1982). Essentially, epidermal hyperplasia accompanied by involution of sebaceous glands, hyperkeratinization of the epidermis, and keratinization of dermal cysts are the hallmarks of hairless mouse "chloracne."

These gross morphologic changes were accompanied by significant elevations in epidermal transglutaminase activity. By the end of the second week of treatment, the epidermal transglutaminase (ETG) levels were more than sixfold the baseline levels, or the levels in the skin of acetone-treated mice (Fig. 1). By the end of the third week of treatment, ETG levels had decreased from the initial peak but still remained at more than twice the baseline levels at the termination of the experiment at 4 weeks.

To test for the possibility that TCDD present in the treated mouse skins was carried into the ETG assay and exerted a direct activating effect on the enzyme in the epidermal cytosol preparation, 0.2 ng of TCDD was added directly to the ETG assay mixture and the effect monitored. No changes in radioactivity of the resulting precipitates was observed.

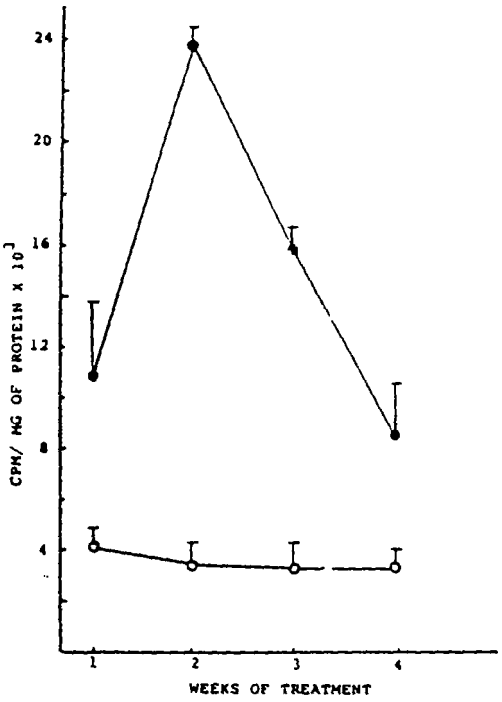

FIG. 1. Epidermal transglutaminase activity in skin of hairless mice treated with TCDD (● —— ●) and in controls (○ —— ○), expressed as cpm incorporated during 30 min of incubation/mg of epidermal cytosol protein. See Methods for details.

In Vitro Studies

The ionic concentration of calcium in the medium has been well established as a regulator of mouse epidermal cell terminal differentiation in *in vitro* tissues cultures (Hennings *et al.*, 1980) and our results were in line with this finding. In low calcium medium, mouse keratinocytes did not undergo terminal differentiation but continued to proliferate as basal cells in monolayers (Fig. 2A). Addition of 10^{-9} M TCDD did not change this pattern of growth at least in so far as could be determined by light microscopy (Fig. 2B). Nor did addition of TCDD have any effect on the rate of cell proliferation as measured by comparison of total cell counts of cultures, 24, 48, 72, and 96 hr after the addition of TCDD or DMSO to the low calcium medium. Total protein content (measured to the twelfth day) was similar in cultures grown with or without TCDD. Cells grown in high calcium medium started to stratify and differentiate 72 hr after plating (Fig. 2C).

ETG activity in the TCDD-treated cells in low calcium medium gradually increased over the 12-day period of growth, so that on the twelfth day ETG levels in the TCDD-treated, undifferentiated cells were almost identical to levels in the fully differentiating cells grown in high calcium medium (Fig. 3). ETG levels in the undifferentiating cells grown in low calcium medium without the addition of TCDD also increased slightly over the 12-day incubation period, but remained at about half the level of activity in the previously described cultures.

That this was a genuine increase of ETG production by the cells, rather than an activation of ETG activity already present in the cells, was shown by the fact that 10^{-9} M TCDD added directly to the transglutaminase assay did not have any effect on the results.

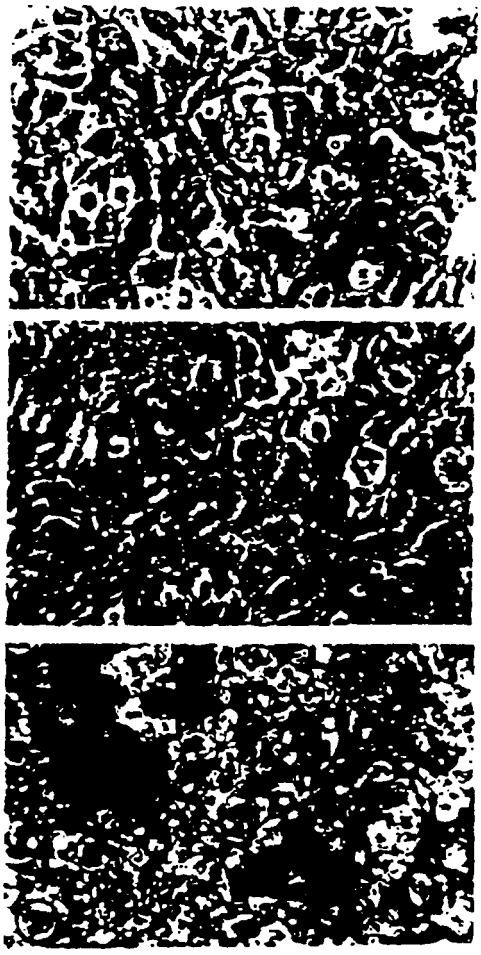

FIG. 2. Neonatal mouse epidermal cell cultures (A) in 0.07 mM Ca^{2+} medium; (B) in 0.07 mM Ca^{2+} and 10^{-9} M TCDD; and (C) in 1.2 mM Ca^{2+} medium at 7 days after plating. Note that TCDD did not affect cell culture morphology in the low calcium medium.

Changing keratinocyte cultures from low calcium to high calcium medium on Day 7, at a time when it had been established that ETG activity was high in the TCDD-treated, undifferentiated cells, indicated that terminal differentiation was not the same in TCDD-treated cells as in control cells grown in low calcium medium without the presence of TCDD. The cornified envelope count was consistently slightly higher in the TCDD-treated cells (0.7%) than in the control cells (0.3%), but it remained much lower than the counts of cornified envelopes in cells grown in high Ca^{2+} medium from the beginning (12 to 14%). Morphologically, terminal differentiation and cell death were delayed in the TCDD-treated cultures, in a manner similar to what has been reported for retinoic acid-treated cultures by Yuspa *et al.* (1981) (Fig. 4).

DISCUSSION

The changes induced in human skin by TCDD exposure are among the more observable and well-defined biological effects of this potent man-made toxin. In the hairless mouse model, topical application of minute amounts of TCDD induces a distinct hyperproliferative, hyperkeratinizing response (Puhvel *et al.* 1982; Knutson and Poland, 1982). Epidermal transglutaminase is considered a marker enzyme for terminal epidermal differentiation (Goldsmith and Martin, 1975; Buxman and Wuepper, 1976). This soluble, calcium-dependent enzyme which catalyses the formation of co-

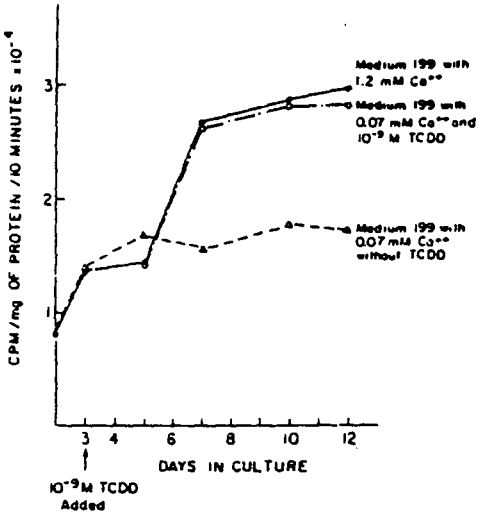

FIG. 3. Epidermal transglutaminase activity in cultures grown in 1.2 mM Ca^{2+} (● —— ●), in cultures grown in 0.07 mM Ca^{2+} plus 10^{-9} M TCDD (○ —— ○), and in 0.07 mM Ca^{2+} without TCDD (Δ —— Δ).

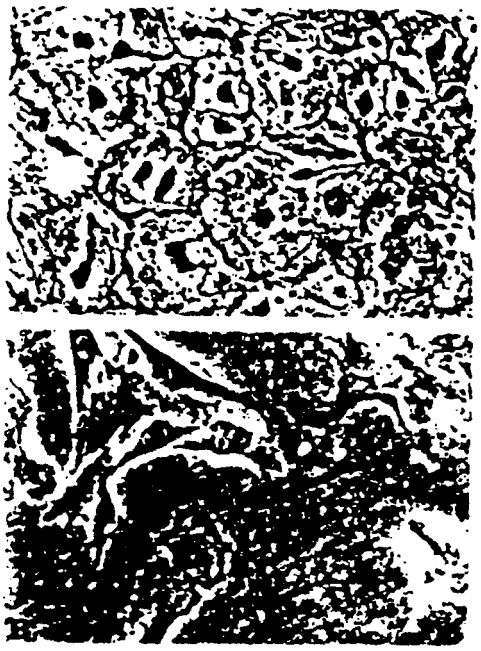

FIG. 4. Illustration of the delay in terminal differentiation of mouse epidermal cell cultures following treatment with 10^{-9} M TCDD. Parallel cultures were first grown in 0.07 mM Ca^{2+} for 7 days in the presence (A) and without the presence of 10^{-9} M TCDD (B). Cultures were then switched to 1.2 mM Ca^{2+} (without TCDD). Terminal differentiation and cell death were delayed in the TCDD-treated cultures (A) compared to controls (B). The photograph was taken 5 days after transfer to 1.2 mM Ca^{2+} medium.

valent crosslinks, involving ε (γ-gluytamyl-lysine) dipeptide bonds, is thought to be involved in the conversion of soluble structural protein beneath the plasma membranes of epidermal cells, to insoluble, high-molecular-weight proteins which form the cornified cell envelopes of differentiated keratinocytes.

Levels of transglutaminase activity *in vivo* in mouse ear epidermis are affected by agents which alter epidermal differentiation, such as anthralin, retinoic acid, and fluocinolone acetonide (DeYoung and Ballaron, 1982). In the present *in vivo* studies, a significant increase of this enzyme activity was demonstrated following changes in cutaneous differentiation after TCDD application. One possible complication in interpreting results of *in vivo* experiments which involve analyses of crude epidermal extracts is that during the dermal–epidermal separation procedure, dermal transglutaminases may theoretically contaminate the epidermal preparations. Substances applied topically to the skin, particularly those which induce an inflammatory cutaneous response, may affect the dermal as well as epidermal transglutaminase levels. Previous studies by DeYoung and Ballaron (1982) which investigated this problem suggested that their results were not affected by inflammatory changes. In the present paper, *in vitro* tissue culture studies were used to confirm the *in vivo* observations in a system which was free of dermal components.

The observation that mouse epidermal keratinocytes in low Ca^{2+} medium have lower levels of transglutaminase activity than differentiating keratinocytes in high Ca^{2+} medium has been established previously by Hennings *et al.* (1981). Our finding that TCDD increases unexpressed transglutaminase activity in the nondifferentiating cells in low Ca^{2+} medium confirms our *in vivo* observations about the increase of this enzyme by TCDD in epidermal cells.

Very similar effects on transglutaminase induction by epidermal basal cells *in vitro* have been demonstrated by the addition of retinoic acid (Yuspa *et al.*, 1981) or 12-*O*-tetradecanoylphorbol-13-acetate and other tumor promotors (Yuspa *et al.*, 1980) to low calcium mouse epidermal tissue cultures. In those studies as in the present experiments, it appeared that the effect was one of induction rather than activation of enzyme activity, since addition of the chemical (in this case 10^{-9} M TCDD) directly to the enzyme assay had no effect on the results. In the studies by Yuspa *et al.* (1980, 1981) retinoic acid had a different effect on terminal differentiation of the cell cultures after transfer to high calcium (1.2 mM) medium. Normally, when epidermal basal cells are transferred to high calcium medium after being cultured in low calcium medium for 5 to 7 days, terminal differentiation accompanied by cell death occurs within 2 to 5 days after transfer. In cells grown in the presence of retinoic acid (at 10^{-6} M concentration),

this pattern of terminal differentiation was significantly delayed. Phorbol esters did not affect the rate of terminal differentiation. In the present study, TCDD also delayed terminal differentiation of the cultures, despite the fact that insoluble cell envelope counts appeared to be higher in the TCDD-treated transferred cultures than in the untreated controls.

Knutson and Poland (1982) have suggested that cutaneous sensitivity to TCDD in mice is associated with the gene for hairlessness, and that hr/hr (hairless) animals have a more acute cutaneous response to TCDD than do the hr/+ (haired) counterparts. In the present studies, epidermal cell cultures were established with BALB/c hr/+ (haired) neonatal mice as tissue donors. Interestingly, such cells in culture responded to TCDD exposure. It could be that the effects of TCDD on epidermal cell cultures would be even more striking in epidermal cultures from hr/hr (hairless) skin donors.

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REFERENCES

BRADFORD, M. (1976). A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein dying binding. *Anal. Biochem.* 72, 248–254.

BUXMAN, M. M., AND WUEPPER, K. D. (1976). Isolation, purification and characterization of epidermal transglutaminase. *Biochim. Biophys. Acta* 452, 356–369.

DEYOUNG, L., AND BALLARON, S. (1982). The effect of topical drugs on mouse ear transglutaminase activity. *J. Invest. Dermatol.* 79, 189–193.

GOLDSMITH, L. A., AND MARTIN, C. M. (1975). Human epidermal transamidase. *J. Invest. Dermatol.* 64, 316–321.

HENNINGS, H., MICHAEL, D., CHENG, C., STEINERT, P., HOLBROOK, K., AND YUSPA, S. H. (1980). Calcium regulation of growth and differentiation of mouse epidermal cells in culture. *Cell* 19, 245–254.

HENNINGS, H., STEINERT, P., AND BUXMAN, M. M. (1981). Calcium induction of transglutaminase and the formation of ε (γ glutamyl) lysine cross-links in cultured mouse epidermal cells. *Biochem. Biophys. Res. Commun.* 102, 739–745.

KNUTSON, J. C., AND POLAND, A. (1982). Response of murine epidermis to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Interaction of the *Ah* and *hr* loci. *Cell* 30, 225–234.

MARCELO, C., KIM, Y. G., KLEINE, J. L., AND VORHEES, J. J. (1978). Stratification, specialization and proliferation of primary keratinocyte cultures. *J. Cell Biol.* 79, 356–370.

MOORE, J. A. (1978). Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Ecol. Bull (Stockholm)* 27, 134–144.

OGAWA, H., AND GOLDSMITH, L. A. (1976). Human epidermal transglutaminase. *J. Biol. Chem.* 251, 7281–7288.

PUHVEL, S. M., SAKAMOTO, M., ERTL, D. C., AND REISNER, R. M. (1982). Hairless mice as models for chloracne: a study of cutaneous changes induced by topical application of established chloracnegens. *Toxicol. Appl. Pharmacol.* 64, 492–503.

YUSPA, S. H., BEN, T., HENNINGS, H., AND LICHTI, U. (1980). Phorbol ester tumor promoters induce epidermal transglutaminase activity. *Biochem. Biophys. Res. Commun.* 97, 700–706.

YUSPA, S. H., LICHTI, U., BEN, T., AND HENNINGS, H. (1981). Modulation of terminal differentiation and responses to tumor promoters by retinoids in mouse epidermal cell cultures. *Ann. N.Y. Acad. Sci.* 359, 260–273.

YUSPA, S., BEN, T., AND STEINERT, P. (1982). Retinoic acid induces transglutaminase activity but inhibits cornification of cultured epidermal cells. *J. Biol. Chem.* 257, 9906–9908.

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Accidental exposure to dioxins: human health aspects. Edited by Frederick Coulston, Francesco Pocchiari. New York: Academic Press, 1983. 294p.

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A

Abelson PH: Chlorinated dioxins [editorial] Science 1983 Jun 24;220(4604):1337
ANIMAL/ DERMATITIS, CONTACT, etiology/ *DIOXINS, adverse effects/ DIOXINS, toxicity/ HUMAN/ TETRACHLORODIBENZODIOXIN, adverse effects/ TETRACHLORODIBENZODIOXIN, toxicity

Alberani V, Stalacalchi P, Di Marco L, et al: Degradazione dell'ambiente. III. Igiene del suolo e provvedimenti concernenti le zone colpite da contaminazione da TCDD. Ann Ist Super Sanita 1981;17(2):323-35 (Ita)
*DIOXINS/ *ENVIRONMENTAL POLLUTION/ ITALY/ LEGISLATION/ *SOIL POLLUTANTS/ *TETRACHLORODIBENZODIOXIN

B

Bąk W, Faff J, Kisielifiski T: Wartości niektórych składników krwi świnek morskich w ostrym zatruciu 2,3,7,8-czterodwubenzo-p-dioksyną (TCDD). Med Pr 1982;33(5-6):269-75 (Eng. Abstr.) (Pol)
ACUTE DISEASE/ ANIMAL/ *DIOXINS, poisoning/ ENGLISH ABSTRACT/ ERYTHROCYTE COUNT/ *ERYTHROCYTES, metabolism/ ERYTHROCYTES, pathology/ GUINEA PIGS/ HEMOGLOBINS, analysis/ LEUKOCYTE COUNT/ *LEUKOCYTES, metabolism/ LEUKOCYTES, pathology/ MALE/ REFERENCE VALUES/ *TETRACHLORODIBENZODIOXIN, poisoning

Ball LM, Chhabra RS: Intestinal absorption of nutrients in rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). J Toxicol Environ Health 1981 Oct;8(4):629-38
ANIMAL/ *DIOXINS, toxicity/ EATING, drug effects/ GLUCOSE, metabolism/ *INTESTINAL ABSORPTION, drug effects/ LEUCINE, metabolism/ MALE/ RATS/ RATS, INBRED STRAINS/ *TETRACHLORODIBENZODIOXIN, toxicity

Bałkowska J: Hepatotoksyczność wybranych polichlorowanych węglowodorów aromatycznych. Rocz Panstw Zakl Hig 1982;33(4):303-5 (Eng. Abstr.) (Pol)
ANIMAL/ *CHLOROBENZENES, toxicity/ *CHLOROPHENOLS, toxicity/ *DIOXINS, toxicity/ ENGLISH ABSTRACT/ *HEXACHLOROBENZENE, toxicity/ LIVER DISEASES, chemically induced/ *LIVER, drug effects/ *PENTACHLOROPHENOL, toxicity/ PORPHYRIA, chemically induced/ RATS/ *TETRACHLORODIBENZODIOXIN, toxicity

Barr M: Neuropsychiatric effects of herbicides [letter] Aust NZ J Psychiatry 1982 Jun;16(2):88-9
*DIOXINS, adverse effects/ HUMAN/ MALE/ *NERVOUS SYSTEM DISEASES, chemically induced/ *ORGANIC MENTAL DISORDERS, SUBSTANCE-INDUCED, etiology/ *TETRACHLORODIBENZODIOXIN, adverse effects/ VETERANS, psychology/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Bickel MH: Polychlorinated persistent compounds. Experientia 1982 Aug 15;38(8):879-82
ADIPOSE TISSUE, metabolism/ ANIMAL/ CHEMISTRY/ DOGS/ DDT, metabolism/ *ENVIRONMENTAL POLLUTION/ GUINEA PIGS/ HUMAN/ *HYDROCARBONS, CHLORINATED, metabolism/ HYDROCARBONS, CHLORINATED, toxicity/ KINETICS/ POLYCHLOROBIPHENYL COMPOUNDS, metabolism/ RATS/ TETRACHLORODIBENZODIOXIN, metabolism

Bickel MH, Muehlebach S: Pharmacokinetics and ecodisposition of polyhalogenated hydrocarbons: aspects and concepts. Drug Metab Rev 1980;11(2):149-90 (237 ref.)
ANIMAL/ BIODEGRADATION/ BIOTRANSFORMATION/ DDT, analysis/ *ENVIRONMENTAL POLLUTANTS, analysis/ *HYDROCARBONS, HALOGENATED, metabolism/ KINETICS/ POLYCHLOROBIPHENYL COMPOUNDS, analysis/ REVIEW/ TETRACHLORODIBENZODIOXIN, analysis

Bisanti L, Bonetti F, Caramaschi F, et al: Experiences from the accident of Seveso.
Acta Morphol Acad Sci Hung 1980;28(1-2):139-57
ABNORMALITIES, DRUG-INDUCED, occurrence/ ABORTION, chemically induced/ ABORTION, occurrence/ *ACCIDENTS, OCCUPATIONAL/ ACNE, chemically induced/ ACNE, occurrence/ ADOLESCENCE/ ADULT/ AGE FACTORS/ BIRTH RATE/ CHILD/ CHILD, PRESCHOOL/ *DIOXINS, toxicity/ *ENVIRONMENTAL POLLUTION/ FEMALE/ HUMAN/ INFANT/ ITALY/ MORTALITY/ PREGNANCY/ SOIL, analysis/ TETRACHLORODIBENZODIOXIN, analysis/ *TETRACHLORODIBENZODIOXIN, toxicity

