followup of the cohorts might reduce the ambiguity of the results.

A recent report of Albanese (1988) has shown increases in systemic and skin cancers in Ranch Hand personnel (the personnel involved in herbicide spraying during the Vietnam War), who served in Vietnam during 1962-1971, when Agent Orange spraying operations were active. Of 1,045 Ranch Hands, 4.59% had skin or systemic cancers. The relative risk for skin cancer was calculated to be 2.59 ($P < 0.01$). The relative risk for systemic cancers was calculated to be 1.2, and this risk has a probability of 0.67 of occurring by chance. In a recent report, a significant excess of liver cancers was found in the Yusho cohort of persons exposed to PCDFs in contaminated cooking oil (Kuratsune et al., 1987).

Case-Control Studies

Several case-control studies were conducted to assess the possible association between exposure to phenoxy herbicides and chlorophenols and the occurrence of nasal cancer, colon cancer, and lymphoma. No statistically significant association was found between such exposure and colon cancer (Hardell, 1981), although an association was found with lymphoma (Hardell et al., 1981). Nasal cancer was found to be associated with exposure to phenoxy herbicides and chlorophenols in one Swedish study (Hardell et al., 1982) and not to be associated in a Danish study (Olsen and Jensen, 1984). Those differences could be related to differences in the populations used for controls. The Swedish controls were selected from the general population and the Danish controls from among other cancer patients. Some critics have suggested that, as a group, cancer patients have heightened recall of exposures; that would increase the likelihood of a positive finding, compared with controls, who lack similar heightened recall.

Several case-control studies have also assessed the plausibility of the association between exposure to phenoxy herbicides and chlorophenols and soft-tissue sarcoma (STS). Two case-control studies conducted in Sweden, which selected controls from the general population, concluded that exposure to the herbicides or to chlorophenols resulted in a greater than 5-fold excess in STS (Hardell and Sandstrom, 1979; Eriksson et al., 1981). A New Zealand study found no association between STS and potential exposure to phenoxy herbicides (Smith et al., 1984); the study drew controls from other cancer patients in the National Cancer Registry of New Zealand. However, in the New Zealand study, a 5-fold excess of STS was noted in persons who handled animal pelts, which are sometimes preserved with trichlorophenol that contains 2,3,7,8-TCDD.

Because of possible exposure to Agent Orange during tours of duty in Southeast Asia, Vietnam War veterans have been concerned that they have increased risk of developing STS and other cancers. Agent Orange was composed of equal parts of esters of 2,4,5-T and 2,4-D and had 2,3,7,8-TCDD contamination as high as 80 ppm. A study of STS cases reported to the New York State Cancer Registry, with controls selected from New York driver's-license registration files, found no association between STS and a history of Vietnam service or reported exposure to Agent Orange (Greenwald et al., 1984). The major limitation of the study was the demonstration of exposure to Agent Orange. Kang et al. (1987), in a case-control study, studied the incidence of STS in Vietnam

War veterans. They found that the veterans in general did not have an increased risk of STS, compared with men who had never been in Vietnam. The veterans who had higher estimated opportunities for Agent Orange exposure seemed to be at greater risk of STS when their counterparts in Vietnam were taken as a reference group, but this risk was not statistically significant. Therefore, the meaning of these findings is unclear.

Studies of Soft-Tissue Sarcoma from National Census Data

Four studies with different epidemiologic designs have used existing computerized population data to evaluate STS. This type of study based on administrative records is valuable for generating hypotheses but generally provides weak evidence for confirming hypotheses, because individual exposure information cannot be obtained. Three of the studies used broad occupational categories, such as "farmer" and "forester," and assumed that entire groups were more likely to have been exposed to phenoxy herbicides. Milham (1982) examined STS deaths as recorded on death certificates in the state of Washington, and Balarajan and Acheson (1984) used occupations recorded on cancer registrations in the National Cancer Register of England and Wales. Each found excess STS among farmers. Wiklund and Holm (1986) matched Swedish census data on occupation to cancers reported in the cancer registry and found no excess of STS in six categories of agricultural and forestry workers. Kogan (1985) studied causes of death listed on death certificates of veterans who died in Massachusetts between 1972 and 1983 and found that the proportion of deaths due to STS or kidney cancer was significantly higher among veterans who served in Vietnam than among veterans who served elsewhere.

In summary, studies of STS have not been consistent in showing association with PCDD exposure. All the studies had limitations in statistical power or exposure assessment. No definitive evidence yet shows whether STS, lymphoma, and stomach and nasal cancers are associated with exposure to phenoxy herbicides or chlorophenols. The occurrence of STS in several studies warrants further investigation. The subcommittee recommends that a panel of toxicologists, pathologists, statisticians, and epidemiologists be assembled to address the overall significance of the association of STS and exposure to phenoxy herbicides or chlorophenols.

SUMMARY OF EFFECTS OF PCDDs IN HUMANS AND ANIMALS

In humans, short-term exposures to high concentrations of PCDDs (especially 2,3,7,8-TCDD) are associated with chloracne. Various other effects in humans--such as altered heme synthesis, changes in liver function tests, peripheral neuropathy, and changes in serum lipid concentrations--are less well established. The adverse effects of 2,3,7,8-TCDD on the human immune system are unknown. Some of the acute symptoms and signs disappear when exposure ceases. Chloracne is probably the most persistent lesion of high-dose exposure.

Studies concerning reproductive effects have not shown adverse effects among progeny of men who were occupationally exposed to PCDDs. The results of human cancer studies of exposure to PCDDs are inconsistent, but in general the studies are of low power and inconclusive exposure assessment. Some studies showed increased incidence of STS, others did not. Studies of industrial workers who were exposed to higher concentrations of PCDDs have not shown a consistent pattern of increased risk of cancer. The overall evidence from human studies does not indicate a greatly increased risk of cancer in association with the exposures experienced.

Studies in animals have shown increased risk of cancer, adverse reproductive effects, and alterations in immune function. Acute effects include body-weight loss, thymic atrophy, neurotoxicity, and liver effects. These results have been demonstrated in a wide range of animal studies, but none has been found convincingly to occur in humans in association with exposure to PCDDs.

RISK ASSESSMENT

Four risk assessments conducted to set re-entry guidelines for office buildings after transformer fires that caused PCDD contamination are reviewed here: that by the New York State Department of Health for the Binghamton State Office Building (Kim and Hawley, 1985), that by the California Department of Health Services for One Market Plaza (Gravitz et al., 1983), that by the New Mexico Expert Advisory Panel for the New Mexico State Highway Department Office Building (Melius, 1985), and that by the International Technology Corporation for the Louisiana State University Medical Center (Marshall, 1988). The risk assessments are summarized in Tables 1 and 2, which include the Committee on Toxicology's recommended exposure limits, ranges of estimated lifetime carcinogenic risks in humans, and the data sources and assumptions on which the assessments were based.

The guidelines in Table 1 for allowable exposures refer to 2,3,7,8-TCDD equivalents, as defined by toxicity equivalence factors (TEFs). The 2,3,7,8-TCDD congener has been studied more exhaustively by scientists than the other congeners in this group. In fact, there is almost no information on the adverse effects of some of the other congeners in humans or other species. With the exception of 2,3,7,8-TCDD and 2,3,7,8-TCDF, the TEFs are not based on results of major animal (reproductive and carcinogenic) studies. Generally, TEFs are based on estimates of relative toxicity in in vitro tests whose relationship to the chronic effects or concerns is largely presumptive. With this method, a potency factor was assigned to the individual chemicals relative to the potency of 2,3,7,8-TCDD. It was then assumed that, if animals or humans were to be exposed to a mixture of chemicals that had been assigned these potency factors, the toxicity of the mixture would be additive and would yield a potency number or TEF (U.S. EPA, 1987). Others, such as the New York State Department of Health (Kim and Hawley, 1985), have also used this approach. The fraction of toxicity that is assigned to different isomers varies with different approaches. The final number that is calculated is then equated to an equivalent amount of 2,3,7,8-TCDD. Since it is known what the effects of 2,3,7,8-TCDD are in animals at that dose or how that dose fits into the risk calculations that have been made for cancer for the 2,3,7,8-TCDD isomer, so a risk associated with the mixture can be predicted (WHO, 1988).