Bishop CM, Jones AH: Non-Hodgkin's lymphoma of the scalp in workers exposed to dioxins [letter] Lancet 1981 Aug 15;2(8242):369
AGED/ CASE REPORT/ *DIOXINS, adverse effects/ HUMAN/ *LYMPHOMA, chemically induced/ MALE/ MIDDLE AGE/ *OCCUPATIONAL DISEASES, chemically induced/ *SCALP/ *SKIN NEOPLASMS, chemically induced/ TETRACHLORODIBENZODIOXIN, analogs & derivatives/ *TETRACHLORODIBENZODIOXIN, adverse effects

Blackburn AB: Review of the effects of Agent Orange: a psychiatric perspective on the controversy.
Milit Med 1983 Apr;148(4):333-40
ANIMAL/ *DIOXINS, toxicity/ HUMAN/ *PSYCHOSES, SUBSTANCE-INDUCED, psychology/ SKIN DISEASES, chemically induced/ *TETRACHLORODIBENZODIOXIN, toxicity/ UNITED STATES/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

Boorman GA, Lauter MI, Dean JH, et al: Assessment of myelotoxicity caused by environmental chemicals.
Environ Health Perspect 1982 Feb;43:129-35
ANIMAL/ BENZOPYRENES, toxicity/ *BONE MARROW, drug effects/ DIETHYLSTILBESTROL, toxicity/ *ENVIRONMENTAL POLLUTANTS, toxicity/ ERYTHROPOIESIS, drug effects/ FEMALE/ GRANULOCYTES, drug effects/ HEMATOPOIETIC STEM CELLS, drug effects/ MACROPHAGES, drug effects/ MICE/ POLYBROMOBIPHENYL COMPOUNDS, toxicity/ TETRACHLORODIBENZODIOXIN, toxicity

Bradlaw JA, Garthoff LH, Hurley NE, et al: Comparative induction of aryl hydrocarbon hydroxylase activity in vitro by analogues of dibenzo-p-dioxin.
Food Cosmet Toxicol 1980 Dec;18(6):627-35
ANIMAL/ *ARYL HYDROCARBON HYDROXYLASES, biosynthesis/ CELLS, CULTURED/ COMPARATIVE STUDY/ *DIOXANES, toxicity/ *DIOXINS, toxicity/ ENZYME INDUCTION, drug effects/ HALOGENS, toxicity/ HEPATOMA, EXPERIMENTAL, enzymology/ RATS/ TETRACHLORODIBENZODIOXIN, toxicity

Bumb RR, Crummett WB, Cutie SS, et al: Trace chemistries of fire: a source of chlorinated dioxins. Science 1980 Oct; 210(4468):385-90
AIR POLLUTANTS, analysis/ AUTOMOBILE EXHAUST, analysis/ CHEMISTRY/ CHROMATOGRAPHY, HIGH PRESSURE LIQUID/ *DIOXINS/ DIOXINS, analysis/ *FIRES/ POWER PLANTS/ SMOKE, analysis/

SOIL POLLUTANTS, analysis/ TETRACHLORODIBENZODIOXIN, analysis/ WATER POLLUTANTS, CHEMICAL, analysis

C

Castoni L, Salmona M, Rizzardini M: Porphyrogenic effect of chronic treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin in female rats. Dose--effect relationship following urinary excretion of porphyrins. Toxicol Appl Pharmacol 1981 Feb; 57(2):156-63
ANIMAL/ *DIOXINS, toxicity/ DOSE-RESPONSE RELATIONSHIP, DRUG/ FEMALE/ KIDNEY, metabolism/ LIVER, metabolism/ *PORPHYRINS, biosynthesis/ PORPHYRINS, urine/ RATS/ SPLEEN, metabolism/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, toxicity

Caramaschi F, del Corno G, Favaretti C, et al: Chloracne following environmental contamination by TCDD in Seveso, Italy. Int J Epidemiol 1981 Jun;10(2):135-43
ACCIDENTS, OCCUPATIONAL/ ACNE, chemically induced/ ACNE, diagnosis/ *ACNE, occurrence/ ADOLESCENCE/ CHILD/ CHILD, PRESCHOOL/ *DIOXINS, toxicity/ *ENVIRONMENTAL POLLUTANTS, toxicity/ FEMALE/ HUMAN/ ITALY/ MALE/ RESIDENCE CHARACTERISTICS/ SYNDROME/ *TETRACHLORODIBENZODIOXIN, toxicity

Cattaneo M, Remotti G, Coviello D, et al: Reperti istologici placentari in soggetti provenienti da area inquinata da TCDD. Ann Ostet Ginecol Med Perinat 1981 May-Jun; 102(3):155-64 (Eng. Abstr.) (Ita)
*ABORTION, chemically induced/ ADULT/ AIR POLLUTANTS, adverse effects/ *DIOXINS, adverse effects/ ENGLISH ABSTRACT/ *ENVIRONMENTAL POLLUTANTS, adverse effects/ FEMALE/ HUMAN/ *PLACENTA DISEASES, chemically induced/ PREGNANCY/ SOIL POLLUTANTS, adverse effects/ *TETRACHLORODIBENZODIOXIN, adverse effects

Cheung MO, Gilbert EF, Peterson RE: Cardiovascular teratogenicity of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin in the chick embryo. Toxicol Appl Pharmacol 1981 Nov; 61(2):197-204
*ABNORMALITIES, DRUG-INDUCED/ ANIMAL/ *BLOOD VESSELS, abnormalities/ CHICK EMBRYO/ *DIOXINS, toxicity/ DOSE-RESPONSE RELATIONSHIP, DRUG/ *HEART DEFECTS, CONGENITAL, chemically induced/ SUPPORT, NON-U.S. GOV'T/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, toxicity

Coggon D, Acheson ED: Do phenoxy herbicides cause cancer in man? Lancet 1982 May 8;1(8280):1057-9
CHLOROPHENOLS, adverse effects/ DIOXINS, adverse effects/ HUMAN/ LYMPHOMA, chemically induced/ *OCCUPATIONAL DISEASES, chemically induced/ *SARCOMA, chemically induced/ *SOFT TISSUE NEOPLASMS, chemically induced/ TETRACHLORODIBENZODIOXIN, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Cook RR: Dioxin, chloracne, and soft tissue sarcoma [letter] Lancet 1981 Mar 14;1(8220 Pt 1):618-9
ACNE, chemically induced/ COCARCINOGENESIS/ *DIOXINS, poisoning/ HUMAN/ MIDDLE AGE/ *OCCUPATIONAL DISEASES, chemically induced/ *SARCOMA, chemically induced/ SMOKING/ *SOFT TISSUE NEOPLASMS, chemically induced/ *TETRACHLORODIBENZODIOXIN, poisoning

Cooper CL, Omokhay S, Taftashi M, et al: Anencephaly: agent orange implications? J Natl Med Assoc 1983 Jan; 75(1):93-4
*ABNORMALITIES, DRUG-INDUCED, etiology/ ADULT/ *ANENCEPHALY, chemically induced/ CASE REPORT/ *DIOXINS, adverse effects/ FEMALE/ FETAL DEATH, chemically induced/ HUMAN/ PREGNANCY

D

Dickins M, Seefeld MD, Peterson RE: Enhanced liver DNA synthesis in partially hepatectomized rats pretreated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Appl Pharmacol 1981 May;58(3):389-98
ANIMAL/ COMPARATIVE STUDY/ *DIOXINS, toxicity/ *DNA, biosynthesis/ HEPATECTOMY/ *LIVER REGENERATION, drug effects/ *LIVER, drug effects/ LIVER, physiology/ MALE/ RATS/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, toxicity/ THYMIDINE, metabolism/ TIME FACTORS

Dickson D: The embarrassing odyssey of Seveso's dioxin [news] Science 1983 Jun 24;220(4604):1362-3
*DIOXINS, adverse effects/ FRANCE/ INDUSTRIAL WASTE, adverse effects/ ITALY/ *TETRACHLORODIBENZODIOXIN, adverse effects

di Domenico A, Silano V, Viviano G, et al: Accidental release of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at Sèveso, Italy. V. Environmental persistence of TCDD in soil. Ecotoxicol Environ Safety 1980 Sep;4(3):339-45
ACCIDENTS, OCCUPATIONAL/ *DIOXINS, analysis/ ITALY/ *SOIL POLLUTANTS, analysis/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, analysis

di Domenico A, Silano V, Viviano G, et al: Accidental release of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at Sèveso, Italy. IV. Vertical distribution of TCDD in soil. Ecotoxicol Environ Safety 1980 Sep;4(3):327-38
ACCIDENTS, OCCUPATIONAL/ *DIOXINS, analysis/ ITALY/ SOIL POLLUTANTS, analysis/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, analysis/ TIME FACTORS

di Domenico A, Silano V, Viviano G, et al: Accidental release of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at Sèveso, Italy. III. Monitoring of residual TCDD levels in reclaimed buildings. Ecotoxicol Environ Safety 1980 Sep;4(3):321-6
ACCIDENTS, OCCUPATIONAL/ *DIOXINS, analysis/ *ENVIRONMENTAL POLLUTANTS, analysis/ ITALY/ SOIL POLLUTANTS, analysis/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, analysis

di Domenico A, Silano V, Viviano G, et al: Accidental release of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at Sèveso, Italy. II. TCDD distribution in the soil surface layer. Ecotoxicol Environ Safety 1980 Sep;4(3):298-320
ACCIDENTS, OCCUPATIONAL/ *DIOXINS, analysis/ ITALY/ *SOIL POLLUTANTS, analysis/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, analysis

di Domenico A, Silano V, Viviano G, et al: Accidental release of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at Sèveso, Italy. Ecotoxicol Environ Safety 1980 Sep; 4(3):283-97
ACCIDENTS, OCCUPATIONAL/ *DIOXINS, analysis/ *ENVIRONMENTAL POLLUTANTS, analysis/ ITALY/ MASS FRAGMENTOGRAPHY/ PLANTS, analysis/ SOIL POLLUTANTS, analysis/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, analysis

Donatelli L, Lampa E, Cresso E: Considerations on the epidemiology of the Seveso accident. Toxicol Eur Res 1981 Jan;3(1):9-16
*ACCIDENTS, OCCUPATIONAL/ AGED/ ANIMAL/ *DIOXINS, poisoning/ DRUG INTERACTIONS/ FEMALE/ HUMAN/ INFANT, NEWBORN/ ITALY/ LETHAL DOSE 50/ MALE/ SPECIES SPECIFICITY/ TETRACHLORODIBENZODIOXIN, poisoning/

TETRACHLORODIBENZODIOXIN, toxicity

Dunagin WG: Dioxin effects on human health. Mo Med 1983 Mar;80(3):127-31 (29 ref.)
ACCIDENTS, OCCUPATIONAL/ ACNE, chemically induced/ *DIOXINS, adverse effects/ ENVIRONMENTAL EXPOSURE/ GERMANY, WEST/ HUMAN/ ITALY/ MILITARY MEDICINE/ OCCUPATIONAL DISEASES, chemically induced/ REVIEW/ *TETRACHLORODIBENZODIOXIN, adverse effects/ UNITED STATES/ VIETNAM

F

Fanelli R, Chiabrando C, Bonaccorsi A: TCDD contamination in the Seveso incident. Drug Metab Rev 1982;13(3):407-22
ANIMAL/ CATTLE/ *DIOXINS, analysis/ *ENVIRONMENTAL POLLUTANTS, analysis/ ENVIRONMENTAL POLLUTANTS, poisoning/ ITALY/ MILK, analysis/ RABBITS/ SOIL POLLUTANTS, analysis/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, analysis/ TETRACHLORODIBENZODIOXIN, poisoning/ TISSUE DISTRIBUTION

Fanelli R, Bertoni MP, Castelli MG, et al: 2,3,7,8-Tetrachlorodibenzo-p-dioxin toxic effects and tissue levels in animals from the contaminated area of Seveso, Italy. Arch Environ Contam Toxicol 1980; 9(5):569-77
ACCIDENTS, OCCUPATIONAL/ ANIMAL/ BIRDS/ CATS/ CATTLE/ CHICKENS/ *DIOXINS, toxicity/ ENVIRONMENTAL POLLUTANTS/ GOATS/ GUINEA PIGS/ HORSES/ ITALY/ RABBITS/ SHEEP/ SUPPORT, NON-U.S. GOV'T/ SWINE/ TETRACHLORODIBENZODIOXIN, analysis/ *TETRACHLORODIBENZODIOXIN, toxicity

Felde G: Get the facts on Agent Orange. Imprint 1982 Sep; 29(3):17, 61
*CHEMICAL WARFARE/ *DIOXINS, poisoning/ HUMAN/ MILITARY MEDICINE/ *TETRACHLORODIBENZODIOXIN, poisoning/ UNITED STATES/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, poisoning/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, poisoning

Filippini G, Bordo B, Cressa P, et al: Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8-tetrachlorodibenzo-dioxin. Scand J Work Environ Health 1981 Dec;7(4):257-62
ACNE, chemically induced/ ADOLESCENCE/ ADULT/ CHILD/ CHILD, PRESCHOOL/ *DIOXINS, poisoning/ ELECTROPHYSIOLOGY/ *ENVIRONMENTAL POLLUTANTS, poisoning/ HUMAN/ ITALY/ LIVER, enzymology/ MIDDLE AGE/ *PERIPHERAL NERVE DISEASES, chemically induced/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, poisoning

Flak DJ: Exposure to agent orange [letter] JAMA 1980 Sep 5;244(10):1094-5
ENVIRONMENTAL EXPOSURE/ HUMAN/ TETRACHLORODIBENZODIOXIN, toxicity/ VIETNAM/ WAR/ *2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

Flowers FP, Fenske NA, Whisman PA: Agent Orange: what's it all about? J Fla Med Assoc 1981 Dec; 68(12):991-2
*DIOXINS, adverse effects/ *HERBICIDES, adverse effects/ HUMAN/ MILITARY MEDICINE/ *TETRACHLORODIBENZODIOXIN, adverse effects/ UNITED STATES/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects

G

Garattini S: TCDD toxicology with particular reference to Seveso: introductory remarks. Drug Metab Rev 1982; 13(3):345-53 (36 ref.)
ANIMAL/ *DIOXINS, toxicity/ *ENVIRONMENTAL POLLUTANTS, toxicity/ HUMAN/ ITALY/ KIDNEY, pathology/ LIVER, pathology/ REVIEW/ *TETRACHLORODIBENZODIOXIN, toxicity/ TETRACHLORODIBENZODIOXIN, urine

Geiger LE, Neal RA: Mutagenicity testing of 2,3,7,8-tetrachlordibenzo-p-dioxin in histidine auxotrophs of Salmonella typhimurium. Toxicol Appl Pharmacol 1981 Jun 15;59(1):125-9
ANIMAL/ *DIOXINS, toxicity/ HAMSTERS/ HISTIDINE, metabolism/ MALE/ MESOCRICETUS/ MUTAGENICITY TESTS/ *MUTAGENS/ RATS/ *SALMONELLA TYPHIMURIUM, drug effects/ SALMONELLA TYPHIMURIUM, metabolism/ SUPPORT, U.S. GOV'T, P.H.S./ TETRACHLORODIBENZODIOXIN, metabolism/ *TETRACHLORODIBENZODIOXIN, toxicity

Gluvini E, Prati M, Vismara C: Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin administered to pregnant rats during the preimplantation period. Environ Res 1982 Oct;29(1):185-9
*ABNORMALITIES, DRUG-INDUCED, etiology/ ANIMAL/ *DIOXINS, adverse effects/ FEMALE/ NIDATION/ PREGNANCY/ *PREGNANCY, ANIMAL, drug effects/ RATS/ RATS, INBRED STRAINS/ SUPPORT, NON-U.S. GOV'T/ TETRACHLORODIBENZODIOXIN, administration & dosage/ *TETRACHLORODIBENZODIOXIN, adverse effects

Gluvini E, Prati M, Vismara C: Rabbit teratology study with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ Res 1982 Feb;27(1):74-8
*ABNORMALITIES, DRUG-INDUCED, etiology/ ABORTION, chemically induced/ ANIMAL/ *DIOXINS, adverse effects/ FEMALE/ KIDNEY, abnormalities/ PREGNANCY/ RABBITS/ RIBS, abnormalities/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, adverse effects

Gluvini E, Prati M, Vismara C: Embryotoxic effects of 2,3,7,8 tetrachlorodibenzo-p-dioxin administered to female rats before mating. Environ Res 1983 Jun; 31(1):105-10
ABNORMALITIES, DRUG-INDUCED/ ANIMAL/ BODY WEIGHT, drug effects/ *DIOXINS, toxicity/ *EMBRYO, drug effects/ FEMALE/ *MATERNAL-FETAL EXCHANGE/ OVULATION, drug effects/ PREGNANCY/ *PREGNANCY, ANIMAL, drug effects/ RATS/ SUPPORT, NON-U.S. GOV'T/ *TERATOGENS/ *TETRACHLORODIBENZODIOXIN, toxicity

Goldstein JA, Linko P, Bergman H: Induction of porphyria in the rat by chronic versus acute exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Biochem Pharmacol 1982 Apr 15;31(8):1607-13
AMINOLEVULINIC ACID SYNTHETASE, metabolism/ ANIMAL/ ARYL HYDROCARBON HYDROXYLASES, metabolism/ *DIOXINS, toxicity/ FEMALE/ LIVER, enzymology/ MIXED FUNCTION OXIDASES, metabolism/ *PORPHYRIA, chemically induced/ RATS/ RATS, INBRED STRAINS/ *TETRACHLORODIBENZODIOXIN, toxicity/ TIME FACTORS

Gross ML: Application of mass spectrometric methods to analysis of xenobiotics in biological systems. IARC Sci Publ 1982;(39):443-62
ANIMAL/ *DIOXINS, analysis/ FOURIER ANALYSIS/ HUMAN/ MACACA MULATTA/ MASS FRAGMENTOGRAPHY, methods/ MILK, HUMAN, analysis/

*SPECTRUM ANALYSIS, MASS, methods/ SUPPORT, U.S. GOV'T, NON-P.H.S./ *TETRACHLORODIBENZODIOXIN, analysis/ TETRACHLORODIBENZODIOXIN, metabolism/ VETERANS

Gunby P: Light at end of tunnel in Orange controversy [news] JAMA 1982 Mar 12;247(10):1382
*DIOXINS, poisoning/ HUMAN/ LEGISLATION, DRUG/ MILITARY MEDICINE/ *TETRACHLORODIBENZODIOXIN, poisoning/ UNITED STATES/ VIETNAM/ WAR/ *2,4-DICHLOROPHENOXYACETIC ACID, poisoning/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, poisoning

Gunby P: More questions, not answers, emerge from Agent Orange studies [news] JAMA 1983 May 27; 249(20):2743-6
*ABNORMALITIES, DRUG-INDUCED, etiology/ *DIOXINS, poisoning/ FATHERS/ FEMALE/ HUMAN/ INFANT, NEWBORN/ MALE/ MATERNAL-FETAL EXCHANGE/ PREGNANCY/ *TETRACHLORODIBENZODIOXIN, poisoning/ UNITED STATES/ VETERANS DISABILITY CLAIMS, legislation & jurisprudence/ *2,4-DICHLOROPHENOXYACETIC ACID, poisoning/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, poisoning

H

Hall P, Sellinger B, Field B, et al: Antipodean 2,4,5-T [letter] Nature 1981 Mar 5;290(5801):8
ABNORMALITIES, DRUG-INDUCED, etiology/ ANIMAL/ AUSTRALIA/ COMMERCE/ HUMAN/ *2,4-DICHLOROPHENOXYACETIC ACID/ 2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Hall RF: Herbicides: liberators or poisoners of humankind? Vet Hum Toxicol 1983 Apr;25(2):92-5
ANIMAL/ ENVIRONMENTAL POLLUTANTS, analysis/ *HERBICIDES, toxicity/ HUMAN/ SOIL, analysis/ TETRACHLORODIBENZODIOXIN, metabolism/ TETRACHLORODIBENZODIOXIN, toxicity/ 2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

Hardell L, Eriksson M: Soft-tissue sarcomas, phenoxy herbicides, and chlorinated phenols [letter] Lancet 1981 Aug 1;2(8240):250
*CHLOROPHENOLS, poisoning/ *HERBICIDES, poisoning/ HUMAN/ OCCUPATIONAL DISEASES, chemically induced/ *SARCOMA, chemically induced/ *SOFT TISSUE NEOPLASMS, chemically induced/ TETRACHLORODIBENZODIOXIN, poisoning/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, poisoning

Harvey WK, Lindahl R: Activity of various aldehyde-metabolizing enzymes in chemically-induced rat hepatomas. Biochem Pharmacol 1982 Mar 15; 31(6):1153-5
ALCOHOL OXIDOREDUCTASES, analysis/ ALDEHYDE OXIDOREDUCTASES, analysis/ *ALDEHYDES, metabolism/ ANIMAL/ HEPATOMA, EXPERIMENTAL, chemically induced/ *HEPATOMA, EXPERIMENTAL, enzymology/ MALE/ RATS/ RATS, INBRED STRAINS/ SUPPORT, NON-U.S. GOV'T/ SUPPORT, U.S. GOV'T, P.H.S./ TETRACHLORODIBENZODIOXIN, toxicity/ 2-ACETYLAMINOFLUORENE, toxicity

Hassoun EM, Dencker L: TCDD embryotoxicity in the mouse may be enhanced by beta-naphthoflavone, another ligand of the Ah-receptor. Toxicol Lett 1982 Jul; 12(2-3):191-8
ANIMAL/ *BENZOFLAVONES, pharmacodynamics/ *DIOXINS, toxicity/ FEMALE/ FETAL DEATH, chemically induced/ *FLAVONES, pharmacodynamics/ LIGANDS/ MICE/ MICE, INBRED C57BL/ PREGNANCY/ *RECEPTORS, DRUG, metabolism/ SUPPORT, NON-U.S. GOV'T/ *TERATOGENS/ *TETRACHLORODIBENZODIOXIN, toxicity

Hay A: Phenoxy herbicides, trichlorophenols, and soft-tissue sarcomas [letter] Lancet 1982 May 29; 1(8283):1240
*DIOXINS, poisoning/ *HERBICIDES, poisoning/ HUMAN/ *SARCOMA, chemically induced/ *SOFT TISSUE NEOPLASMS, chemically induced/ *TETRACHLORODIBENZODIOXIN, poisoning

Hay A: Chlorinated dioxins and the environment [news] Nature 1981 Jan 29;289(5796):351-2
ANIMAL/ BIOTRANSFORMATION/ *DIOXINS, toxicity/ *ENVIRONMENTAL POLLUTANTS, toxicity/ HUMAN/ *SOIL MICROBIOLOGY/ *TERATOGENS/ TETRACHLORODIBENZODIOXIN, metabolism/ *TETRACHLORODIBENZODIOXIN, toxicity

Helder T: Effects of 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) on early life stages of rainbow trout (Salmo gairdneri, Richardson). Toxicology 1981;19(2):101-12
ANIMAL/ CELLULAR INCLUSIONS/ *DIOXINS, toxicity/ LIVER, pathology/ OVUM, drug effects/ PANCREAS, pathology/ *SALMONIDAE, growth & development/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, toxicity/ *TROUT, growth & development

Henck JM, New MA, Kociba RJ, et al: 2,3,7,8-tetrachlorodibenzo-p-dioxin: acute oral toxicity in hamsters. Toxicol Appl Pharmacol 1981 Jun 30; 59(2):405-7
ANIMAL/ BODY WEIGHT, drug effects/ *DIOXINS, toxicity/ HAMSTERS/ LETHAL DOSE 50/ MALE/ MESOCRICETUS/ *TETRACHLORODIBENZODIOXIN, toxicity

Hess P, Ambauer J, Hollander H: The possible formation of tetrachlorodibenzo-p-dioxines in the production of chloranil. Ecotoxicol Environ Safety 1982 Aug; 6(4):336-46
ANIMAL/ CHLORANIL, analysis/ *CHLORANIL, chemical synthesis/ CHLORANIL, toxicity/ CHLOROPHENOLS, analysis/ CHLOROPHENOLS, chemical synthesis/ CHLOROPHENOLS, toxicity/ *DIOXINS, chemical synthesis/ FEMALE/ LETHAL DOSE 50/ MASS FRAGMENTOGRAPHY/ *QUINONES, chemical synthesis/ RATS/ RATS, INBRED STRAINS/ TETRACHLORODIBENZODIOXIN, analogs & derivatives/ TETRACHLORODIBENZODIOXIN, analysis/ *TETRACHLORODIBENZODIOXIN, chemical synthesis

Hinsdill RD, Couch DL, Speirs RS: Immunosuppression in mice induced by dioxin (TCDD) in feed. J Environ Pathol Toxicol 1980 Sep;4(2-3):401-25
ANIMAL/ ANTIBODIES, analysis/ BLOOD PROTEINS, analysis/ *DIOXINS, toxicity/ FEMALE/ HEMAGGLUTINATION, drug effects/ *IMMUNOSUPPRESSIVE AGENTS/ MICE/ SALMONELLA TYPHIMURIUM, immunology/ SUPPORT, NON-U.S. GOV'T/ SUPPORT, U.S. GOV'T, P.H.S./ TETANUS TOXOID, immunology/ *TETRACHLORODIBENZODIOXIN, toxicity

Holden C: Reviewers pan Agent Orange study plan [news] Science 1981 Dec 4;214(4525):1107
*DIOXINS, adverse effects/ HUMAN/ MILITARY MEDICINE/ *OCCUPATIONAL

DISEASES, chemically induced/ *TETRACHLORODIBENZODIOXIN, adverse effects/ UNITED STATES/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Hervath EP Jr: The Agent Orange controversy—physician's dilemma. Wis Med J 1981 Mar; 80(3):16-8
ABORTION, etiology/ ANIMAL/ *DIAGNOSIS/ *DIOXINS, adverse effects/ FEMALE/ HUMAN/ LIVER DISEASES, diagnosis/ LIVER DISEASES, etiology/ LIVER NEOPLASMS, diagnosis/ LIVER NEOPLASMS, etiology/ MALE/ MICE/ *PHYSICIANS, FAMILY/ PHYSICIANS, FAMILY, psychology/ RATS/ SARCOMA, diagnosis/ SARCOMA, etiology

Huff JE, Moore JA, Saracci R, et al: Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. Environ Health Perspect 1980 Jun; 36:221-40 (135 ref.)
ABNORMALITIES, DRUG-INDUCED, etiology/ ACCIDENTS, OCCUPATIONAL/ ACNE, chemically induced/ ANIMAL/ ANTHROPOIDEA/ *BENZOFURANS, poisoning/ CHICKENS/ *DIOXINS, poisoning/ FEMALE/ GUINEA PIGS/ HUMAN/ LIVER DISEASES, chemically induced/ MALE/ MICE/ OCCUPATIONAL DISEASES, chemically induced/ RATS/ REVIEW/ STRUCTURE-ACTIVITY RELATIONSHIP/ SUPPORT, NON-U.S. GOV'T/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, poisoning

I

Ideo G, Bellati G, Bellobuono A, et al: Increased urinary D-glucaric acid excretion by children living in an area polluted with tetrachlorodibenzoparadioxin (TCDD). Clin Chim Acta 1982 Apr 23;120(3):273-83
CHILD/ *DIOXINS, toxicity/ ENVIRONMENTAL EXPOSURE/ FEMALE/ *GLUCARIC ACID, urine/ HUMAN/ ITALY/ MALE/ MICROSOMES, LIVER, drug effects/ *MICROSOMES, LIVER, enzymology/ PROSPECTIVE STUDIES/ RETROSPECTIVE STUDIES/ SKIN DISEASES, chemically induced/ *SUGAR ACIDS, urine/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, toxicity

J

Jensen DJ, Hummel RA: Secretion of TCDD in milk and cream following the feeding of TCDD to lactating dairy cows. Bull Environ Contam Toxicol 1982 Oct; 29(4):440-6
ANIMAL FEED/ ANIMAL/ CATTLE/ *DAIRY PRODUCTS/ DIET/ *DIOXINS, metabolism/ FEMALE/ LACTATION/ *MILK, metabolism/ TETRACHLORODIBENZODIOXIN, analysis/ *TETRACHLORODIBENZODIOXIN, metabolism/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, metabolism

Jensen DJ, Getzendaner ME, Hummel RA, et al: Residue studies for (2,4,5-trichlorophenoxy)acetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin in grass and rice. J Agric Food Chem 1983 Jan-Feb;31(1):118-22
*DIOXINS, analysis/ *GRASSES, analysis/ *PESTICIDE RESIDUES, analysis/ *RICE, analysis/ *TETRACHLORODIBENZODIOXIN, analysis/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, analysis

Jones KG, Cole FM, Sweeney GD: The role of iron in the toxicity of 2,3,7,8-tetrachlorodibenzo-(p)-dioxin (TCDD). Toxicol Appl Pharmacol 1981 Oct;61(1):74-88
ANIMAL/ COMPARATIVE STUDY/ *DIOXINS, toxicity/ IRON, deficiency/ *IRON, pharmacodynamics/ *LIVER, drug effects/ LIVER, pathology/ MALE/ MICE/ MICE, INBRED C57BL/ MICE, NUDE/ PORPHYRIA, chemically induced/ *PORPHYRIA, prevention & control/ SKIN, drug effects/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, toxicity/ THYMUS GLAND, drug effects/ TIME FACTORS

K

Kellogg ST, Chatterjee DK, Chakrabarty AM: Plasmid-assisted molecular breeding: new technique for enhanced biodegradation of persistent toxic chemicals. Science 1981 Dec 4;214(4525):1133-5
*BACTERIA, genetics/ BACTERIA, metabolism/ BIOTRANSFORMATION/ CELL DIVISION/ KINETICS/ NUCLEIC ACID HYBRIDIZATION/ *PLASMIDS/ SUPPORT, NON-U.S. GOV'T/ SUPPORT, U.S. GOV'T, NON-P.H.S./ *2,4,5-TRICHLOROPHENOXYACETIC ACID, metabolism

Kociba RJ, Schwetz BA: Toxicity of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD). Drug Metab Rev 1982;13(3):387-406 (69 ref.)
ACNE, chemically induced/ ACUTE DISEASE/ ANIMAL/ CARCINOGENS/ CHRONIC DISEASE/ *DIOXINS, toxicity/ DISEASE MODELS, ANIMAL/ ENZYME INDUCTION, drug effects/ HUMAN/ IMMUNITY, drug effects/ MICE/ MUTAGENS/ REVIEW/ *TETRACHLORODIBENZODIOXIN, toxicity

Kolmodin-Hedman B, Erne K: Estimation of occupational exposure to phenoxy acids (2,4-D and 2,4,5-T). Arch Toxicol [Suppl] 1980;4:318-21
*AIR POLLUTANTS, analysis/ *AIR POLLUTANTS, OCCUPATIONAL, analysis/ HUMAN/ *2,4-DICHLOROPHENOXYACETIC ACID, analysis/ 2,4-DICHLOROPHENOXYACETIC ACID, metabolism/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, analysis/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, metabolism

L

Lacey P, Lacey VA: Agent orange: government responsibility for the military use of phenoxy herbicides. J Leg Med (Chicago) 1982 Mar;3(1):137-78
CHEMICAL WARFARE AGENTS/ *DIOXINS, adverse effects/ *ETHICS/ HUMAN/ *LEGISLATION/ MILITARY SCIENCE/ *TETRACHLORODIBENZODIOXIN, adverse effects/ UNITED STATES/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Lamb JC 4th, Moore JA, Marks TA, et al: Development and viability of offspring of male mice treated with chlorinated phenoxy acids and 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Toxicol Environ Health 1981 Nov-Dec;8(5-6):835-44
ABNORMALITIES, DRUG-INDUCED/ ANIMAL/ *DIOXINS, toxicity/ FEMALE/ *FETUS, drug effects/ MALE/ MICE/ MICE, INBRED C57BL/ PREGNANCY/ SPERMATOZOA, drug effects/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, toxicity/ *2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

Lamb JC 4th, Marks TA, Gladen BC, et al: Male fertility, sister chromatid exchange, and germ cell toxicity following exposure to mixtures of chlorinated phenoxy acids containing 2,3,7,8-tetrachlorodibenzo-p-dioxin.

J Toxicol Environ Health 1981 Nov-Dec;8(5-6):825-34
ANIMAL/ *CROSSING OVER (GENETICS), drug effects/ *DIOXINS, toxicity/ DOSE-RESPONSE RELATIONSHIP, DRUG/ *FERTILITY, drug effects/ MALE/ MICE/ MICE, INBRED C57BL/ *SISTER CHROMATID EXCHANGE, drug effects/ *SPERMATOZOA, drug effects/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, toxicity/ *2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

Lamb JC 4th, Marks TA, McConnell EE, et al: Toxicity of chlorinated phenoxy acids in combination with 2,3,7,8-tetrachlorodibenzo-p-dioxin in C57BL/6 male mice. J Toxicol Environ Health 1981 Nov-Dec; 8(5-6):815-24
ANIMAL/ BODY WEIGHT, drug effects/ *DIOXINS, toxicity/ EATING, drug effects/ LIVER, drug effects/ MALE/ MICE/ MICE, INBRED C57BL/ ORGAN WEIGHT, drug effects/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, toxicity/ THYMUS GLAND, drug effects/ *2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

LaVecchia FA, Pashayan HM, Singer W: Agent Orange and birth defects [letter] N Engl J Med 1983 Mar 24; 308(12):719-20
*ABNORMALITIES, DRUG-INDUCED, etiology/ *DIOXINS, adverse effects/ FATHERS/ HUMAN/ INFANT, NEWBORN/ MALE/ *TETRACHLORODIBENZODIOXIN, adverse effects/ VETERANS/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Lee IP, Suzuki K: Induction of aryl hydrocarbon hydroxylase activity in the rat prostate glands by 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Pharmacol Exp Ther 1980 Dec;215(3):601-5
ANIMAL/ *ARYL HYDROCARBON HYDROXYLASES, biosynthesis/ CYCLOHEXIMIDE, pharmacodynamics/ CYTOCHROME P-450, analysis/ DACTINOMYCIN, pharmacodynamics/ *DIOXINS, toxicity/ ENZYME INDUCTION/ MALE/ PROSTATE, drug effects/ *PROSTATE, enzymology/ RATS/ *TETRACHLORODIBENZODIOXIN, toxicity/ TIME FACTORS

M

McDaniel HG: The agent orange controversy [letter] Ala J Med Sci 1980 Jul-Oct;17(3-4):256-7
ABNORMALITIES, DRUG-INDUCED, etiology/ *DEFOLIANTS, CHEMICAL, adverse effects/ DIOXINS, adverse effects/ *HERBICIDES, adverse effects/ HUMAN/ NEOPLASMS, chemically induced/ 2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

McNulty WP, Pomerantz I, Farrell T: Chronic toxicity of 2,3,7,8-tetrachlorodibenzofuran for rhesus macaques. Food Cosmet Toxicol 1981 Feb;19(1):57-65
ANIMAL/ *BENZOFURANS, toxicity/ *ENVIRONMENTAL POLLUTANTS, toxicity/ GASTRIC MUCOSA, drug effects/ MACACA MULATTA/ MALE/ POLYCHLOROBIPHENYL COMPOUNDS, toxicity/ SEBACEOUS GLANDS, drug effects/ SUPPORT, U.S. GOV'T, P.H.S./ TETRACHLORODIBENZODIOXIN, toxicity/ THYMUS GLAND, drug effects

Masuda L, Coccia P, Croci T: Persistent tissue levels of TCDD in the mouse and their reduction as related to prevention of toxicity. Drug Metab Rev 1982; 13(3):423-46
ANIMAL/ CHARCOAL/ CHOLIC ACIDS, administration & dosage/ *DIOXINS, metabolism/ DISEASE MODELS, ANIMAL/ MICE/ MICE, INBRED C3H/ MICE, INBRED C57BL/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, metabolism/ TETRACHLORODIBENZODIOXIN, toxicity/ TISSUE DISTRIBUTION

Matsumura F: Biochemical aspects of action mechanisms of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related chemicals in animals. Pharmacol Ther 1982; 19(2):195-209 (84 ref.)
ANIMAL/ ARYL HYDROCARBON HYDROXYLASES, metabolism/ CELL MEMBRANE, drug effects/ CELL MEMBRANE, metabolism/ *DIOXINS, pharmacodynamics/ ENZYME INDUCTION, drug effects/ REVIEW/ SUPPORT, NON-U.S. GOV'T/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, pharmacodynamics/ TETRACHLORODIBENZODIOXIN, poisoning

Mattison DR, Shiromizu K, Nightingale MS: Oocyte destruction by polycyclic aromatic hydrocarbons. Prog Clin Biol Res 1983;117:191-202 (46 ref.)
ANIMAL/ ARYL HYDROCARBON HYDROXYLASES, metabolism/ BENZOPYRENES, toxicity/ BIOTRANSFORMATION/ CHROMATOGRAPHY, HIGH PRESSURE LIQUID/ FEMALE/ HUMAN/ MICE/ *OOCYTES, drug effects/ OVARIAN DISEASES, chemically induced/ OVARY, metabolism/ *OVUM, drug effects/ *POLYCYCLIC HYDROCARBONS, toxicity/ RATS/ REVIEW/ SPECIES SPECIFICITY/ TETRACHLORODIBENZODIOXIN, toxicity

May G: Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. Br J Ind Med 1982 May; 39(2):128-35
ABORTION, chemically induced/ *ACCIDENTS, OCCUPATIONAL/ ACNE, chemically induced/ ADULT/ ALKALINE PHOSPHATASE, analysis/ BILIRUBIN, blood/ *CHEMICAL INDUSTRY/ CHLOROPHENOLS, chemical synthesis/ CHOLESTEROL, analysis/ *DIOXINS, poisoning/ ENGLAND/ FEMALE/ GLUCARIC ACID, urine/ GLUTAMYL TRANSPEPTIDASE, analysis/ HUMAN/ INFANT, NEWBORN/ MALE/ OCCUPATIONAL DISEASES, chemically induced/ PREGNANCY/ *TETRACHLORODIBENZODIOXIN, poisoning/ TIME FACTORS/ TRIGLYCERIDES, analysis

Moses M, Selikoff IJ: Soft tissue sarcomas, phenoxy herbicides, and chlorinated phenols [letter] Lancet 1981 Jun 20;1(8234):1370
CASE REPORT/ *DIOXINS, poisoning/ HUMAN/ MALE/ MIDDLE AGE/ *NEURILEMMOMA, chemically induced/ *OCCUPATIONAL DISEASES, chemically induced/ *RETROPERITONEAL NEOPLASMS, chemically induced/ *TETRACHLORODIBENZODIOXIN, poisoning/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, poisoning

Mulcahy MT: Chromosome aberrations and 'agent orange' [letter] Med J Aust 1980 Nov 15;2(10):573-4
*CHROMOSOME ABERRATIONS/ *MILITARY MEDICINE/ TETRACHLORODIBENZODIOXIN, adverse effects/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

N

Nau H, Bass R: Transfer of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to the mouse embryo and fetus. Toxicology 1981;20(4):299-308
ANIMAL/ CLEFT PALATE, chemically induced/ *DIOXINS, metabolism/ *EMBRYO, metabolism/ FEMALE/ *FETUS, metabolism/ *MATERNAL-FETAL EXCHANGE/ MICE/ PREGNANCY/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, metabolism/ TETRACHLORODIBENZODIOXIN, toxicity

Neal RA, Olson JR, Gasiewicz TA, et al: The toxicokinetics of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin in mammalian systems. Drug Metab Rev 1982;13(3):355-85 (57 ref.)
ABSORPTION/ ADMINISTRATION, ORAL/ AIR POLLUTANTS, ENVIRONMENTAL, toxicity/ ANIMAL/ CHEMISTRY/ CYTOCHROME P-450, metabolism/ *DIOXINS, toxicity/ DOSE-RESPONSE RELATIONSHIP, DRUG/ FEMALE/ HUMAN/ INJECTIONS, INTRAPERITONEAL/ INTESTINAL ABSORPTION/ KINETICS/ MALE/ MICROSOMES, LIVER, metabolism/ PREGNANCY/ REVIEW/ SKIN ABSORPTION/ SUPPORT, U.S. GOV'T, NON-P.H.S./ TETRACHLORODIBENZODIOXIN, metabolism/ *TETRACHLORODIBENZODIOXIN, toxicity/ TISSUE DISTRIBUTION

O

Olson JR, Holscher MA, Neal RA: Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the golden Syrian hamster. Toxicol Appl Pharmacol 1980 Aug;55(1):67-78
ANIMAL/ BLOOD CHEMICAL ANALYSIS/ BODY WEIGHT/ *DIOXINS, toxicity/ FEMALE/ HAMSTERS/ INTESTINES, pathology/ LETHAL DOSE 50/ LIVER, ultrastructure/ MALE/ MESOCRICETUS/ ORGAN WEIGHT/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, toxicity

Orris P: Unjustified conclusion? [letter] JOM 1981 Jan; 23(1):7-8
*DIOXINS, poisoning/ HUMAN/ *NEOPLASMS, chemically induced/ OCCUPATIONAL DISEASES, chemically induced/ *TETRACHLORODIBENZODIOXIN, poisoning

P

Passi S, Nazzaro-Porro M, Boniforti L, et al: Analysis of lipids and dioxin in chloracne due to tetrachloro-2,3,7,8-p-dibenzodioxin. Br J Dermatol 1981 Aug;105(2):137-43
*ACNE, chemically induced/ ACNE, metabolism/ CHILD, PRESCHOOL/ CHROMATOGRAPHY, GAS/ *DIOXINS, analysis/ FEMALE/ HUMAN/ *LIPIDS, analysis/ MALE/ TETRACHLORODIBENZODIOXIN, adverse effects

Pazderova-Vejlupkova J, Lukas E, Nincova M, et al: The development and prognosis of chronic intoxication by tetrachlordibenzo-p-dioxin in men.
Arch Environ Health 1981 Jan-Feb;36(1):5-11
ADULT/ CHRONIC DISEASE/ *DIOXINS, poisoning/ HUMAN/ LIPIDS, metabolism/ LIVER DISEASES, chemically induced/ MALE/ MIDDLE AGE/ NERVOUS SYSTEM DISEASES, chemically induced/ OCCUPATIONAL DISEASES, chemically induced/ PORPHYRINS, metabolism/ PROGNOSIS/ SKIN DISEASES, chemically induced/ *TETRACHLORODIBENZODIOXIN, poisoning