EPA's Risk Assessment Forum (U.S. EPA, 1987) concluded that there is a sufficiently plausible basis for a TEF approach to estimating risks associated with exposures to TCDDs and TCDFs and recommended that EPA adopt the approach on an interim basis. The general approach to estimating risks associated with TCDDs and TCDFs has also been used by other regulatory groups.

New York Risk Assessment

The recommended allowable intake of PCDDs for office workers on workdays is 2 pg/kg per day (Kim and Hawley, 1985), whether exposure is from contaminated air, contaminated surfaces, or a combination of the two (Table 1). The guideline corresponds to using an uncertainty factor of 500 below a no-observed-effect level (NOEL) for reproductive toxicity of 1 ng/kg per day in rats (Kociba et al., 1978; Murray et al., 1979) and a calculated range of lifetime cancer risks of 9×10^{-8} to 2×10^{-4}. The guideline was chosen after review of the risks of reproductive effects and carcinogenesis. The cancer risks were derived from various analyses of the Kociba et al. (1978) data and the 1982 National Toxicology Program (NTP, 1982a) bioassay data, assuming either that the TCDD concentrations remained constant or decayed exponentially with the half-life indicated in Table 2. The assumptions made in translating 2 pg/kg per day into equivalent air contamination or surface contamination (10 pg/m^3 or 25 ng/m^2, respectively) are also given in Table 2. Although an allowance for decay of TCDD over time was considered, the recommended air and surface re-entry guidelines were based on constant contamination. The associated range of lifetime carcinogenic risks does, however, reflect the possibility of decay.

TABLE 1

Summary of Recommended Re-entry Exposure Guidelines for Office Buildings Contaminated with PCDDs or PCDFs as a Result of Transformer Fires

Source	Recommended Concentrations[a] Air	Surface	Basis for Recommendation	Reported Lifetime Cancer Risk Estimates[b]
New York	10 pg/m^3	25 ng/m^2	c	9×10^{-8} to 2×10^{-4}
California	10 pg/m^3	3 ng/m^2	d	1×10^{-6} to 5×10^{-5}
New Mexico	2 pg/m^3	1 ng/m^2	e	$<1 \times 10^{-6}$
Louisiana	1.5 pg/m^3	25 ng/m^2	f	None reported
COT	10 pg/m^3	25 ng/m^2	g	$< 2 \times 10^{-4}$

[a] Expressed in TCDD-equivalent units.

[b] Risks correspond to contamination from single source--either air or surface. Risks and exposures for simultaneous exposure are additive. For example, risks reported by New York apply for exposure to 10 pg/m^3 of air only, 25 ng/m^2 of surface only, or 5 pg/m^3 of air plus 12.5 ng/m^2 of surface. Simultaneous exposure at 10 pg/m^3 of air and 25 ng/m^2 of surface implies risks twice as large as given values.

[c] Exposures based on intake of 2 pg/kg per day on workdays (0.59 pg/kg per day daily for life), corresponding to uncertainty factor of 500 below NOEL of 1 ng/kg per day in Sprague-Dawley rats. No carcinogenicity or other toxicity observed (Kociba et al., 1978; Murray et al., 1979). Various data sets used for cancer risk estimates. Two scenarios: with and without decay.

[d] Lifetime cancer risk about 10^{-6} according to plausible assumptions, based on hepatocellular carcinomas in male B6C3F1 mice observed in gavage study at 2 doses/wk (NTP, 1982a). Both "plausible" and "worst-case" computations. Single data set for risk estimates.

[e] Lifetime cancer risk below 10^{-6} for person spending rest of working life in building. Potency of TCDD isomers determined with TEFs.