Poland A, Knutson JC: 2,3,7,8-tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons: examination of the mechanism of toxicity.
Annu Rev Pharmacol Toxicol 1982;22:517-54 (221 ref.)
ANIMAL/ ARYL HYDROCARBON HYDROXYLASES, biosynthesis/ ARYL HYDROCARBON HYDROXYLASES, genetics/ CARCINOGENS/ COMPARATIVE STUDY/ *DIOXINS, toxicity/ FEMALE/ *HYDROCARBONS, HALOGENATED, toxicity/ MALE/ MICE/ MODELS, BIOLOGICAL/ NEOPLASMS, EXPERIMENTAL, chemically induced/ PREGNANCY/ RATS/ RECEPTORS, DRUG, drug effects/ REVIEW/ SUPPORT, U.S. GOV'T, P.H.S./ TETRACHLORODIBENZODIOXIN, analogs & derivatives/ TETRACHLORODIBENZODIOXIN, metabolism/ *TETRACHLORODIBENZODIOXIN, toxicity

Potter CL, Sipes IG, Russell DH: Hypothyroxinemia and hypothermia in rats in response to 2,3,7,8-tetrachlorodibenzo-p-dioxin administration.
Toxicol Appl Pharmacol 1983 Jun 15;69(1):89-95
ANIMAL/ BLOOD GLUCOSE, metabolism/ *DIOXINS, toxicity/ GLUCAGON, blood/ *HYPOTHERMIA, chemically induced/ INSULIN, metabolism/ MALE/ RATS/ RATS, INBRED STRAINS/ SOMATOTROPIN RELEASE INHIBITING HORMONE, metabolism/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, toxicity/ *THYROXINE, blood

Pulvel SM, Sakamoto M, Ertl DC, et al: Hairless mice as models for chloracne: a study of cutaneous changes induced by topical application of established chloracnegens. Toxicol Appl Pharmacol 1982 Jul; 64(3):492-503
*ACNE, chemically induced/ ANIMAL/ ARYL HYDROCARBON HYDROXYLASES, metabolism/ DISEASE MODELS, ANIMAL/ ENZYME INDUCTION, drug effects/ *HYDROCARBONS, CHLORINATED, toxicity/ MICE/ MICE, INBRED HRS/ NAPHTHALENES, toxicity/ POLYCHLOROBIPHENYL COMPOUNDS, toxicity/ SUPPORT, U.S. GOV'T, NON-P.H.S./ SUPPORT, U.S. GOV'T, P.H.S./ TETRACHLORODIBENZODIOXIN, toxicity

R

Remotti G, Sesneria M, Bianco V, et al: Primi risultati sull'abortività spontanea nel periodo Luglio 1976 - Giugno 1978 nell'area di Seveso inquinata da TCDD. Ann Ostet Ginecol Med Perinat 1982 Jul-Aug; 103(4):249-53 (Eng. Abstr.) (Ita)
ABORTION, chemically induced/ *ABORTION, occurrence/ *AIR POLLUTANTS, toxicity/ *AIR POLLUTANTS, ENVIRONMENTAL, toxicity/ *DIOXINS, toxicity/ ENGLISH ABSTRACT/ FEMALE/ HUMAN/ ITALY/ PREGNANCY/ *TETRACHLORODIBENZODIOXIN, toxicity

Remotti G, De Virgilis G, Bianco V, et al: The morphology of early trophoblast after dioxin poisoning in the Seveso area. Placenta 1981 Jan-Mar;2(1):53-62
*ABORTION, THERAPEUTIC/ CELLULAR INCLUSIONS, ultrastructure/ COMPARATIVE STUDY/ *DIOXINS, poisoning/ ELECTRON PROBE MICROANALYSIS/ ENVIRONMENTAL POLLUTION/ FEMALE/ HUMAN/ ITALY/ MICROSCOPY, ELECTRON/ PLACENTA, ultrastructure/ PREGNANCY TRIMESTER, FIRST/ PREGNANCY/ *TETRACHLORODIBENZODIOXIN, poisoning/ TROPHOBLAST, drug effects/ *TROPHOBLAST, ultrastructure

Riihimäki V, Asp S, Hernberg S: Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland: first report of an ongoing prospective cohort study. Scand J Work Environ Health 1982 Mar; 8(1):37-42
ADULT/ FINLAND/ HUMAN/ MALE/

MIDDLE AGE/ *MORTALITY/ NEOPLASMS, chemically induced/ *NEOPLASMS, mortality/ OCCUPATIONAL DISEASES, chemically induced/ *OCCUPATIONAL DISEASES, mortality/ *OCCUPATIONS/ PROSPECTIVE STUDIES/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Rinder DF, Fleeker JR: A radioimmunoassay to screen for 2,4,-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid in surface water. Bull Environ Contam Toxicol 1981 Mar;26(3):375-80
ANIMAL/ FRESH WATER, analysis/ RABBITS, immunology/ RADIOIMMUNOASSAY, methods/ STAPHYLOCOCCAL PROTEIN A, immunology/ SUPPORT, NON-U.S. GOV'T/ *WATER POLLUTANTS, analysis/ *WATER POLLUTANTS, CHEMICAL, analysis/ *2,4-DICHLOROPHENOXYACETIC ACID, analysis/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, analysis

Rogers AM, Andersen ME, Back KC: Mutagenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin and perfluoro-n-decanoic acid in L5178Y mouse-lymphoma cells. Mutat Res 1982 Dec;105(6):445-9
ANIMAL/ CELL SURVIVAL, drug effects/ *DECANOIC ACIDS, pharmacodynamics/ DECANOIC ACIDS, toxicity/ *DIOXINS, pharmacodynamics/ *LEUKEMIA L5178, physiopathology/ *LEUKEMIA, EXPERIMENTAL, physiopathology/ MICE/ MUTAGENICITY TESTS/ *MUTAGENS/ *MUTATION/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, pharmacodynamics/ TETRACHLORODIBENZODIOXIN, toxicity

S

Safe S, Robertson LW, Safe L, et al: Halogenated biphenyls: molecular toxicology. Can J Physiol Pharmacol 1982 Jul; 60(7):1057-64
ANIMAL/ ARYL HYDROCARBON HYDROXYLASES, biosynthesis/ ENZYME INDUCTION/ HUMAN/ MICE/ *POLYCHLOROBIPHENYL COMPOUNDS, adverse effects/ POLYCHLOROBIPHENYL COMPOUNDS, metabolism/ RATS/ RECEPTORS, DRUG, metabolism/ STRUCTURE-ACTIVITY RELATIONSHIP/ SUPPORT, NON-U.S. GOV'T/ SUPPORT, U.S. GOV'T, P.H.S./ TETRACHLORODIBENZODIOXIN, analogs & derivatives/ TETRACHLORODIBENZODIOXIN, adverse effects/ TETRACHLORODIBENZODIOXIN, metabolism

Santi L, Boeri R, Remotti G, et al: Five years after Seveso [letter] Lancet 1982 Feb 6;1(8267):343-4
*ABNORMALITIES, DRUG-INDUCED, etiology/ ACCIDENTS, OCCUPATIONAL/ CHILD/ *DIOXINS, poisoning/ FEMALE/ HUMAN/ INFANT, NEWBORN/ ITALY/ MALE/ PREGNANCY/ *TETRACHLORODIBENZODIOXIN, poisoning

Sarma PR, Jacobs J: Thoracic soft-tissue sarcoma in Vietnam veterans exposed to Agent Orange [letter] N Engl J Med 1982 May 6;306(18):1109
ADULT/ CASE REPORT/ *DEFOLIANTS, CHEMICAL, poisoning/ *DIOXINS, poisoning/ *HERBICIDES, poisoning/ HUMAN/ MALE/ MIDDLE AGE/ *MILITARY MEDICINE/ *SARCOMA, chemically induced/ *SOFT TISSUE NEOPLASMS, chemically induced/ *TETRACHLORODIBENZODIOXIN, poisoning/ *THORACIC NEOPLASMS, chemically induced/ UNITED STATES/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, poisoning/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, poisoning

Seńczuk W, Pogorzelska H: Budowa chemiczna a toksykodynamiczne właściwości pochodnych kwasów fenoksykarboksylowych. Cz. III. Przebieg wchłaniania do krwi oraz pomiary wydalania z moczem pochodnych kwasów fenoksyoctowego i fenoksypropionowego. Rocz Panstw Zakl Hig 1981;32(5-6):419-26 (Eng. Abstr.) (Pol)
ABSORPTION/ ANIMAL/ CHEMISTRY/ ENGLISH ABSTRACT/ *GLYCOLATES, metabolism/ MALE/ MCPA, analogs & derivatives/ MCPA, metabolism/ MCPA, toxicity/ *PHENOXYACETATES, metabolism/ PHENOXYACETATES, toxicity/ *PROPIONATES, metabolism/ PROPIONATES, toxicity/ RATS/ STRUCTURE-ACTIVITY RELATIONSHIP/ TIME FACTORS/ 2,4-DICHLOROPHENOXYACETIC ACID, metabolism/ 2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, metabolism/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

Singer R, Moses M, Valciukas J, et al: Nerve conduction velocity studies of workers employed in the manufacture of phenoxy herbicides. Environ Res 1982 Dec; 29(2):297-311
ADULT/ AGE FACTORS/ ALCOHOL DRINKING/ ENVIRONMENTAL EXPOSURE/ HUMAN/ MEDIAN NERVE, physiology/ *NEURAL CONDUCTION, drug effects/ *OCCUPATIONAL MEDICINE/ SUPPORT, U.S. GOV'T, P.H.S./ SURAL NERVE, physiology/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Smith AG, Francis JE, Kay SJ, et al: Hepatic toxicity and uroporphyrinogen decarboxylase activity following a single dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin to mice. Biochem Pharmacol 1981 Oct;30(20):2825-30
ANIMAL/ *CARBOXY-LYASES, antagonists & inhibitors/ *DIOXINS, toxicity/ DOSE-RESPONSE RELATIONSHIP, DRUG/ FEMALE/ KINETICS/ *LIVER, drug effects/ LIVER, enzymology/ MALE/ MICE/ MICE, INBRED C57BL/ MICE, INBRED DBA/ *PORPHYRINS, metabolism/ SEX FACTORS/ *TETRACHLORODIBENZODIOXIN, toxicity/ *UROPORPHYRINOGEN DECARBOXYLASE, antagonists & inhibitors

Stanley T: Vietnam veterans [letter] Aust NZ J Psychiatry 1982 Sep;16(3):196-7
*DIOXINS, adverse effects/ HUMAN/ MALE/ *ORGANIC MENTAL DISORDERS, SUBSTANCE-INDUCED, psychology/ *TETRACHLORODIBENZODIOXIN, adverse effects/ *VETERANS, psychology/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects

Stevens KM: Agent Orange toxicity: a quantitative perspective. Hum Toxicol 1981;1(1):31-9
ABNORMALITIES, DRUG-INDUCED, etiology/ ANIMAL/ BENZOFURANS, toxicity/ *DIOXINS, toxicity/ *ENVIRONMENTAL POLLUTANTS, toxicity/ FEMALE/ FOOD CONTAMINATION/ *HERBICIDES, toxicity/ HUMAN/ MALE/ PREGNANCY/ SOIL POLLUTANTS, toxicity/ *TETRACHLORODIBENZODIOXIN, toxicity/ VIETNAM/ *2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

Stohs SJ, Hassan MQ, Murray WJ: Lipid peroxidation as a possible cause of TCDD toxicity. Biochem Biophys Res Commun 1983 Mar 29; 111(3):854-9

ANIMAL/ *DIOXINS, toxicity/ FEMALE/ *LIPID PEROXIDES, metabolism/ *MICROSOMES, LIVER, drug effects/ MICROSOMES, LIVER, metabolism/ OXIDATION-REDUCTION/ RATS/ RATS, INBRED STRAINS/ *TETRACHLORODIBENZODIOXIN, toxicity

Strik JJ: Detection of chemical-induced porphyria in man. Possibilities in biomonitoring of exposure to chemicals. Dev Toxicol Environ Sci 1980;8:537-43
*AIR POLLUTANTS, toxicity/ *AIR POLLUTANTS, ENVIRONMENTAL, toxicity/ CHILD/ CHILD, PRESCHOOL/ COMPARATIVE STUDY/ ENVIRONMENTAL EXPOSURE/ FEMALE/ HUMAN/ *LIVER DISEASES, chemically induced/ MALE/ *PORPHYRIA, chemically induced/ PORPHYRINS, urine/ TETRACHLORODIBENZODIOXIN, toxicity

Strik JJ, de Wit JM: Health aspects of rabbits in a low-TCDD contaminated area. Int J Biochem 1980; 12(5-6):999-1001
ANIMAL/ BODY WEIGHT, drug effects/ CREATININE, metabolism/ CYTOCHROMES, metabolism/ *DIOXINS, adverse effects/ FEMALE/ GLUCARIC ACID, metabolism/ KIDNEY, drug effects/ *KIDNEY, pathology/ LIVER GLYCOGEN, metabolism/ LIVER, drug effects/ LIVER, metabolism/ *LIVER, pathology/ MALE/ ORGAN WEIGHT, drug effects/ PORPHYRINS, metabolism/ RABBITS/ *SOIL POLLUTANTS, adverse effects/ *TETRACHLORODIBENZODIOXIN, adverse effects

Strik JJ, Janssen MM, Colombi AM: The incidence of chronic hepatic porphyria in an Italian family. Int J Biochem 1980;12(5-6):879-81
CHRONIC DISEASE/ FEMALE/ HUMAN/ ITALY/ LIVER DISEASES, chemically induced/ *LIVER DISEASES, familial & genetic/ MALE/ PEDIGREE/ PORPHYRIA, chemically induced/ *PORPHYRIA, familial & genetic/ SKIN DISEASES, chemically induced/ *SKIN DISEASES, familial & genetic/ TETRACHLORODIBENZODIOXIN, adverse effects

Swift LL, Gasiewicz TA, Dunn GD, et al: Characterization of the hyperlipidemia in guinea pigs induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Appl Pharmacol 1981 Jul;59(3):489-99
ADIPOSE TISSUE, metabolism/ ANIMAL/ *DIOXINS, toxicity/ FATTY ACIDS, metabolism/ GUINEA PIGS/ *HYPERLIPIDEMIA, chemically induced/ LIPIDS, blood/ LIPOPROTEINS, blood/ MALE/ SUPPORT, U.S. GOV'T, P.H.S./ *TETRACHLORODIBENZODIOXIN, toxicity

T

Tedeschi LG: Dioxin. A case in point. Am J Forensic Med Pathol 1980 Jun;1(2):145-8
ABNORMALITIES, DRUG-INDUCED/ ABORTION, chemically induced/ ANIMAL/ CATS/ *DEFOLIANTS, CHEMICAL, adverse effects/ *DIOXINS, adverse effects/ DOGS/ FEMALE/ *HERBICIDES, adverse effects/ HORSE DISEASES, chemically induced/ HORSES/ HUMAN/ INFANT, NEWBORN/ LIVER DISEASES, chemically induced/ MALE/ MENTAL DISORDERS, chemically induced/ MICE/ MISSOURI/ PREGNANCY/ RATS/ *SKIN DISEASES, chemically induced/ UNITED STATES/ VIETNAM

Terracini B: Considerations on the epidemiology of the Seveso accident [letter] Toxicol Eur Res 1981 Sep; 3(5):262-3
ACCIDENTS/ CHEMICAL INDUSTRY/ *DIOXINS, poisoning/ HUMAN/ ITALY/ *TETRACHLORODIBENZODIOXIN, poisoning

Thiess AM, Frentzel-Beyme R, Link R: Mortality study of persons exposed to dioxin in a trichlorophenol-process accident that occurred in the BASF AG on November 17, 1953. Am J Ind Med 1982;3(2):179-89
*ACCIDENTS, OCCUPATIONAL/ ADOLESCENCE/ ADULT/ AGED/ COLONIC NEOPLASMS, chemically induced/ *DIOXINS, adverse effects/ FOLLOW-UP STUDIES/ HUMAN/ LUNG NEOPLASMS, chemically induced/ MALE/ MIDDLE AGE/ *NEOPLASMS, chemically induced/ NEOPLASMS, mortality/ *OCCUPATIONAL DERMATITIS, chemically induced/ STOMACH NEOPLASMS, chemically induced/ *TETRACHLORODIBENZODIOXIN, adverse effects

Thomas JA: Target organ toxicity: endocrine system. Introductory remarks: the testis. Environ Health Perspect 1981 Apr;38:3-4
ANDROGENS, metabolism/ ANIMAL/ BIOTRANSFORMATION/ DDT, metabolism/ DDT, pharmacodynamics/ *GENITALIA, MALE, metabolism/ HUMAN/ MICE/ ORGAN SPECIFICITY/ PROSTATE, drug effects/ SEVIN, metabolism/ *TESTIS, metabolism/ TETRACHLORODIBENZODIOXIN, metabolism/ 2,4-DICHLOROPHENOXYACETIC ACID, metabolism/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, metabolism

Thunberg T, Ahlborg UG: Effects of dietary vitamin A (retinol) on the reduction of hepatic retinol storage caused by 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin. Dev Toxicol Environ Sci 1980;8:521-4
ANIMAL/ *DIOXINS, toxicity/ *LIVER, drug effects/ LIVER, metabolism/ MALE/ RATS/ RATS, INBRED STRAINS/ SUPPORT, NON-U.S. GOV'T/ TETRACHLORODIBENZODIOXIN, antagonists & inhibitors/ *TETRACHLORODIBENZODIOXIN, toxicity/ UDP GLUCURONOSYLTRANSFERASE, metabolism/ VITAMIN A, metabolism/ *VITAMIN A, pharmacodynamics

Tognoni G, Bonaccorsi A: Epidemiological problems with TCDD (a critical view). Drug Metab Rev 1982; 13(3):447-69
*ACCIDENTS, OCCUPATIONAL/ *DIOXINS, poisoning/ *ENVIRONMENTAL POLLUTANTS, poisoning/ EPIDEMIOLOGY/ HUMAN/ ITALY/ PUBLIC HEALTH/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, poisoning

Townsend DI: The use of dioxin isomer group ratios to identify sources and define background levels of dioxins in the environment. J Environ Sci Health [B] 1980; 15(5):571-609
*DIOXINS, analysis/ *ENVIRONMENTAL POLLUTANTS, analysis/ ISOMERISM/ KINETICS/ MATHEMATICS/ MODELS, THEORETICAL/ OXIDATION-REDUCTION/ STRUCTURE-ACTIVITY RELATIONSHIP/ TETRACHLORODIBENZODIOXIN, analysis

Townsend JC, Bodner KM, Van Peenen PF, et al: Survey of reproductive events of wives of employees exposed to chlorinated dioxins. Am J Epidemiol 1982 May; 115(5):695-713
ABNORMALITIES, DRUG-INDUCED/ ABORTION, chemically induced/ ADOLESCENCE/ ADULT/ COMPARATIVE STUDY/ *DIOXINS, poisoning/ ENVIRONMENTAL EXPOSURE/ FATHERS/ FEMALE/ FETAL DEATH, chemically induced/ HUMAN/ MALE/ MICHIGAN/ PREGNANCY/ QUESTIONNAIRES/ *REPRODUCTION, drug effects/ *TETRACHLORODIBENZODIOXIN, poisoning

Tuchmann-Duplessis H: The experimental approach to teratogenicity. Ecotoxicol Environ Safety 1980 Dec; 4(4):422-33
ANIMAL/ EMBRYO, drug effects/ ENVIRONMENTAL POLLUTANTS, toxicity/ FEMALE/ FETUS, drug effects/ PREGNANCY/ RESEARCH DESIGN/

SPECIES SPECIFICITY/ *TERATOGENS, toxicity/ TETRACHLORODIBENZODIOXIN, toxicity/ THALIDOMIDE, toxicity/ TOXICOLOGY

Turner JN, Collins DN: Liver morphology in guinea pigs administered either pyrolysis products of a polychlorinated biphenyl transformer fluid or 2,3,7,8-tetrachlorodibenzo-p-dioxin.
Toxicol Appl Pharmacol 1983 Mar 15;67(3):417-29
ANIMAL/ *DIOXINS, toxicity/ FEMALE/ GUINEA PIGS/ HEAT/ *LIVER, drug effects/ LIVER, pathology/ LIVER, ultrastructure/ MALE/ MICROSCOPY, ELECTRON/ *POLYCHLOROBIPHENYL COMPOUNDS, toxicity/ *TETRACHLORODIBENZODIOXIN, toxicity

V

van Logten MJ, Gupta BN, McConnell EE, et al: The influence of malnutrition on the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats.
Toxicology 1981;21(1):77-88
ANIMAL/ BODY WEIGHT/ CALORIC INTAKE/ DIET/ DIETARY PROTEINS, pharmacodynamics/ *DIOXINS, toxicity/ EATING/ FEMALE/ *NUTRITION DISORDERS, physiopathology/ ORGAN WEIGHT/ PROTEIN DEFICIENCY, physiopathology/ RATS/ RATS, INBRED F344/ *TETRACHLORODIBENZODIOXIN, toxicity