[f] TCDD equivalents extrapolated from PCB guidelines with use of smallest observed ratio of PCBs to TCDD equivalents as in worst case scenario. Represents exposure to maximum of 26 pg/d, compared with recommended allowable daily intake of 650 pg/d. Recommended allowable intake was based on safety factor of 100 below experimental NOEL for reproductive effects in rats (Murray et al., 1979). Dissipation/decay with 5-yr half-life assumed.

[g] Based on all risk assessments, with primary reference to New York. For comparison, EPA CAG risk assessment gives upper limit risk of 9.2×10^{-5} for 2 pg/kg per day on workdays--allowable daily intake from which exposure guidelines have been derived.

TABLE 2

Assumptions Underlying Some Risk Assessments Summarized in Table 1

Factor or Component	New York	California	Louisiana
Average human body weight, kg	50	65, 70	65
Human surface area, m^2	1.46	1.46	1.75
Average human lifetime, yr	70	70	--
Arms as % of total surface area	19	20	--
% of arms exposed	10-50	50	--
Hands as % of total surface area	4.5	5	4.5
% of hands exposed	--	--	50
Respiratory volume (8-h workday), m^3	10	7	10
% contaminant inhaled	--	--	100
% inhaled contaminant absorbed	100	100	50
% contaminant transferred to hands or arms after surface contact	100	--	100
% contaminant absorbed through hands or arms	1-10	10	1
% ingested from hands	5-25	10	10
% ingested contaminant absorbed	--	--	10
Daily exposure time, h	8	8	8
Yearly exposure time, d	250	241, 250	240
Average working lifetime, yr	30	20, 40	40
Dissipation half-life, yr	∞, 4.5	∞, 5	5
Potency of TCDD isomers	TEFs	Equal potency	TEFs
Basis of interspecies scaling	Body weight	Surface area	Body weight

California Risk Assessment

The recommended guidelines for allowable exposures of office workers are 10 pg/m^3 and 3 ng/m^2 for air and surface contamination, respectively. The basis for the guidelines is reportedly a lifetime cancer risk for office workers of about 10^{-6} with plausible assumptions. That risk was calculated from data on hepatocellular carcinomas in male B6C3F1 mice in the NTP (1982a) gavage study. Table 1 gives a reported range of lifetime cancer risks that is bounded by "plausible" and "worst-case" scenarios defined by the assumptions in Table 2. In reviewing these data, the Subcommittee noted that there might be discrepancies between the final re-entry guidelines recommended by the state of California and the values obtained by extrapolation to a 10^{-6} risk in the "plausible" and "worst-case" scenarios (Gravitz et al., 1983).

New Mexico Risk Assessment

Recommendations were based on cancer risk potential, as in the California risk assessment, rather than the NOEL-safety factor approach for noncarcinogenic effects that was used in the New York risk assessment. The re-entry guidelines of 2 pg/m^3 and 1 ng/m^2 for air and surface contamination, respectively (Table 1), were reported to correspond to a lifetime cancer risk below 10^{-6} for persons spending the rest of their working lives in the New Mexico State Highway Department Office Building (Melius, 1985).

Louisiana Risk Assessment

The primary focus of the Louisiana risk assessment was on setting guidelines for PCBs. It was stated that observed ratios of PCBs to TCDD equivalents suggested that the PCB guidelines would provide a sufficient margin for cleanup of PCDDs and PCDFs. Thus, separate guidelines for TCDD equivalents were not set. Table 1 reports the estimated TCDD contaminant concentrations implied by the PCB guidelines. They were estimated from the smallest observed ratios of PCBs to TCDD equivalents, as in a "worst-case" scenario. The implied TCDD concentrations are 1.5 pg/m^3 for air and 25 ng/m^2 for surfaces. The estimated initial total daily intake derived from those contaminant concentrations (i.e., 22 pg/day, air; 4 pg/day, surface) may be compared with the Louisiana recommended TCDD allowable daily intake (650 pg/day). That recommended intake was based on a safety factor of 100 below the experimental NOEL for reproductive effects in rats (Murray et al., 1979). Corresponding estimates of lifetime cancer risk were not reported. The assumptions underlying the Louisiana risk assessment are included in Table 2.