Vecchi A, Sironi M, Canegrati MA, et al: Immunosuppressive effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in strains of mice with different susceptibility to induction of aryl hydrocarbon hydroxylase. Toxicol Appl Pharmacol 1983 May;68(3):434-41
ANIMAL/ *ANTIBODY FORMATION, drug effects/ *ARYL HYDROCARBON HYDROXYLASES, biosynthesis/ CROSSES, GENETIC/ *DIOXINS, toxicity/ ENZYME INDUCTION, drug effects/ IMMUNOSUPPRESSION/ MALE/ MICE/ MICE, INBRED STRAINS/ SPECIES SPECIFICITY/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, toxicity

Van JG, Van Leeuwen FX, de Jong P: Acnegenic activity of 3-methylcholanthrene and benzo[a]pyrene, and a comparative study with 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rabbit and hairless mouse. Toxicology 1982;23(2-3):187-96
*ACNE, chemically induced/ ANIMAL/ *BENZOPYRENES, toxicity/ COMPARATIVE STUDY/ *DIOXINS, toxicity/ *METHYLCHOLANTHRENE, toxicity/ MICE/ MICE, INBRED HRS/ RABBITS/ SKIN, pathology/ *TETRACHLORODIBENZODIOXIN, toxicity

W

Weber H, Poiger H, Schlatter C: Fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin metabolites from dogs in rats. Xenobiotica 1982 Jun;12(6):353-7
ANIMAL/ BILE, metabolism/ *DIOXINS, urine/ DOGS/ FECES, analysis/ FEMALE/ RATS/ SPECIES SPECIFICITY/ TETRACHLORODIBENZODIOXIN, toxicity/ *TETRACHLORODIBENZODIOXIN, urine

Weber H, Poiger H, Schlatter C: Acute oral toxicity of TCDD-metabolites in male guinea pigs. Toxicol Lett 1982 Nov;14(1-2):117-22
ANIMAL/ BILE, metabolism/ BODY WEIGHT, drug effects/ *DIOXINS, toxicity/ GUINEA PIGS/ LIVER, metabolism/ MALE/ METABOLIC DETOXICATION, DRUG/ TETRACHLORODIBENZODIOXIN, metabolism/ *TETRACHLORODIBENZODIOXIN, toxicity

Y

Yang KH, Yoo BS, Choe SY: Effects of halogenated dibenzo-p-dioxins on plasma disappearance and biliary excretion of ouabain in rats. Toxicol Lett 1983 Feb; 15(2-3):259-64
ANIMAL/ *BILE, metabolism/ BODY WEIGHT, drug effects/ *DIOXINS, toxicity/ LIVER, drug effects/ MALE/ *OUABAIN, metabolism/ RATS/ RATS, INBRED STRAINS/ SUPPORT, NON-U.S. GOV'T/ TETRACHLORODIBENZODIOXIN, analogs & derivatives/ *TETRACHLORODIBENZODIOXIN, toxicity

Yang KH, Choi EJ, Choe SY: Cytotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin on primary cultures of adult rat hepatocytes.
Arch Environ Contam Toxicol 1983 Mar;12(2):183-8
ANIMAL/ CELLS, CULTURED/ *DIOXINS, toxicity/ ENZYME INDUCTION, drug effects/ *LIVER, drug effects/ LIVER, metabolism/ MALE/ RATS/ RATS, INBRED STRAINS/ SUPPORT, NON-U.S. GOV'T/ *TETRACHLORODIBENZODIOXIN, toxicity

ANONYMOUS

Am Fam Physician
Agent orange [editorial] Am Fam Physician 1982 Apr; 25(4):91-2
*DIOXINS, toxicity/ HUMAN/ *TETRACHLORODIBENZODIOXIN, toxicity/ *2,4-DICHLOROPHENOXYACETIC ACID, toxicity/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, toxicity

Am J Forensic Med Pathol
Agent Orange [letter] Am J Forensic Med Pathol 1983 Jun;4(2):190-2
ABORTION, etiology/ *DIOXINS, poisoning/ FEMALE/ HUMAN/ MALE/ MILITARY MEDICINE/ PREGNANCY/ *TETRACHLORODIBENZODIOXIN, poisoning/ VIETNAM/ *WAR/ *2,4-DICHLOROPHENOXYACETIC ACID, poisoning/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, poisoning

JAMA
Health effects of Agent Orange and dioxin contaminants. Council on scientific affairs. JAMA 1982 Oct 15; 248(15):1895-7
ACCIDENTS, OCCUPATIONAL/ ACNE, chemically induced/ AGRICULTURAL WORKERS' DISEASES, chemically induced/ AMERICAN MEDICAL ASSOCIATION/ ANIMAL/ *DEFOLIANTS, CHEMICAL, adverse effects/ DEFOLIANTS, CHEMICAL, classification/ *DIOXINS, adverse effects/ FEMALE/ *HERBICIDES, adverse effects/ HUMAN/ MALE/ PREGNANCY/ *TETRACHLORODIBENZODIOXIN, adverse effects/ TETRACHLORODIBENZODIOXIN, classification/ UNITED STATES/ VIETNAM/ WAR/ *2,4-DICHLOROPHENOXYACETIC ACID, adverse effects/ 2,4-DICHLOROPHENOXYACETIC ACID, classification/ *2,4,5-TRICHLOROPHENOXYACETIC ACID, adverse effects/ 2,4,5-TRICHLOROPHENOXYACETIC ACID, classification

Lancet
Seveso after five years [editorial] Lancet 1981 Oct 3;

2(8249):731-2
ACCIDENTS, OCCUPATIONAL/ *ACNE, chemically induced/ ACNE, history/ *DIOXINS, poisoning/ HISTORICAL ARTICLE/ HISTORY OF MEDICINE, 20TH CENT./ HUMAN/ ITALY/ *TETRACHLORODIBENZODIOXIN, poisoning

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BIRMINGHAM ACCIDENT HOSPITAL

SIR,—With regard to your report on the threat to the Birmingham Accident Hospital (March 19, p. 644) may I say that the Birmingham Accident Hospital is not a centre of excellence, it is a centre of adequate care seen against a background of appalling accident services throughout the rest of the country. The Accident Hospital developed concepts such as multidisciplinary teamwork, integrated rehabilitation, and continuity of care into a working system in the 1940s. Thirty years later many of us are still struggling with such concepts, though reports and inquiries state daily that these are basic requirements of any service in any discipline and that the lack of them is responsible for tragedies.

Specifically the Accident Hospital tackled the problems of casualty departments, the forgotten patient, separation of the severely ill from the walking wounded, multiple surgeons treating multiple injuries, the injured drunk, and real training for junior medical staff in a pragmatic, largely successful manner.

As for dispersal, the Accident Hospital has been dispersing its doctors for years; all have learned that these concepts and problems can be faced. But dispersal of the core of this working example of teamwork will be a tragedy, not simply for Birmingham, nor only for accident surgery but for those of us who are trying to make the integration of care more than a concept in whatever discipline.

South Lothian District,
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NORMAN VETTER

LONG-TERM EFFECTS OF DIOXIN EXPOSURE

SIR,—In July, 1976, a reactor on a chemical plant outside Milan exploded releasing a cloud of toxic fumes which settled over the town of Seveso. The fall-out contained 2, 3, 7, 8 tetrachlorodibenzo-para-dioxin (dioxin), one of the most toxic compounds known. Within days of the accident hundreds of small animals had died and many of the town's inhabitants had developed chloracne, one of the less serious manifestations of dioxin exposure.

Dioxin is both teratogenic and fetotoxic in animals.[1] The chemical also has a wide range of toxicity in man, including hepatic, renal, and neurological damage and even death.[2] The long-term effects of dioxin exposure are virtually unknown. In 1971 we treated a young patient with dioxin poisoning and her sister and mother who were also exposed to dioxin but to a lesser extent. After the Seveso catastrophe we were asked to follow-up our patient, and we report our findings in the hope that they will interest the physicians and health authorities responsible for the care of the population of Seveso.

A 6-year-old girl presented in August, 1971, with a brief history of nosebleeds, headaches, diarrhœa, blood in her urine, and painful micturition. Her past medical record was unremarkable. She lived on a horse-breeding farm in eastern Missouri. In May, 1971, an indoor arena on the farm had been sprayed with waste oil as a dust-control measure. Shortly afterwards hundreds of birds and several dogs and cats having access to the arena died. Fourteen horses manifested a variety of symptoms including weight loss, staggering gait, polydipsia, oral ulcerations, alopecia, conjunctivitis, diarrhœa, and hæmaturia. Several horses died, and were found at necropsy to have ascites, cirrhosis, and submucosal bowel hæmorrhage.

The patient had played on the arena floor daily from the day of the spraying until the onset of her symptoms. Her sister (age 10 years) and mother also frequented the arena but their symptoms were limited to abdominal pain, diarrhœa, and intermittent headaches.

On admission the patient had moderate suprapubic tenderness. A urinalysis revealed 1+ protein and numerous red and white blood cells on microscopic examination. A urine culture was negative. Serum electrolytes, blood urea nitrogen, creatinine, and liver function tests were all normal. A voiding cystogram showed a much contracted œdematous bladder but no evidence of obstruction. On intravenous pyelogram the kidneys and upper tracts appeared normal, except for a calyceal diverticulum in the right mid kidney. The only other abnormality was a systolic murmur thought to be functional.

The temporal relationship between the patient's symptoms and the unexplained loss of farm animals raised the possibility of a common toxic agent. Following notification to the Center for Disease Control, Atlanta, Georgia, a toxicology search was undertaken which resulted in the identification of dioxin as a contaminant of the sprayed oil residue.[1]

The patient's symptoms resolved in 3-4 days and did not [illegible] and proteinuria were absent after 1 week. [illegible] voiding cystogram 3 months later appeared normal, [illegible] at this time demonstrated numerous [illegible] hæmorrhagic areas in the bladder, especially in the region [illegible] trigone. 5 1/2 years after the dioxin exposure, we re-investigated the patient with the informed consent of herself and her mother. In the 5-year interval the patient had grown normally, and both her height and weight were above the 75th percentiles. Physical examination, including a detailed neurological examination, was normal. Her urine was protein free and the urine sediment was normal. A cystogram was normal. The intravenous pyelogram demonstrated normal interval growth of the kidneys the only abnormality being the diverticulum in the calyceal system of the right kidney. Blood urea-nitrogen, serum creatinine, and inulin clearance (133 ml/min/1·73 m² surface area) were all normal. The functional heart murmur was still present but the electrocardiogram was normal and the cardiac response to exercise under standardised conditions was normal. From this test it was calculated that the patient's work capacity (730 kg/min/m²) was above average. Liver function tests, including transaminases, were normal, as was the urinary excretion of uroporphyrins and coproporphyrins. Thyroid function was normal.

The same studies were done on the patient's sister and the results were normal, as was an evaluation of the patient's mother.

There are a number of difficulties in comparing the situation in Seveso to the conditions on the Missouri farm. People living in the two areas were exposed to different concentrations of dioxin for variable periods of time. In the patient presented here the toxicity of the compound appeared relatively early and was self-limited. However, our experience demonstrates that people exposed to dioxin can recover completely with no apparent sequelæ from the toxin. It remains to be determined whether the exposure to dioxin in these children will result in abnormal pregnancies or affect their offspring.

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1. Courtney, K. D., Gaylor, D. W., Hogan, M. D., Falk, H. L., Bates, R. R., Mitchell, I. Science, 1970, 168, 864.
2. Kimbrough, R. D. [illegible] Lancet, 1976, ii, 44.
3. Carter, C. D., Kimbrough, R. D., Liddle, J. A., Cline, R. E., Zack, M. M., Jr., Barthel, W. F., Koehler, R. E., Phillips, P. E. Science, 1975, 188, [illegible]

INCONTINENT WOMEN

SIR,—As a gynæcologist doing urodynamics, I heartily agree with your editorial of March 5 (p. 521).

We are now beginning to understand incontinence of urine, but in England and Wales adequate facilities for investigating this common and distressing condition are scarce. Few centres can do proper synchronous pressure/flow studies at filling and voiding cystourethrography recorded on videotape. The equ[illegible]

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Medical and morbidity surveillance findings among employees potentially exposed to TCDD

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Medical and morbidity surveillance findings among employees potentially exposed to TCDD

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ABSTRACT Available medical and morbidity surveillance findings from 1976 to 1978 for two employee cohorts potentially exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) were compared with those of matched unexposed employees. The medical surveillance findings were derived from a screening programme offered to all active employees and included an analysis of various medical history questions and blood chemistry results. Group medical insurance claims served as the source of morbidity surveillance data and the period prevalence of selected diseases was analysed. Few significant differences between the exposed and unexposed were detected. Among the cohort of employees potentially exposed during the manufacture of 2,4,5-trichlorophenoxyacetic acid (2,4,5,-T), a significantly greater frequency of *x*-ray proved ulcer was reported and significantly more members of this group had diseases of the digestive system diagnosed. Such findings were absent in the more highly TCDD-exposed cohort engaged in 2,4,5-trichlorophenol production, making it unlikely that dioxin was a cause.

The trace impurity 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is formed as a byproduct during the manufacture of 2,4,5-trichlorophenol (TCP) under alkaline conditions at raised temperatures and high pressures. Since TCP is a precursor for the production of the herbicide 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), low level contamination of the herbicide by TCDD is expected. Thus the potential for occupational exposure to TCDD may arise among employees making either TCP or 2,4,5-T.

Recent evidence suggests that TCDD may also be formed during the routine combustion of carbonaceous fuels.[1] Chlorinated dioxins have been found in trace amounts in samples gathered from incinerator stacks as well as from chemical tar burners and a fossil fuelled power plant, vehicle silencers, fireplaces, chimneys, cigarette smoke, and portions of charcoal broiled steaks.

Mortality studies and case summaries of occupational cohorts presumably exposed to high levels of TCDD during the production of TCP, or exposed to lower levels during the synthesis of 2,4,5-T, have been published[2–9] (J A Zack, unpublished observations). Reports have appeared of soft tissue sarcoma among employees with exposure severe enough to cause chloracne[4–7]; however, no consistent unique mortality patterns have been noted among those with lower level exposure[9] (J A Zack). A survey of reproductive outcomes among wives of employees exposed to dioxins was also recently completed and indicated no biologically important associations.[10] Available evidence suggests that occupational cohorts exposed to lower levels of TCDD in the manufacture of 2,4,5-T experience no important long term health risks.

Investigations, including the evaluation of health examination findings and morbidity data for TCDD-exposed individuals with long latency, have only recently been started.[11] Clinical follow up 10 years later of 41 out of 79 individuals who developed chloracne in a 1968 TCP production accident, showed that other than minor persistent chloracne, there was no evidence of adverse health effects.[12] While relatively little data are available from sound epidemiological follow up of other exposed cohorts, reported systemic health effects after exposure to large amounts of TCDD include impaired liver function, nephropathy, gastrointestinal irritation, myopathy, and neuropathy, including depression and irritation of the central nervous system. These symptoms have not been progressive and have been reported to disappear with time. Vietnam war veterans, presumably exposed to lower levels of

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TCDD and for shorter periods than industrial cohorts, have alleged a number of medical complaints—for instance, weight loss, liver damage, recurrent rashes, deformed offspring, stillbirths, cancer, sterility, personality changes, and "other" illnesses—which they attribute to their exposure to Agent Orange.[11] To date, there have been no well controlled epidemiological studies to substantiate the allegations that these complaints are attributable to exposure to the trace amounts of TCDD in Agent Orange.

Medical follow up of inhabitants of Seveso exposed to TCDD as a result of an explosion of a trichlorophenol reactor has continued to document a lack of severe lasting health effects. While the findings are still regarded as preliminary, no organs or body functions, except the skin, have been found to be impaired; no excessive derangement of gestation, fetal lethality and loss, gross malformations, growth retardation at term or cytogenetic abnormalities have yet occurred.[13]

The present study reports the cross sectional medical and morbidity surveillance findings from 1976 to 1978 among employees at Dow Chemical, Michigan, who were considered potentially exposed to TCDD and for whom mortality surveys have been reported.[2 9] The objective of the present investigation was to determine whether patterns of selected health examination findings from the routinely administered medical surveillance examination, and indices of morbidity as reflected in medical insurance claims for employees potentially exposed to TCDD, differed from those of employees not exposed.

Methods and materials

The study population was assembled from two previously identified cohorts: (1) a group of employees who had been engaged in the manufacture of 2,4,5-T for at least one month between 1950 and 1971 and (2) a cohort of employees involved in a 1964 chloracne incident in the area of TCP production.

The methods for the selection of these cohorts have been described previously.[2 9] Briefly, the 204 white men comprising the 2,4,5-T cohort were identified from annual department census lists and work history records as having worked one month or longer between 1950 and 1971 on one of four job assignments (reactor operator, salt wheel operator, acid wheel operator, or dryer operator) in the 2,4,5-T process. The TCP cohort of 61 white male employees was identified from monthly department census lists and lists of maintenance personnel who were known to have worked in the process area during a 1964 chloracne incident. The two cohorts have been considered separately in the analysis to allow for differences in their potential for TCDD exposure, and for differences in their exposures to other agents.

Data of interest were derived from two separate sources: health examination findings from the routinely administered medical surveillance programme and morbidity surveillance as reflected in diagnoses from external medical service providers reported for payment of fee to the group insurance department.

The medical surveillance examination has been offered to all employees since 1967. The time required for the programme to cycle through the entire manufacturing complex is about two years. Only cohort members who had participated in a medical surveillance examination between 1976 and 1978 were eligible for consideration for this portion of the study.

Controls for the medical surveillance analyses were selected from among other white men employed at this location who had also participated in such an examination between 1976 and 1978. Employees considered at high risk because of a history of a job assignment as a pipe coverer, in the production or packaging of arsenical pesticides, considered as potentially exposed to high levels of vinyl chloride, or potentially exposed to dioxins were excluded from consideration as potential controls. Four controls were then matched from those eligible to each exposed on year of birth ± five years, whether hourly or salaried, smoking habit (never smoker, ex-smoker, current smoker) and, when possible, month and year of the most recent medical surveillance examination taken. When more than four controls were eligible for matching, the four with the date of hire nearest that of the exposed were selected.

Based on a review of relevant reports on animal and human exposure to TCDD, selected medical history questions and blood chemistry results were considered for analyses. The matching was retained throughout. For the dichotomous questionnaire responses (yes or no), the analysis was that which has been proposed for a fixed R:1 matching ratio with R = 4.[14] Exact confidence limits were calculated with $\alpha = 0{\cdot}10$ using a packaged set of programmes for a programmable calculator.[15] Blood chemistry values for each exposed subject were contrasted with the mean for the four matched controls, and a paired *t*-test was used to test the hypothesis that the mean difference between the exposed and matched controls was zero. Linear regression was done to test the correlation between $\log_{10}$ (days of employment in 2,4,5-T production) and the difference in blood chemistry values.

Group medical insurance claims filed by employees for medical expenses incurred between 1 January 1976 and 31 December 1978 served as the source of morbidity data. Members of the original study cohorts who were eligible for benefits on 31 December 1978 from the Medical Care Programme administered by the group insurance department were included for study. This time restriction ensured that morbid events reported were independent of mortality as reported in earlier studies of these cohorts.[3 9] Controls for morbidity comparisons were selected from among all white male employees eligible for Medical Care Programme benefits as of 31 December 1978. Employees with a history of certain job assignments were excluded from consideration as controls, as has been described above. From among the pool of eligible controls, four were matched to each exposed on the basis of year of birth ± five years, and whether hourly or salaried. When more than four controls were eligible, the four with the date of hire nearest that of the exposed were selected.

Diagnoses and expense dates were abstracted from Medical Care Programme claims by a registered nurse, who was unaware of the exposure status of the subjects. Only diagnoses for claims for hospital inpatient care, hospital outpatient care, surgery, diagnostic expenses, or emergency first aid were considered. This excluded diagnoses from physician office visits, unless diagnostic expenses were incurred or surgery was done, and information from drug prescriptions. No validation of diagnoses with any external source was attempted.

Coding of diagnoses to the international classification of diseases—ninth revision—clinical modification (ICD-9-CM) was done by trained coders without knowledge of the exposure status of subjects. Diagnostic categories of interest were derived based on the relevant animal and human toxicology data.

An individual could contribute, at most, only one observation to each diagnostic category. Period prevalence of all cancer, various site specific malignancies, diseases of porphyrin metabolism, digestive system diseases, hepatic disorders, renal disorders, and diseases of skin and subcutaneous tissue was compared, using an analysis that maintained the matching.[14]

Results

DEMOGRAPHIC CHARACTERISTICS

Table 1 presents the vital and employment status distributions for the two cohorts, together with eligibility for the medical surveillance and morbidity surveillance portions of the study. Two years of additional follow up with company records of the 2,4,5-T cohort identified two deaths not previously reported—one from cerebrovascular disease and the other from cardiovascular disease. Some 44% of the original 61 members of the TCP cohort and 43% of the 204 members of the 2,4,5-T cohort participated in medical surveillance examination between 1976 and 1978. Of those who were actively employed and thus eligible to participate, 68% of the TCP cohort and 72% of the 2,4,5-T cohort did so. These participation rates are significantly lower than the participation rate of 80% among all other white men employed at this location ($p = 0{\cdot}04$ and $p = 0{\cdot}02$, respectively). Of the 49 individuals in the original TCP cohort who had evidence of acne like lesions in 1964, 22 participated in a medical surveillance examination. Nearly all members of both cohorts (94% of TCP and 97% of 2,4,5-T), who were active or retired, were eligible for medical care programme benefits and thus could be surveyed for morbidity in this study.

Table 1 *Vital and employment status of exposed cohorts as of 31 December 1978. (Percentage of original cohorts in parentheses)*

Status	TCP cohort	2,4,5-T cohort
Original	61	204
Employed	40	116
Retired	11	21
Deceased	4	11
Left other than through retirement:	6	56
Deceased	0	2
Known alive	6	2
Unknown	0	52
Participated in medical surveillance exam	27(44)	87(43)
Eligible for medical care programme and morbidity surveillance	48(79)	135(66)

Table 2 presents a comparison of demographic data for the subjects of each original cohort eligible for the medical surveillance examination and for morbidity surveillance and their matched controls. The exposed cohorts and their matched controls compared well with respect to all variables considered. In the analysis, potential confounding by cigarette smoking, age, year of hire, and socioeconomic status was controlled by matching and stratification on these variables or correlates.

MEDICAL SURVEILLANCE FINDINGS

Table 3 presents a comparison of the frequency of positive screens with selected questions from the medical surveillance examination for the two exposed cohorts and their matched controls. The frequency of positive screens was low for nearly all the questions, and the exposed and controls responded comparably. The only statistically

Table 2 *Comparison of exposed cohorts and their matched controls on selected demographic variables*

Demographic variable	*TCP cohort*	*Controls*	*2,4,5-T cohort*	*Controls*
Medical surveillance:				
No eligible for study	27	108	87	348
Mean age ± SD	45·4 ± 7·6	45·4 ± 7·8	42·8 ± 8·2	42·8 ± 8·3
Year of hire	1953·6 ± 7·9	1953·3 ± 9·2	1957·1 ± 8·5	1956·6 ± 10·0
Salaried	5	20	14	56
Paid by the hour	22	88	73	292
Current smoker	6	24	25	100
Ex-smoker	10	40	37	148
Non-smoker	11	44	25	100
Morbidity surveillance:				
No eligible for study	48	192	135	540
Mean age ± SD	49·2 ± 9·5	49·2 ± 9·6	45·3 ± 10·2	45·3 ± 10·2
Year of hire	1951·4 ± 8·0	1951·7 ± 10·5	1956·7 ± 7·9	1955·0 ± 10·6
Salaried	5	20	17	68
Paid by the hour	43	172	118	472

Table 3 *Frequency of positive screens to selected medical surveillance examination questions among TCP and 2,4,5-T cohorts and matched controls, most recent exam 1976–8*

Question	*TCP cohort*		*2,4,5-T cohort*	
	N_E (n = 27)	N_C (n = 108)	N_E (n = 87)	N_C (n = 348)
Since your last Dow physical exam or health inventory, have you had any of the following?				
Skin trouble	2	5	6	14
Yellow jaundice	0	0	0	0
Problems with urination	0	0	1	5
Albumin or sugar in urine	0	0	0	3
Blood in urine	0	1	0	2
Frequent indigestion or heartburn	0	5	4	19
Intestinal trouble	0	0	1	2
Loss of weight	0	4	3	6
Coughing up of blood	0	0	0	1
Change in bowel habits	0	0	0	0
Blood in stools	0	1	0	2
Tarry stools	0	1	0	1
Do you have or have you had any of the following?				
High blood pressure	1	7	6	24
Liver trouble (hepatitis)	1	4	2	12
Kidney or bladder trouble	2	7	5	19
Cancer or malignant growth	0	0	0	3
x-ray proved ulcer	2	7	9*	18

*R_{ML} = 2·11; X_{MH} = 1·78, 90% CI = 1·06–4·20.
N_E = Number of exposed responding "Yes."
N_C = Number of controls responding "Yes."

significant difference was the greater frequency of positive screens for x-ray proved ulcer among members of the 2,4,5-T cohort (R_{ML} = 2·11, 90% CI = 1·06–4·20), based on nine of those exposed having reported such a history. As asked, the question of x-ray proved ulcer does not discriminate between incidence or prevalence, so the temporal relation between exposure and disease is not known.

Table 4 presents a comparison of results for nine selected blood chemistry tests performed as a part of the medical surveillance examination. Mean total bilirubin was slightly lower in both exposed cohorts and mean serum aspartate transaminase was lower in the 2,4,5-T cohort than in their respective controls; and while these differences were statistically significant at α = 0·10, two tailed, they were not regarded as clinically significant. Given the number of comparisons done and the level of accepting a type 1 error, some statistically significant differences were to be expected.

When the mean difference between blood chemistry values for the exposed and their matched controls was regressed against $\log_{10}$ (days of employment in 2,4,5-T), there was a lack of significant association for all laboratory tests except for a significant positive slope for blood urea nitrogen (p 0·022); however, the independent variable explained only 6% of the variability in the dependent variable, suggesting that duration of employment in 2,4,5-T was not an important determinant.

Analyses of medical surveillance findings among only those members of the TCP cohort who had

Table 4 *Comparison of exposed cohorts with matched controls for nine selected laboratory tests, most recent medical surveillance examinations 1976–8*

Test procedure	Trichlorophenol cohort M ± SD	Trichlorophenol cohort less controls d ± 90% CI	2,4,5-T cohort M ± SD	2,4,5-T cohort less controls d ± 90% CI
Total bilirubin (mg/100 ml)	0·51 ± 0·17 (n = 26)	−0·08 ± 0·07	0·50 ± 0·21 (n = 84)	−0·06 ± 0·04
Total protein (g/100 ml)	7·17 ± 0·45 (n = 26)	0·04 ± 0·16	7·10 ± 0·33 (n = 84)	−0·01 ± 0·07
Protein albumin (g/100 ml)	4·16 ± 0·43 (n = 26)	0·002 ± 0·12	4·11 ± 0·35 (n = 84)	−0·05 ± 0·06
Blood urea nitrogen	16·08 ± 3·79 (n = 26)	0·37 ± 1·34	16·07 ± 3·64 (n = 84)	0·61 ± 0·65
Lactic dehydrogenase (mi-u/ml)	114·7 ± 30·4 (n = 26)	4·08 ± 6·75	108·3 ± 23·9 (n = 82)	−3·67 ± 4·49
Serum aspartate transaminase (u/ml)	27·69 ± 8·84 (n = 26)	5·32 ± 6·39	29·99 ± 7·72 (n = 85)	−2·53 ± 1·83
Serum alanine transaminase (u/ml)	32·26 ± 13·34 (n = 23)	1·21 ± 5·20	33·24 ± 14·66 (n = 79)	0·59 ± 2·95
Alkaline phosphatase	70·88 ± 21·52 (n = 26)	−0·36 ± 6·18	71·05 ± 24·13 (n = 84)	0·21 ± 4·54
Albumin-globulin ratio	1·38 ± 0·23 (n = 23)	−0·008 ± 0·08	1·40 ± 0·32 (n = 78)	−0·003 ± 0·06

(n = Number of matched quintuplets)

Table 5 *Comparison of number of prevalent cases of selected disease conditions by exposure group: diagnoses from Medical Care Programme, 1976–8*

Disease category	No of prevalent cases			
	TCP cohort		2,4,5-T cohort	
	N_E (n = 48)	N_C (n = 192)	N_E (n = 135)	N_C (n = 540)
Malignant neoplasms (140–209)	1	4	4	9
Mn of liver (155)	0	0	0	1
Mn of trachea, bronchus, and lung (162)	1*	0	1	1
Mn of connective and other soft tissue (171)	0	1	0	0
Mn of skin (172–173)	0	1	0	2
Malignant lymphoma (200–202)	1*	0	0	0
Diseases of porphyria metabolism (277·1)	0	0	0	0
Diseases of the digestive system excluding liver disease (530–535, 555–558, 564·1)	3	10	17†	27
Disorders of the liver (570–573)	0	5	2	5
Glomerulonephritis (580–583)	0	0	0	0
Renal failure (584–586)	0	0	0	1
Infections of kidney (590)	0	0	0	0
Diseases of skin and subcutaneous tissues (680–686, 692, 695)	0	2	2	11

*Refers to a single individual.
†R_{ML} = 2·51 X_{MH} = 2·957, 90% CI = 1·50–4·18.
N_E = Number of prevalent cases among exposed cohort.
N_C = Number of prevalent cases among controls.

exhibited acne like lesions in 1964 produced similar results to the analysis of the total eligible cohort.

MORBIDITY SURVEILLANCE FINDINGS

Of the 915 members of the exposed cohorts and the matched control groups eligible for Medical Care Programme benefits, 656 (71·7%) filed at least one claim for medical services during the study period 1976–8. A total of 6539 separate diagnostic entries were abstracted and coded and constituted the total morbidity data base from which the analyses of conditions of interest were carried out. The diagnostic entries were distributed fairly evenly across the study years with 2126 entries in 1976, 2245 in 1977, and 2168 in 1978. Most of the diagnoses were on claims for physician's services (58·4%) and claims for hospital services (35·3%), with few diagnoses provided solely from laboratories (4·7%) or other sources (1·5%). About one quarter of all diagnoses provided were precoded to some disease categorisation scheme by the service provider.

Table 5 presents a comparison of the number of prevalent cases of disease conditions of interest for each of the exposed cohorts and their matched con-

Table 6 *Detailed breakdown of diseases of digestive system among 2,4,5-T cohort and matched controls. Diagnoses from Medical Care Programme, 1976–8*

Disease category	*No of prevalent cases*	
	N_E	N_C
Diseases of oesophagus (530)	2	1
Gastric ulcer (531)	2	3
Duodenal ulcer (532)	3	3
Peptic ulcer, site unspecified (533)	2	7
Gastrojejunal ulcer (534)	0	0
Gastritis and duodenitis (535)	3	4
Regional enteritis (555)	0	1
Other non-infectious gastroenteritis and colitis (558)	6	10
Irritable colon (564·1)	4	5

Note: An individual may have more than one condition.
N_E = Number of prevalent cases among 2,4,5-T cohort.
N_C = Number of prevalent cases among matched controls.

trol groups. The period prevalence of most conditions was low and was comparable between the exposed and their controls. An exception was the significantly greater prevalence of diseases of the digestive system excluding liver disease among the 2,4,5-T cohort (R_{ML} = 2·51, 90% CI = 1·50– 4·18) based on 17 prevalent cases among the exposed. Table 6 gives a detailed breakdown of the distribution of prevalent cases among the 2,4,5-T cohort and their controls by disease within this category. The difference in prevalence cannot be explained on the basis of a preponderance of any one specific disease entity; instead, the 2,4,5-T cohort had relatively more cases of each condition.

Discussion

Results from this cross sectional examination of medical and morbidity surveillance findings among two cohorts who were potentially exposed to TCDD at some point in the past and their matched unexposed controls showed few differences. Those employees who were engaged in 2,4,5-T production at some point, between 1950 and 1971, reported the prevalence of *x*-ray proved ulcer significantly more often than their matched controls, and recorded significantly more diagnoses of diseases of the digestive system. The lack of a similar finding among the more highly TCDD-exposed in the TCP cohort makes it unlikely that the dioxin is associated with this finding. The departmental unit under which the 2,4,5-T process was first organised was also responsible for manufacturing various other products. Thus many of the individuals in the 2,4,5-T cohort were potentially exposed to numerous other substances during their employment with this unit.

The 2,4,5-T dust concentrations found in the plant were often high enough to be noticeably irritating, and were believed to have resulted primarily from finishing operations where the end product was dried and fed through a hammer mill. One could postulate that ingested dust could lead to a greater frequency of diseases of the digestive system. The 2,4,5-T exposures, however, were incurred by subjects in this study a minimum of five years before the indication of disease prevalence, thus making latency an important issue.

A limitation of cross sectional studies is the uncertainty surrounding the temporal sequence in the exposure disease relationship. As was the case in this study, it is usually not possible to discriminate between disease incidence and prevalence, so that one is uncertain whether or not the exposure preceded the disease and could possibly be a cause.

Data on health outcome from medical and morbidity surveillance of the two cohorts in the present study were limited to the active or recently retired workforce. Members of the two cohorts who left the company for reasons other than retirement could not be studied. Inferences from the present study concerning the health status of former employees must be drawn carefully owing to possible retirement of former employees on the basis of health.

The study was further limited to medical and morbidity surveillance for a three year period (1976–8). Owing to the large amount of time required to locate and code archived medical claims, a larger sample was deemed unfeasible.

With the completion of this study, these employees have now been surveyed for morbidity, mortality, and reproductive outcomes. To date, the available data do not indicate serious long term health risks associated with exposures to TCDD at the levels encountered by these two industrial cohorts. Consideration is being given to continued medical and morbidity surveillance of these cohorts, and we recommend that other cohorts with similar exposures also be surveyed.

We gratefully acknowledge the contributions of Mr Bernard Lasich, Mr Stewart Gudmundsen, Mrs Janice Cartmill, Mrs Jean Townsend, Mrs Elsie McLaren, Dr Robert Kolesar, and Mrs Angie Grzegorczyk of Dow Chemical, USA, and of Mr Larry Silverstein, formerly of Dow Chemical, USA, and now with the Dow Corning Corporation.

References

1 Bumb RR, Crummett WB, Cuties SS, *et al.* Trace chemistries of fire: a source of chlorinated dioxins. *Science* 1980;210:385–9.
2 Cook RR, Townsend JC, Ott MG, Silverstein LG. Mortality experience of employees exposed to 2,3,7,8-tetrachloro-

dibenzo-p-dioxin (TCDD). *JOM* 1980;22:530–2.
[7] Zack JA, Suskind RR. The mortality experience of workers exposed to tetrachlorodibenzodioxins in a trichlorophenol process accident. *JOM* 1980;22:11–4.
[8] Theiss AM, Frentzel-Beyme R. Mortality study of persons exposed to dioxin in a trichlorophenol-process accident that occurred in the BASF AG on November 17, 1953. *American Journal of Industrial Medicine* 1982;3:179–89.
[9] Hoechst PA, Halperin WE. 2,4,5-T, Trichlorophenol and soft-tissue sarcomas. *Lancet* 1981;i:268–9.
[10] Cook RR. Dioxins, chloracne, and soft-tissue sarcomas. *Lancet* 1981;i:618–9.
[11] Cook RR. Soft-tissue sarcomas: clues and caution. In: Tucker R, Young AL, Gray AP, eds. *Environmental science research and theory*. Vol 26. *Human and environmental risks of chlorinated dioxins and related compounds* New York: Plenum Publishing Corporation, 1983.
[12] International Agency for Research on Cancer. *Evaluation of the carcinogenic risk of chemicals to humans. Some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and miscellaneous industrial chemicals*. Lyon: IARC, 1977. (Monograph 15.)
[13] Ott MG, Holder BB, Olson RD. A mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid. *JOM* 1980;22:47–50.
[14] Townsend JC, Bodner KM, Van Peenen PFD, Olson RD, Cook RR. Survey of reproductive events of wives of employees exposed to chlorinated dioxins. *Am J Epidemiol* 1982;115:695–713.
[15] Council on Scientific Affairs Advisory Panel on Toxic Substances. *The health effects of "Agent Orange" and polychlorinated dioxin contaminants*. Chicago: American Medical Association, 1981.
[16] May G. Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. *Br J Ind Med* 1982;39:128–35.
[17] Huff JE, Moore JA, Saracci R, Tomatis L. Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. *Environ Health Perspect* 1980;36:221–40.
[18] Miettinen OS. Estimation of relative risk from individually matched series. *Biometrics* 1970;26:75–86.
[19] Rothman K, Boice J. *Epidemiologic analysis with a programmable calculator*. Washington: US Government Printing Office, 1979:19–24. (NIH Publication No 79–1649.)

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2,3,7,8-Tetrachlorodibenzo-p-dioxin: A Potent Inducer of δ-Aminolevulinic Acid Synthetase

Abstract. *2,3,7,8-Tetrachlorodibenzo-p-dioxin, a [illegible] contaminant [illegible] formed during the synthesis of the herbicide 2,4,5-trichlorophenoxyacetic acid, is shown to be a potent inducer of hepatic δ-aminolevulinic acid synthetase in the chick embryo. As little as 4.66 × 10⁻¹⁵ mole of the contaminant per egg produces a significant increase in the activity of the enzyme. Induction of the enzyme is related to the dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin and, in contrast to that produced with other drugs, is prolonged in time, with 70 percent of the maximum induced activity present 5 days after a single dose. This contaminant is implicated as the likely causative agent in an outbreak of porphyria cutanea tarda in workers in a factory where 2,4,5-trichlorophenoxyacetic acid was being synthesized.*

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is an unwanted contaminant formed during the syntheses of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (*1*) (Fig. 1). This contaminant, TCDD, is perhaps the most potent small-molecule toxin known; the oral LD_{50} (mean lethal dose) in guinea pigs is 1 μg per kilogram of body weight (3×10^{-9} mole/kg) (*2*). The widespread use of 2,4,5-T as a defoliant in Vietnam (*1*, *2*) and the discovery of the teratogenic potency of TCDD (*3*) have caused concern about the potential public health hazard created by contamination of the environment with TCDD. The chemistry of the toxin has been extensively investigated, but little is known about its biological actions (*1*, *4*).

In 1964, Bleiberg *et al.* (*5*) reported an outbreak of occupationally related acne and porphyria cutanea tarda (PCT) among workers in a factory where 2,4,5-T was being produced. The acne was shown to be directly attributable to TCDD (*6*). Porphyria cutanea tarda is an acquired defect in hepatic porphyrin metabolism characterized by uroporphyrinuria, photosensitivity as manifested by blisters, and mechanical fragility of the skin (*7*). The etiology of PCT in these factory workers is unclear, but upon reinvestigation of the factory in 1969, we discovered that the PCT had disappeared in all workers following the institution of procedures to reduce TCDD contamination (*8*). Hepatic porphyria can be produced experimentally by a number of drugs, all of which have the ability to stimulate the activity of the initial enzyme in heme synthesis, δ-aminolevulinic acid synthetase (ALA synthetase) (*9*, *10*). Stimulation of this enzyme is thought to represent induction, that is, enhanced protein synthesis (*9*).

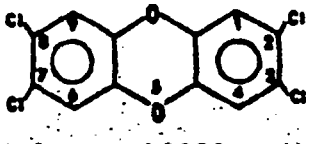


Fig. 1. Structure of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

We report here that TCDD is an inducer of ALA synthetase, and is at least three orders of magnitude more potent than any other compound known to produce experimental porphyria.

The chick embryo was chosen as the experimental animal because (i) it is highly sensitive to the toxic effects of TCDD (*11*), (ii) induction of ALA synthetase in the liver is well characterized in the chick embryo (*12*), and (iii) the [illegible] closed system, which [illegible] of laboratory con-

[illegible] dioxins were [illegible]. Fertile chicken eggs, 15 to 20 days of gestation, were injected with 25 μl of the chemical solution or of solvent alone, through a small hole punched into the shell over the air sac. After the appropriate time interval, the animals were killed, and the activity of hepatic ALA synthetase was assayed (*13*). The TCDD produced a dose-related increase in ALA synthetase activity (Fig. 2). Even at the lowest dose tested, 4.66×10^{-15} mole per egg (1.5 ng), there was significant ($P < .05$) doubling of enzyme activity. Enzyme activity increased more than 35 fold at the highest dose tested, 1.55×10^{-9} mole per egg (0.5 mg). The in vitro addition of TCDD to a reaction mixture containing control liver did not increase enzyme activity. The stimulation of ALA synthetase in

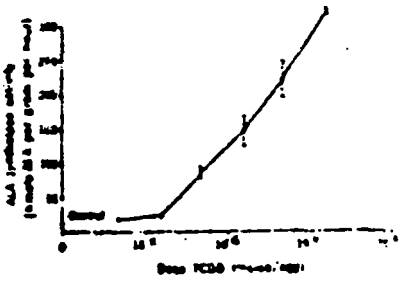
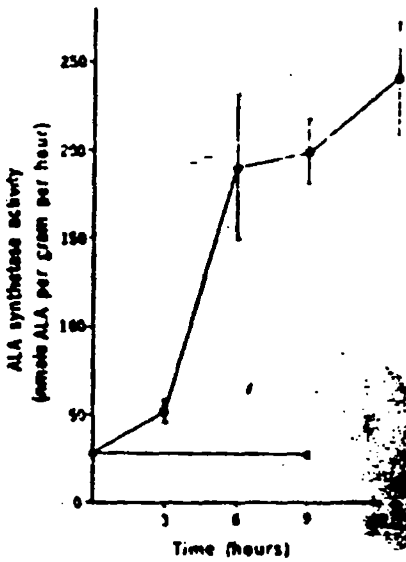


Fig. 2. The induction by TCDD of ALA synthetase: dose-response relationship. Chicken eggs of 17 days' gestation were injected with 25 μl of solvent (control), or of solvent containing various doses of TCDD. The embryos were killed 48 hours later and assayed for hepatic ALA synthetase activity (*13*). The points represent the mean ± standard error of three or four groups of pooled livers.