Discussion

The California air contamination guideline of 10 pg/m^3 is identical with that of New York (Table 1), but its surface contamination guideline of 3 ng/m^2 is lower than the 25 ng/m^2 of New York. Because of differences in data and assumptions, the total daily intake that corresponds to the California air and surface re-entry guidelines is only 1.86 pg/workday in the "worst-case" scenario and only 23.7 pg/workday in the "plausible" scenario. Those numbers can be compared with New York's 100 pg/workday (2 pg/kg per workday x 50 kg). Similarly, the implied TCDD guidelines resulting from the Louisiana risk assessment, 1.5 pg/m^3 in air and 25 ng/m^2 on surfaces, lead to a total intake of 26 pg/d. The surface concentration is identical with New York's, and the air concentration is similar to New Mexico's. The New Mexico guidelines are both at the low ends of the ranges. Discrepancies of this type make the various risk assessments difficult to compare with respect to actual risks that would be associated with the given re-entry guidelines.

A partial solution of the problem, at least with respect to estimating carcinogenic risk, would include considering the calculated risks associated with allowable daily intakes corresponding to air or surface guidelines. This discussion focuses on New York's recommended allowable intake of 2 pg/kg per day. The risk estimates reported by New York (Table 1) correspond to the allowable

intake, irrespective of the actual air and surface contamination to which it translates. To evaluate the exposure magnitude, consider the estimate of lifetime cancer risk derived from the risk assessment performed by EPA's Carcinogen Assessment Group (CAG) (U.S. EPA, 1985). The CAG risk assessment was based on hepatocellular adenomas and carcinomas in female rats in the Kociba et al. (1978) study. The CAG estimate of the daily intake corresponding to an upper limit on the increased lifetime cancer risk of 10^{-6} is 0.0064 pg/kg per day, which translates to 0.0217 pg/kg per day on workdays. Alternatively, a daily intake of 2 pg/kg per day on workdays (0.59 pg/kg per day for a lifetime) corresponds to a CAG-based risk estimate of 9.2×10^{-5}. That estimate is close to the highest risk estimated by New York (Table 1). The CAG estimate is actually presumed to be an upper bound on the true risk. Although the upper-bound risk in humans is almost 100 times higher than what is usually considered "acceptable" for the general population, it is not so different from risks (10^{-4}) that have sometimes been accepted for small working populations (Travis et al., 1987; Travis and Hattemer-Frey, 1988). Because the New York allowable intake was derived in part by dividing an experimental NOEL by a safety factor of 500, the risk of toxic effects other than carcinogenesis is presumed to be zero.

Most of the assumptions in Table 2 are reasonable. The assumption regarding the constancy of contamination, particularly surface contamination, might be too conservative. In addition to the expected dissipation or decay of TCDD over time, surface contamination would decrease as a result of the wiping of surfaces by office workers and in normal office cleaning. Apart from possible recontamination of wiped surfaces by contaminated air, there is only a fixed amount of contamination available for a worker to absorb, even assuming 100% absorption of the total initial contamination.

Given the allowable intake of 2 pg/kg per day set by New York, a 50-kg person working 250 d/yr for 30 yr would have a total allowable lifetime exposure of 750 ng. Considering the allowable surface area contamination of 25 ng/m^2 set by New York on the basis of constant contamination, workers would have to ingest or absorb the total contamination from 30 m^2 of surface contaminated at the allowable 25 ng/m^2 to get 750 ng. An average desktop might be expected to have a surface area of only approximately 2 m^2, and only a fraction of the contaminant that is transferred to the skin is assumed to be either ingested or absorbed. Thus, it seems unlikely that a worker would ever achieve the total allowable lifetime exposure of 750 ng with an initial surface contamination of 25 ng/m^2. It should, however, be noted that exposure to PCDD and related chemicals also occurs from other sources and that the exposure is cumulative. Although the New York surface re-entry guideline is acknowledged to be conservative (J. Hawley, personal communication), there are no plans to revise the risk assessment for Binghamton, and the building will be cleaned up to conform to the established guidelines (E. Horn, personal communication).