Fig. 3. Time course of induction of ALA synthetase. Chicken eggs of 20 days' gestation were injected with 25 μl of solvent containing 4.66×10^{-10} mole of TCDD (●) or of solvent alone (○). At the indicated intervals, the embryos were killed, and their livers were assayed for ALA synthetase activity (13). Each point represents the mean ± standard error of four groups of pooled livers.



vivo can be prevented by the simultaneous administration of actinomycin D (30 μg) or cycloheximide (10 μg), at doses which did not kill the embryos. Hence, the stimulation of ALA synthetase produced by TCDD and other drugs probably represents increased synthesis of the enzyme, and not activation or decreased degradation (14).

The time course of enzyme induction (Fig. 3) has an initial lag phase, probably representing drug absorption and synthesis of messenger RNA, and then a rapid rise in enzyme activity reaching near maximum levels by 6 hours. In contrast to other porphyrigenic compounds that have been tested in this system (for example, allylisopropylacetamide and diethyl-1,4-dihydro-2,4,6-trimethylpyridine-3,5-dicarboxylate), which have transient effects on ALA synthetase, the induction by TCDD was prolonged. Embryos (15 days old) given 4.66×10^{-10} mole of TCDD per egg (150 ng) still had 70 percent of their maximum induced enzyme activity after 5 days. The prolonged duration of induction is a reflection of the long biological half-life of TCDD (15).

Studies with other halogenated dibenzo-p-dioxins suggest that the halogen atoms must occupy at least three of the 2,3,7, and 8 positions on the ring, in order to induce ALA synthetase. The 2,3,7-trichloro- and 2,3,7-tribromo-isomers are potent inducers, while 2,3-dichloro-, 2,7-dichloro-, 2,8-dichloro-, 1,3,6,8-tetrachloro-, and 1,2,3,4-tetrachloro-isomers all fail to induce at doses up to 2.5 μg per egg. Of the limited number of halogenated dibenzo-p-dioxins which have been tested for lethality and the ability to produce acne (16), those which are toxic at low doses also induce ALA synthetase.

Induction of ALA syn[illegible]se by TCDD is the first specific b[illegible]emical action identified for this [illegible] compound. The relationship bet[illegible] enzyme induction and the delay[illegible]patic necrosis presumably responsib[illegible] the lethality of TCDD is not known. However, it seems most likely that the outbreak of PCT in workers in the factory producing 2,4,5-T is attributable to induction of hepatic ALA synthetase by TCDD. While other chlorinated compounds present in the factory were found to stimulate ALA synthetase activity in our system, TCDD is by far the most potent inducer, and the reversal of the porphyria occurred when TCDD contamination was reduced. We suggest routinely monitoring the urinary porphyrins in workers in factories producing 2,4,5-T to assess their exposure to TCDD.

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References and Notes

1. "Report on 2,4,5-T. A Report of the Panel on Herbicides of the President's Science Advisory Committee" (Government Printing Office, Washington, D.C., March 1971).
2. "Report of the Advisory Committee on 2,4,5-T to the Administrator of the Environmental Protection Agency" (Government Printing Office, Washington, D.C., May 1971).
3. K. D. Courtney, D. W. Gaylor, M. D. Hogan, H. L. Falk, R. R. Bates, I. Mitchell, *Science* 168, 864 (1970); G. L. Sparschu, F. L. Dunn, V. K. Rowe, *Food Cosmet. Toxicol.* 9, 405 (1971).
4. N. P. Buu-Hoï, P.-H. Chanh, G. Sesqué, M. C. Azum-Gelade, G. Saint-Ruf, *Naturwissenschaften* 59, 173 (1972); N. P. Buu-Hoï, D.-P. Hien, G. Saint-Ruf, J. Servoin-Sidoine, *C.R. Acad. Sci. Paris Ser. D* 272, 1447 (1971).
5. J. Bleiberg, M. Wallen, R. Brodkin, I. Applebaum, *Arch. Dermatol.* 89, 793 (1964).
6. L. Schwartz, L. Tulipan, D. J. Birmingham, *Occupational Diseases of the Skin* (Lea & Febiger, Philadelphia, 1957), p. 336; J. Kimmig and K. H. Schulz, *Naturwissenschaften* 44, 337 (1957); K. H. Schulz, *Arch. Klin. Exp. Dermatol.* 206, 589 (1957).
7. H. Marver and R. Schmid, in *The Metabolic Basis of Inherited Disease*, J. Stanbury, J. Wyngaarden, D. Fredrickson, Eds. (McGraw-Hill, New York, ed. 3, 1972), p. 1124.
8. A. Poland, D. Smith, G. Metter, P. Possick, *Arch. Environ. Health* 22, 316 (1971).
9. S. Granick, *J. Biol. Chem.* 241, 1359 (1966).
10. ——— and S. Sassa, in *Metabolic Regulation*, H. J. Vogel, Ed. (Academic Press, New York, 1971), vol. 5.
11. G. R. Higginbotham, A. Huang, D. Firestone, H. J. Verrett, J. Ress, A. D. Campbell, *Nature* 220, 702 (1968).
12. A. Kappas, C. S. Song, R. Levere, R. Sachson, S. Granick, *Proc. Nat. Acad. Sci. U.S.A.* 61, 509 (1968).
13. Our determination of ALA synthetase activity differs from the method of Marver *et al.* (17) in two significant ways. (i) Disodium ethylenediaminetetraacetate does not significantly inhibit ALA dehydratase in the chick, [illegible] in the rat (25), so this enzyme is [illegible] incubation, and an enriched [illegible] is used to obtain mitochondrial [illegible], but the aminoacetone [illegible] removed by extraction with [illegible] instead of by ion-exchange chromatography. We are grateful to S. Sassa and S. Granick of Rockefeller University for this method. Livers from three to five embryos were pooled, weighed, and homogenized in three volumes of buffer (17). The homogenate was centrifuged at 10,000g for 20 minutes, and the pellet was resuspended in the initial volume of buffer. The activity of ALA synthetase was assayed in a portion of the resuspended pellet, which was equivalent to 25 mg of liver in a final incubation volume of 1.2 ml, pH 7.4. The incubation medium contained 25 mM glycine, 75 mM sodium citrate, 100 mM sucrose, 75 mM Na_2HPO_4, 25 mM tris(hydroxymethyl)aminomethane, 15 mM $MgCl_2$, and 2 mM pyridoxal 5'-phosphate. The samples were incubated for 60 minutes at 37°C, and the reaction was terminated by the addition of trichloroacetic acid at a final concentration of 5 percent; the reaction mixture was then centrifuged. We added 0.25 volume of 2M sodium acetate containing 8 percent acetylacetone to a portion of the supernatant. The samples were heated at 85°C for 10 minutes to form the ALA- and AA-pyrrole (18). The pH of the samples was adjusted to 7.0 with 1M sodium phosphate buffer (pH 11.0), and AA-pyrrole was extracted with 3 ml of dichloromethane. This procedure removed 92 percent of the AA-pyrrole and less than 5 percent of the ALA pyrrole. A sample of the aqueous phase was then added to an equal volume of modified Ehrlich's reagent (19) and the absorbancy of the chromogen was determined after 15 minutes, at 556 nm, with an extinction coefficient of [illegible] to calculate the concentration of ALA (20).
14. N. Hayashi, B. Yoda, G. Kikuchi, *Arch. Biochem. Biophys.* 131, 83 (1969); *J. Biochem.* 67, 859 (1970); D. Tyrrell and G. S. Marks, *Biochem. Pharmacol.* 21, 2077 (1972).
15. W. N. Piper, J. Q. Rose, P. J. Gehring, paper presented at the meeting of the American Chemical Society, Washington, D.C., September 1971.
16. V. K. Rowe, J. M. Norris, B. A. Schwetz, G. L. Sparschu, P. J. Gehring, paper presented at the meeting of the American Chemical Society, Washington, D.C., September 1971.
17. H. S. Marver, D. P. Tschudy, M. G. Perlroth, A. Collins, *J. Biol. Chem.* 241, 2803 (1966).
18. ———, G. Hunter, *Anal. Biochem.* 14, 53 (1966).
19. D. Mauzerall and S. J. Granick, *J. Biol. Chem.* 219, 435 (1956).
20. F. DeMatteis, *Biochem. J.* 124, 767 (1971).

21. We thank G. Lynn, Dow Chemical Co., and A. Poland, U.S. Food and Drug Administration, who generously provided samples of TCDD and other halogenated dibenzo-p-dioxins. Supported by NIH Special Postdoctoral Fellowship 5 F03 ES46194, Merck Grant for Faculty Development, and NIH Center Grant for Toxicologic Research and Training 2P11-GM15190-06A1.

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dibenzo-p-dioxin (TCDD). *JOM* 1980;22:530–2.
[3] Zack JA, Suskind RR. The mortality experience of workers exposed to tetrachlorodibenzodioxins in a trichlorophenol process accident. *JOM* 1980;22:11–4.
[4] Theiss AM, Prentzel-Beyme R. Mortality study of persons exposed to dioxin in a trichlorophenol-process accident that occurred in the BASF AG on November 17, 1953. *American Journal of Industrial Medicine* 1982;3:179–89.
[5] Hoechst PA, Halperin WE. 2,4,5-T, Trichlorophenol and soft-tissue sarcomas. *Lancet* 1981;i:268–9.
[6] Cook RR. Dioxins, chloracnes, and soft-tissue sarcomas. *Lancet* 1981;i:618–9.
[7] Cook RR. Soft-tissue sarcomas: clues and caution. In: Tucker R, Young AL, Gray AF, eds. *Environmental science research and theory*. Vol 26. *Human and environmental risks of chlorinated dioxins and related compounds* New York: Plenum Publishing Corporation, 1983.
[8] International Agency for Research on Cancer. *Evaluation of the carcinogenic risk of chemicals to humans. Some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and miscellaneous industrial chemicals*. Lyon: IARC, 1977. (Monograph 15.)
[9] Ott MG, Holder BB, Olson RD. A mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid. *JOM* 1980;22:47–50.
[10] Townsend JC, Bodner KM, Van Peenen PFD, Olson RD, Cook RR. Survey of reproductive events of wives of employees exposed to chlorinated dioxins. *Am J Epidemiol* 1982;115:695–713.
[11] Council on Scientific Affairs Advisory Panel on Toxic Substances. *The health effects of "Agent Orange" and polychlorinated dioxin contaminants*. Chicago: American Medical Association, 1981.
[12] May G. Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. *Br J Ind Med* 1982;39:128–35.
[13] Huff JE, Moore JA, Saracci R, Tomatis L. Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. *Environ Health Perspect* 1980;36:221–40.
[14] Miettinen OS. Estimation of relative risk from individually matched series. *Biometrics* 1970;26:75–86.
[15] Rothman K, Boice J. *Epidemiologic analysis with a programmable calculator*. Washington: US Government Printing Office, 1979:19–24. (NIH Publication No 79–1649.)

246 TCDD K-4568 K-6668 (100

DIOXIN [illegible] WEEDS

2,4,5-T [illegible] in the Environmental Protection Agency's [illegible] (See Dec. [illegible], Page [illegible]) [illegible] less likely as a candidate for cancellation. The investigation [illegible] that [illegible] percent of the samples in a beef fat monitoring program showed no TCDD (dioxin) at current detection levels of 10 parts per trillion.

Data on the remaining 10 percent of samples, however, were incomplete and unconfirmed.

In a summary [illegible] of the chemists' conclusions in the Dec. 16 meeting, it was noted that although analytical methodology for determining dioxin content is satisfactory "in general," the data are not complete enough at present "to draw specific conclusions" concerning [illegible] procedures.

The panel also noted: "At [illegible] sensitivities (with which we are working) there are intrinsic uncertainties with the analytical method."

O

ADMINISTRATION STILL BACKS TOXIC SUBSTANCES LAW, TRAIN AFFIRMS

The Administration hasn't backed [illegible] from toxic substances legislation, Environmental Protection Agency Administrator Russell E. Train affirmed this week at his press conference on PCBs (see [illegible]), but he [illegible] a pessimistic estimate of when legislation could be passed.

Noting that Congress has adjourned for the year, he said the House Commerce Committee would probably not [illegible] of a subcommittee bill (See Dec. 10, Page 4) until February or "early spring." Pointing out, also, that the bill is not yet to the full Commerce Committee in the Senate, he said, "Obviously we have a long way to go."

EPA backs the McCollister bill in the House, "with amendments," he said, stating that the agency's suggested amendments were ready to go to Capitol Hill once Congress comes back from its recess.

Just before Congress left, Sen. Tunney (D-Calif.) said that "irreconcilable differences on key provisions" of the legislation "have prevented its enactment into law."

Tunney said, "A strong [illegible] is an absolute necessity to protect the public from environmental pollutants at the time when the costs of control are the lowest." Stating [illegible] costs are lowest at the premarket stage because jobs have not yet been committed and [illegible] equipment not yet purchased, Tunney continued:

> "But even more important [illegible], control at this stage avoids the pain, anxiety, and [illegible], even death, that

Chemical(s) identified: U.S. Dioxins + Furans

K-066651-[illegible]

250

K-003647

D2-0115-3257

Species studied: Exptl. + field animals

Dose:

Health effects:

To attempt t[redacted] proceedings of a meeting such as this one in any rigorous sense is clearly an unreasonably ambitious task. It is made more challenging because of the tentative character of much of the work commented upon here.

This meeting, one of a series (and I hope a growing series) for the National Institute of Environmental Health Sciences, represents an extraordinarily useful concept. It is designed to bring together a variety of scientific bedfellows who have contemplated (and indeed investigated) a subject for its academic interest and for its very timely topical interest. These same scientists would have learned about each other eventually but, in the best tradition of science, it would have taken a long time.

By design, we are witnessing the cutting edge of scientific research for this area. This meeting has, as its avowed and very virtuous purpose, the calling out of the walls a good deal of unmatured and not totally interpreted or confirmed research. It is important to keep this tentative and unconfirmed character in mind.

One is struck, too, by the character of the research which has been reported at this meeting. There are still many gaps in our knowledge about dibenzofurans and dioxins. Yet, the thought that has gone into the design of the research reported here represents a striking degree of sophistication in many cases for which the participants should be very proud. As late as 1970 or 1971, there existed only the crudest hint of a ranking of biological activity of members of the family of chlorinated dioxins. (1, 2) [redacted] I am struck by the fact that the early observations (from the occupational environment) and the early approximations of rankings have been sustained and essentially confirmed by the data reviewed at this meeting.

0295607 74030607
An analytical method for detecting TCDD (dioxin): levels of TCDD in samples from Vietnam.
Baughman R; Meselson M
Environ Health Perspect (United States) .Sep 1973. 5 p27-35. ISSN 0091-6765 Journal Code: EIO
Languages: ENGLISH
Subfile: INDEX MEDICUS
Tags: Animal
Descriptors: CATTLE; CHLORINE; CHLOROBENZENES--Analysis (AN); CHROMATOGRAPHY, GAS; CRUSTACEA; CYPRINIDAE; *DIOXINS--Analysis (AN); Environmental Exposure; FISH PRODUCTS--Analysis (AN); FISHES; Food Contamination--Analysis (AN); Industrial Waste; ISOTOPES; Liver--Analysis (AN); METHODS; SPECTRUM ANALYSIS, MASS; 2,4,5-TRICHLOROPHENOXYACETIC ACID; UNITED STATES; VIETNAM

0295606 74030606
Summary: conference on dibenzodioxins and dibenzofurans, National Institute of Environmental Health Services, April 2-3, 1973.
Burger EJ Jr
Environ Health Perspect (United States) .Sep 1973. 5 p265-6. ISSN 0091-6765 Journal Code: EIO
Languages: ENGLISH
Subfile: INDEX MEDICUS
Tags: Animal; HUMAN
Descriptors: ABNORMALITIES, DRUG-INDUCED--Etiology (ET); *BENZOFURANS; BENZOFURANS--Analysis (AN); BENZOFURANS--Poisoning (PO); CHICKENS; CHROMATOGRAPHY, GAS; CONGRESSES; *DIOXINS; DIOXINS--Analysis (AN); DIOXINS--Metabolism (ME); DIOXINS--Poisoning (PO); DIOXINS--Toxicity (TO); DOSE-RESPONSE RELATIONSHIP, DRUG; EDEMA--Veterinary (VE); ELECTRON SPIN RESONANCE; Environmental Exposure; Environmental Health; Liver--Enzymology (EN); POULTRY DISEASES--Chemically Induced (CI); SPECTRUM ANALYSIS; STRUCTURE-ACTIVITY RELATIONSHIP; 2,4,5-TRICHLOROPHENOXYACETIC ACID--Poisoning (PO); UNITED STATES

0295605 74030605
Tetrachlorodibenzodioxin in the environment: sources, fate, and decontamination.
Kearney PC; Woolson EA; Isensee AR; Helling CS
Environ Health Perspect (United States) .Sep 1973. 5 p273-7. ISSN 0091-6765 Journal Code: EIO
Languages: ENGLISH
Subfile: INDEX MEDICUS
Descriptors: BIOTRANSFORMATION; CARBON TETRACHLORIDE--Chemical Synthesis (CS); CHEMICAL INDUSTRY; CHEMISTRY; CHLOROBENZENES--Analysis (AN); CHLOROBENZENES--Metabolism (ME); Decontamination; *DIOXINS; DIOXINS--Analysis (AN); DIOXINS--Metabolism (ME); *ENVIRONMENT; Environmental Pollution--Prevention and Control (PC); Heat; HERBICIDES; Pesticide Residues--Analysis (AN); Soil; 2,4,5-TRICHLOROPHENO-

XYACETIC ACID--Analysis (AN)

0295603 74030603
Environmental generation and degradation of dibenzodioxins and dibenzofurans.
Crosby DG; Moilanen KW; Wong AS
Environ Health Perspect (United States) .Sep 1973, 5 p259-66, ISSN 0091-6765 Journal Code: EIO
Languages: ENGLISH
Subfile: INDEX MEDICUS
Descriptors: •BENZOFURANS; Biodegradation; •BIOPHYSICS; CHEMISTRY; CHLOROBENZENES; CHROMATOGRAPHY, GAS; •DIOXINS; DIOXINS--Chemical Synthesis (CS); DIOXINS--Radiation Effects (RE); Environmental Exposure; Heat; Pentachlorophenol--Radiation Effects (RE); PHOTOLYSIS; SPECTRUM ANALYSIS, MASS; Sunlight

0295602 74030602
Studies on the bioaccumulation and microbial degradation of 2,3,7,8-tetrachlorodibenzo-p-dioxin.
Matsumura F; Benezet HJ
Environ Health Perspect (United States) .Sep 1973, 5 p253-8, ISSN 0091-6765 Journal Code: EIO
Languages: ENGLISH
Subfile: INDEX MEDICUS
Tags: Animal
Descriptors: AEDES; •BACTERIA--Metabolism (ME); BENZENE HEXACHLORIDE--Metabolism (ME); •BIOTRANSFORMATION; CARBAMATES--Metabolism (ME); CARBON RADIOISOTOPES; CHLOROBENZENES--Metabolism (ME); CRUSTACEA; DDT--Metabolism (ME); •DIOXINS--Metabolism (ME); ECOLOGY; FISHES; LARVA; PESTICIDES--Metabolism (ME); Soil; Water; Xylenes--Metabolism (ME)

Summary: Conference on Dibenzodioxins and Dibenzofurans, National Institute of Environmental Health Services, April 2-3, 1973

by Edward J. Burger, Jr.*

To attempt to summarize the proceedings of a meeting such as this one in any rigorous sense is clearly an unreasonably ambitious task. It is made more challenging because of the tentative character of much of the work commented upon here.

This meeting, one of a series (and I hope a growing series) for the National Institute of Environmental Health Sciences, represents an extraordinarily useful concept. It is designed to bring together a variety of scientific bedfellows who have contemplated (and indeed investigated) a subject for its academic interest and for its very timely topical interest. These same scientists would have learned about each other eventually but, in the best tradition of science, it would have taken a long time.

By design, we are witnessing the cutting edge of scientific research for this area. This meeting has, as its avowed and very virtuous purpose, the calling out of the walls a good deal of unmatured and not totally interpreted or confirmed research. It is important to keep this tentative and unconfirmed character in mind.

One is struck, too, by the character of the research which has been reported at this meeting. There are still many gaps in our knowledge about dibenzofurans and dioxins. Yet, the thought that has gone into the design of the research reported here represents a striking degree of sophistication in many cases for which the participants should be very proud. As late as 1970 or 1971, there existed only the crudest hint of a ranking of biological activity of members of the family of chlorinated dioxins. (*1, 2*) The reports at this conference contained descriptions of dose–response information, some beginning insight into mechanisms, and the first probings toward structure–activity relationships. I am struck by the fact that the early observations (from the occupational environment) and the early approximations of rankings have been sustained and essentially confirmed by the data reviewed at this meeting.

Chemistry, Analysis, and Chemical and Physical Properties

Dr. Langer's paper on the formation of dioxins from precursors through condensation reactions represents a good example of what we should do more of. I speak here of the attempt to predict probable and improbable behavior in the environment from knowledge of physical and chemical properties. Dr. Langer's nuptial analogy is apt in more than one way. He reminded us that chemical courtship leading to marriage (in this case, condensation) was family-specific

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and adhered to some orthodox rules. Family character, and how this is perceived by the other party to the arrangement, seems to be important. It seems to me that Dr. Langer has thrown down the challenge of confirmation for dioxin formation, reported on by some as feasible in the environment. I am sure that this challenge will be taken up.