All the calculated carcinogenic risks were based on standard approaches, which assume that carcinogenic substances with genotoxic properties could pose nonzero risk even at very low concentrations.

However, under certain conditions nongenotoxic carcinogens could pose nonzero risk at low concentrations. If exposure to a promoter results in augmentation of a carcinogenic process that is already producing tumors spontaneously, then an increase in tumors is expected (Crump et al., 1976). That is, a nonzero risk at low concentrations can result from an increase in the promotional aspect of the process. Stated another way, the occurrence of spontaneous tumors implies that a threshold dose already has been surpassed because of the presence of endogenous or exogenous factors that increase the carcinogenic process. Nonetheless, the addition of a nongenotoxic agent operating by an independent mechanism to increase tumors might have a threshold dose. Although current data suggest that TCDD acts as a promoter of carcinogenesis, generally accepted quantitative risk assessment techniques for promoters remain to be established.

EPA recently considered revising its risk assessment for dioxin to make it more in line with assessments of other agencies. In EPA's draft proposal (U.S. EPA, 1988), the allowable human exposure would be 16 times as high as CAG's original acceptable exposure. That is, the risk associated with low concentrations of dioxin would be estimated to be only one-sixteenth of that originally estimated. One motivation for EPA's proposed revision is the consideration that TCDD might act only as a promoter, rather than as an initiator. These proposals are currently being subjected to external peer review and public review.

COMMITTEE ON TOXICOLOGY RECOMMENDATIONS

There is little epidemiologic information that can be used to associate PCDDs with any long-term health effects other than chloracne in humans; nor is there unequivocal evidence to validate the absence of such effects (Fishbein, 1987). The reason for the uncertainty is that most epidemiologic studies have neither sufficient subjects to detect a small increase in risk of cancer or birth defects nor a sufficient observation period to detect an illness with a long latency period between exposure and illness. Because adequate dose-response data on chronic effects of PCDDs are not available from epidemiologic studies, extrapolations from animal toxicity studies (related primarily to carcinogenesis and reproductive effects) to possible human health effects have been used to estimate an acceptable magnitude of risk associated with exposure to PCDDs.

The exposure guidelines recommended by the Committee on Toxicology (Table 1) are the same as those recommended in the New York risk assessment, i.e., 10 pg/m^3 for air and 25 ng/m^2 for surfaces. Those criteria have been used as re-entry guidelines for the Binghamton State Office Building and have been satisfied. Because those concentrations were derived in part with a NOEL-safety factor approach, the likelihood of toxic effects other than carcinogenesis in humans is presumed to be negligible. The reported upper limit on lifetime carcinogenesis risk associated with those concentrations is intended to bound the true risk. The upper limit exceeds the CAG-based upper-limit estimate associated with the recommended allowable intake of 2 pg/kg per day, because different data sets are used. Because of the conservative nature of some of the assumptions that were made to translate New York's recommended allowable daily intake into air and surface guidelines--primarily the assumption of constant contamination over time--the true risk is probably overestimated by the upper limits of the estimates given in Table 1. Nonetheless, this upper limit is comparable with risks that have at times been accepted for small working populations. The Subcommittee accepts the upper limit of risk reported by New York and does not believe it necessary to conduct its own risk assessment.

The carcinogenesis risks associated with the recommended exposure guidelines are based on exposure only through air or only through surface contamination. If exposure occurs simultaneously at the recommended concentrations, the associated risks will increase by a factor of 2 with the assumption of a linear dose-response relation at low doses. Similarly, the safety factor for general toxic effects will decrease by a factor of 2. Even with this additional factor of 2, the Subcommittee considers the recommended guidelines adequate.

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