One other point was raised by Dr. Langer and was echoed independently by others was the spurious formation of condensation products within the chambers of the very instruments used to detect them (e.g., the gas chromatograph).

What is the evidence of "weathering"—the formation in nature of dioxins or furans from chlorinated materials through the addition of energy from somewhere? Crosby et al. and Hutzinger et al. suggested that condensation reactions to form dioxins or dibenzofurans might be promoted by exposure to sunlight and presented the results of a few preliminary experiments to examine this subject. What they properly reminded us of, however, was the fact that the story does not end there. The presence of detectable condensation products depends on the dynamics of both production and ensuing decomposition. Decomposition, they reminded us, occurs typically through reduction and here depends on an available hydrogen source. (They demonstrated the point in their laboratory experiments by using a hydrocarbon medium.) Tetrachlorodibenzo-*p*-dioxin was found to be more labile than the octochlorinated member of the family. It was speculated that there was sufficient organic material in most environmental situations to assure hydrogen donors. In brief, environmental persistence seems unlikely. The evidence seems to suggest that those impurities which are found are of the less toxic varieties. However, we need more samples because of the large variety of commercial products.

A. E. Pohland et al. revealed some of the potential and the limitations of two analytic methods, electron spin resonance and visible light spectroscopy. As I heard this paper, these sounded particularly useful as confirmatory techniques. The authors cited the need for pure standards to realize the potential of their methods.

Dr. Crummett's paper is perhaps the latest in a growing series of examples of how the power of analytic methods tends to "drive" manufacturing procedures to be more rigorous and produce greater degrees of purity. His point is well made. We are all better off as a result.

It is heartening to note the similarity in degrees of resolution reported both by Crummett, et al. and by Drs. Baughman and Meselson for measurement of dioxin through mass spectroscopy. Understandably these results rested, apparently, on an extensive clean-up procedure. (I think some may still be bothered by what I understand is a wide intrasample variability among some of the measurements.) Since they are "pushing" their art to a point near its limits, perhaps these results deserve as much confirmation as possible. Nevertheless, the power of sensitivity and resolution are indeed impressive.

Biological Effects

I think that it is extremely important to acknowledge the fact that the original biological insight into dioxins came from a series of observations made by Dr. Suskind of accidental occupational exposures in the late 1940's. The exposure was the result of accidental release of chemical intermediates in a 2,4,5-T plant in 1949 resulting in exposure of a number of workers to manifest chloracne. In 1957, Kimmig and Schulz reported chloracne among workers in 2,4,5-T plant in Germany. A third occupational incident occurred in a 2,4,5-T plant in the United States in 1964. In a way, it is somewhat disappointing that there is not more human experience reported at this meeting. I think that there is still a clouded issue, an unclear distinction between the effects of PCB, 2,4,5-T and of dioxins and furans. For example, we should somehow ascertain whether Yusho disease in Japan was a reflection of exposure to polychlorinated biphenyls or to furan impurities. Dr. Fire-

stone reviewed the history of the contribution of the [redacted] to our understanding of dioxins. The sleuthing done by the FDA pieced together the story of the large-scale loss of poultry (which happened first in 1957), related it to the use of tallow in poultry feed and, eventually, to the presence of dioxin impurities. Higginbotham et al. first offered a rough approximation of ranking of biological activity of dioxins which has turned out to be strikingly accurate. What has emerged from this meeting is the very wide range of toxicity for the several members of the dioxin family (perhaps as much as 10^5).

This meeting revealed some interesting (and, perhaps, ultimately successful) attempts to relate chemical structure to biological activity. Several participants reminded us that to be a successful toxic dioxin, a candidate needs two halogens at the [redacted] positions and one at [redacted] positions, and also needs halogens on both benezene rings. Bromine confers more biological activity than [redacted] and chlorine [redacted] than fluorine.

I'll say very little about teratogenesis. It seems to me that a strong case can be made for clearing the air about the mechanism of teratogenesis. Is this an example of acute (embryo) toxicity with a steep dose–response curve and a demonstrable threshold? It's not clear that everyone who reports birth defects is talking about the same phenomenon. Dr. Moore, at this meeting, described some fascinating, postnatal effects of maternal exposure to TCDD through a series of cross-fostering and reciprocal cross-fostering studies of mice. These deserve further attempts at interpretation.

The effects on experimental animals are difficult to summarize completely. However, there are some underlying currents showing through:

(1) there is a variation in susceptibility among species—guinea pigs versus rats and mice; (2) there are striking sex differences; (3) delayed effects are very prominent (liver changes 2 weeks after exposure); (4) the major sites of toxic action appear to be the liver (seen as a variety of changes in liver function), the hematopoietic system (platelet depression, altered platelet function, leucocytosis and hemoconcentration) and the lymphatic system (spleen, thymus and lymph nodes). The atrophy of the thymus and the general lymphoid depletion reported at this meeting were very striking.

As for morphological alterations, the changes in the ultrastructure under the electron microscope are of course most interesting. Perhaps the most significant point is that the morphological alterations tend to follow and confirm the functional changes which were described independently. There seems to be a delay (perhaps on the order of 5 days) between exposure and manifest structural changes. The magnitude of the change is dose-related, and the changes are reversible with time. A particularly fascinating finding was that of multinucleated hepatic cells. Do these represent a stage of attempted regeneration and repair? Alternatively, are they possible precursors of neoplastic change? This conference presented little evidence that dioxins would induce or promote neoplastic changes in tissues.

Patterns of absorption into the organism and of distribution among organs once absorbed are beginning to emerge. Not unexpectedly, water and lipid solubility seems to emerge as a major influence, although clearly not the only one. For tetrachlorodibenzo-*p*-dioxin (high doses in male rats), the amount absorbed via the intestine from an ingested dose appears to be about 70%. The majority of the absorbed dose appears in the feces at a rate of 1–2% day and in the urine at a rate of 0.5% day. A small amount can be detected in the expired air (<0.1% day). The material resident in the organism is characteristically found in the adipose tissue and the liver. It is notably absent from certain other fatty tissues such as those of the central nervous system.

By contrast, for octachlorodibenzo-*p*-dioxin only 5% achieves absorption. Again, a large share is found in the liver (50%) and in the adipose tissues (12%). Once in

the liver; this material apparently tends to remain resident for long periods in the liver microsomes.

This meeting served to bring together a remarkable amount of work on the effect of dioxins on cellular enzymes. This was all the more remarkable, as none of this work had even been conceived of two years ago. A number of hepatic enzymes were found to be induced and a few depressed as a result of dioxin exposure. (A general caveat was voiced over what appeared to be unusually high doses of dioxin used in some of the experiments.) The degree of induction was at times striking. The experiments revealed a dose–response relationship. Again, there was an unequivocal sex difference and a characteristic latent period between exposure and induction. Effects were often long-lasting (for example, a persistent threefold increase 38 days after exposure in one experiment). Again, lipid solubility may play a large role.

The meaning of enzyme changes is as yet unclear. There are some striking differences among species. ALA synthetase, whose activity is related to the disease, porphyria, can be induced by dioxin administration in the chick embryo but apparently not in mammals. One has the impression of being very close to some insight into mechanisms yet not close enough. The combination of enzyme induction studies and changes in cellular ultrastructure could prove very helpful.

Where do we stand on our knowledge of biological activity? For furans, we know very little. It seems to me that we still must determine whether Yusho disease was a reflection of PCB exposure or a result of exposure to dibenzofuran or other impurity. For dioxins, we now are better equipped. However, we must now reconcile a number of somewhat paradoxical observations: (1) extraordinarily high degree of biological activity, especially for certain chemical forms (tetrachlorodibenzo-*p*-dioxin was pointed out to be the most potent small molecule toxin known); (2) striking species differences in activity; (3) sex differences; (4) biological activity falls off rapidly with changes in chemical structure; (5) latent period before toxic manifestations; (6) dose-related effects; (7) long-lasting but ultimately reversible effects.

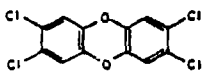
Effects on Wildlife

Understandably there is less work here than one would like. The preliminary work reported by Bowes concerning survey of wildlife is a good model and should be continued. Preliminary results seemed to suggest a very wide variety of chemical species found in the animals examined with an uncertain role for dioxins and furans.

REFERENCES

1. Higginbotham, G. R., Ress, J., and Firestone, D. Chick edema factor in fats and fatty acids. Chem. Eng. News 44: 53 (1966).
2. Higginbotham, G. R., Huong, A., Firestone, D., Verrett, J., Ress, J., and Campbell, A. D. Chemical and toxicological evaluations of isolated derivatives of dibenzo-*p*-dioxin. Nature 220: (1968).

33956s TCDD [2,3,7,8-tetrachlorodibenzo-p-dioxin]. Deadly molecule. Gribble, Gordon W. (Dartmouth Coll., Hanover, N. H.). *Chemistry* 1974, 47(2), 15–18 (Eng).



A review with 13 refs. of the toxicity, teratogenicity, and environmental properties of *TCDD* (I) [1746-01-6], a contaminant in prepns. of 2,4,5-T and other pesticides.

33957t Toxic oxygen effects. Swartz, Harold M. (Dep. Radiol., Med. Coll. Wisconsin, Milwaukee, Wis.). *Int. Rev. Cytol.* 1973, 35, 321–43 (Eng). A review with 65 refs. of toxic effects of *oxygen* [7782-44-7] on cellular processes.

33958u Plutonium. Biomedical research. Bair, W. J.; Thompson, R. C. (Pac. Northwest Lab., Battelle Mem. Inst., Richland, Wash.). *Science* 1974, 183(4126), 715–22 (Eng). A review, with 45 refs., of the chem. and phys. properties, metab., and toxicity of, antidotes for, and health hazards from *plutonium* [7440-07-5].

33959v Effects of ethanol upon lipid metabolism. Lieber, Charles S. (Liver Dis. Nutr. Lab., Bronx Veterans Adm. Hosp., Bronx, N. Y.). *Lipids* 1974, 9(2), 103–16 (Eng). A review with 183 refs.

33960p Fate of metabolites of insecticides in plants and animals. Wongsiri, Siriwat (Dep. Entomol., Univ. California, Davis, Calif.). *Thai J. Agr. Sci.* 1973, 6(4), 315–22 (Eng). A review with 8 refs. on the mode of action and metab. of synthetic org. insecticides including chlorinated hydrocarbons, organophosphate compds., and carbamate compds.

33961q Assimilability of calcium oxalate. Krauze, S.; Oledzka, R. (Pharm. Fac., Med. Akad., Warsaw, Pol.). *Mitt. Geb. Lebensmitteluntersuch. Hyg.* 1973, 64(4), 504–18 (Ger). A review with 61 refs., of the toxicol. of *calcium oxalate* [563-72-4] of plant and animal origin, including its role in nutrition, relation to vitamin D and Ca retention, influence on the Ca/P ratio in bone, tissue distribution, soly. in gastric juice, dialysis behavior, and resorption. E. E. Gansel

33962r Alcohol dehydrogenase system during chronic alcoholism. Gurtovenko, V. M. (Tsentr. Nauchno-Issled. Inst. Sud. Psikhiatr. im. Serbskogo, Moscow, USSR). *Zh. Nevropatol. Psikhiat. im. S. S. Korsakova* 1974, 74(2), 291–6 (Russ). A review with 80 refs. *Ethanol* [64-17-5] metab. in animal tissues is discussed in relation to pathogenesis of chronic alcoholism.

33963s Chemical methods in criminal technology. Maehly, Andreas (Statens Kriminaltek. Lab., Solna, Swed.). *Kem. Tidskr.* 1974, 86(1-2), 38–40 (Swed). A review with no refs. The Swedish criminal lab. organization is discussed with emphasis on anal. methods for *amphetamine* [300-62-9] and marihuana detection. B. Prytz

33964t New advances in the toxicology of carbon disulfide. Teisinger, J. (Dep. Ind. Hyg. Occup. Dis., Inst. Hyg. Epidemiol., Prague, Czech.). *Amer. Ind. Hyg. Ass., J.* 1974, 35(2), 55–61 (Eng). A review with 37 refs.

33965u Biochemistry of alcohol. Batt, R. D. (Massey Univ., Palmerston North, N. Z.). *N. Z. Med. J.* 1974, 79(506), 556–60 (Eng). Disruptions of normal body metab. which are due to *ethanol* [64-17-5] are reviewed with several refs.

33966v Effects of alcohol on the kidney and blood electrolytes. Richmond, D. E. (Dep. Med., Auckland Hosp., Auckland, N. Z.). *N. Z. Med. J.* 1974, 79(506), 561–3 (Eng). A review with 17 refs. The diuretic and osmolality effects of *ethanol* [64-17-5], and the relationship of gout, metabolic acidosis, and *magnesium* [7439-95-4] deficiency to EtOH ingestion are discussed in relation to the kidney and blood electrolytes.

33967w Effects of some air pollutants on farm animals. Jones, L. H. P.; Cowling, D. W. (Dep. Soils Plant Nutr., Grassl. Res. Inst., Hurley/Berks., Engl.). *Nat. Soc. Clean Air, Annu. Conf., Proc.* 1973, 40, Pt. 1, VII, 7 pp. (Eng). A review with 32 refs. The effects of air pollution by fluorides, dusts, and heavy metals on farm animals are discussed.

33968x Effects of pesticides on soil animals. Newman, J. F. (Plant Prot. Ltd., Engl.). *Nat. Soc. Clean Air, Annu. Conf., Proc.* 1973, 40, Pt. 1, VIII, 6 pp. (Eng). A review with 7 refs. Methods for investigation of the effects of pesticides on soil animals, and the effects of insecticides, fungicides, and herbicides on soil animals are discussed.

33969y Developmental studies on some enzymes associated with detoxication. Dutton, G. J. (Med. Sci. Inst., Univ. Dundee, Dundee, Scot.). *Enzyme* 1973, 15(1-6), 304–17 (Eng). The author's work on the activation and induction of glucuronidating, hydroxylating, and assocd. enzymes, esp. *UDP glucuronyltransferase* (*EC 2.4.1.17*) [9030-08-4], during development is summarized and related to the detoxication process. 52 Refs. are included.

33970s DDT. Renaissance. Devlin, Robert M. (Univ. Massachusetts, East Wareham, Mass.). *Environ. Sci. Technol.* 1974, 8(4), 322–5 (Eng). A review with 3 refs. of a general discussion on biol. toxicity of *DDT* [50-29-3].

33971t Toxicological problems of using sewage sludge in agriculture. Hansen, Jens Aa.; Tjell, Jens C. (Lab. Tek. Hyg., Dan. Tek. Hogsk., Lyngby, Den.). *NORDFORSK, Miljovardssekretariatet, Publ.* 1974, (2), 11–28 (Dan). A review, with 26 refs. K. H. Zingraf

33972u Endangering the environment by combustion resistant hydraulic fluid components. Thuenes, Hans W. (Rheinisch-Westfael Tech. Ueberwach. Ver e.V., Essen, Ger.). *Schmiertech. Tribol.* 1974, 21(1), 3–6 (Ger). A review with 17 refs.

33973v Protecting horticultural plants from atmospheric pollutants. Review. Ormrod, D. P.; Adedipe, N. O. (Univ. Guelph, Guelph, Ont.). *HortScience* 1974, 9(2), 108–11 (Eng). A review with 71 refs. Long- and short-term aspns. in the protection of horticultural plants from air pollutant damage are discussed. The edaphic, environmental, and genetic aspects of plant protection, including the use of chem. agents, are emphasized.

33974w Scientific principles for determining approximate safe levels of action of chemical substances on man. Lyublina, E. I.; Mikheev, M. I. (USSR). *Zh. Vses. Khim. Obshchest.* 1974, 19(2), 142–6 (Russ). A review with 26 refs. The relation between phys. and chem. properties of chem. compds. and their toxicity is discussed with special emphasis on volatile org. compds.

33975x Basic trends in the study of pesticide toxicology and prophylaxis of the harmful effect of the pesticides. Kagan, Yu. S. (USSR). *Zh. Vses. Khim. Obshchest.* 1974, 19(2), 192–200 (Russ). A review with 122 refs. Toxic properties of pesticides are discussed with special emphasis on DDT, organophosphorus compds., and carbamate, thiocarbamate, and dithiocarbamate derivs.

33976y Comparative toxicity of rare earth metals and its relation to some of their properties. Spasskii, S. S. (Mosk. Med. Inst. im. Sechenova, Moscow, USSR). *Gig. Sanit.* 1974, (4), 33–6 (Russ). A review with 3 refs.

33977z Supposed mechanism of the action of surfactants on animals. Kumpan, N. B. (Inst. Obshch. Kommunal'n. Gig. im. Sysina, Moscow, USSR). *Gig. Sanit.* 1974, (4), 78–80 (Russ). A review with 23 refs. The effects of surfactants on cell membranes and lipid metab. are discussed.

33978a Biological models of alcohol tolerance and physical dependence. Kalant, H. (Dep. Pharmacol., Univ. Toronto, Toronto, Ont.). *Advan. Exp. Med. Biol.* 1973, 35, 3–14 (Eng). A review, with 38 refs., in which *ethanol* [64-17-5] interference with. The feedback control of physiol. functions is discussed in relation to models of drug dependence.

33979b Addiction to barbiturates and ethanol. Possible biochemical mechanisms. Tabakoff, Boris; Ungar, Frieda; Alivisatos, S. G. A. (Dep. Biochem., Chicago Med. Sch., Chicago, Ill.). *Advan. Exp. Med. Biol.* 1973, 35, 45–55 (Eng). A review, with 43 refs., in which addiction to barbiturates and *ethanol* [64-17-5] is discussed in relation to biogenic amine metab. by the brain.

33980v Exotoxins and the enzymic systems. Busila, V. T.; Dragomirescu, M. (Clin. Boli Infect., Inst. Med. Timisoara, Timisoara, Rom.). *Microbiol., Parazitol., Epidemiol.* 1973, 18(6), 481–8 (Rom). A review with 20 refs. on the effect of bacterial exotoxins on the enzyme systems involved in metabolic pathways.

33981w Problem of permissible limits of potentially toxic substances in the working and general environment of modern man. Truhaut, Rene (Fac. Sci. Pharm. Biol., Univ. Rene Descartes, Paris, Fr.). *Environ. Qual. Saf.* 1973, 2, 135–65 (Fr). A review with 47 refs. The toxicity of pollutants and carcinogenic compds. is discussed in relation to evaluation of permissible doses.

33982x Toxicology and epidemiology of natural hepatotoxin exposure. Kraybill, H. F. (Natl. Cancer Inst., Natl. Inst. Health, Bethesda, Md.). *Isr. J. Med. Sci.* 1974, 10(4), 416–25 (Eng). A review with 48 refs., of hepatotoxins including mycotoxins, plant toxins, bacterial endotoxins, and metals.

33983y Host factors in hepatotoxicity. McLean, Andre E. M. (Univ. Coll. Hosp. Med. Sch., London, Engl.). *Isr. J. Med. Sci.* 1974, 10(4), 431–5 (Eng). A review, with 19 refs., of the relation of liver metab. to liver damage from environmental pollutants, industrial chems. and drugs.

33984z Senecio and other plants as liver poisons. McLean, Elizabeth K. (Maudsley Hosp., London, Engl.). *Isr. J. Med. Sci.* 1974, 10(4), 436–40 (Eng). A review, with 7 refs. of *pyrrolizidine* [643-20-9] alkaloids from *Senecio* and other plants as liver poisons.

33985a Biochemical effects of aflatoxins. Wogan, Gerald N. (Dep. Nutr. Food Sci., Massachusetts Inst. Technol., Cambridge, Mass.). *Isr. J. Med. Sci.* 1974, 10(4), 441–5 (Eng). A review, with 29 refs., of the toxicol. effects of aflatoxins.

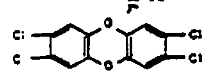
stimulation of several globulins, 4 or 5 haptoglobulins and 3 [illegible]. *Ferrous chloride* [7758-94-3] produced only slight alterations but brought about a stimulation of transferrin after 3 weeks of exposure. Sera analyzed after 3 months of ingestion of heavy metals appeared essentially identical to controls, suggesting that adaptive processes had been elicited which enabled the animals to tolerate const. exposure to high levels of the resp. metals including Hg which is usually considered toxic.

133435v **Subacute oral toxicity of trisodium nitrilotriacetate (Na_3NTA) in dogs.** Buday, John A.; Niewenhuis, R. J.; Buehler, E. V.; Goldenthal, E. I. (Miami Val. Lab., Procter and Gamble Co., Cincinnati, Ohio). *Toxicol. Appl. Pharmacol.* 1973, 26(1), 148–53 (Eng). *Trisodium nitrilotriacetate* [5064-31-3] fed to dogs for 90 days at 0.03, 0.15, and 0.5% of the diet produced no significant changes in general appearance, survival, hematol., serum chem., urinalysis, fecal cation excretion, and microscopic tissue exams. Nitrilotriacetic acid was deposited in bone (123–42 ppm at the 0.5% level), but this was without adverse effect.

133436z **Carrageenan and large-bowel ulceration in mammals.** Grasso, P.; Sharratt, M.; Carpanini, F. M. B.; Gangolli, S. D. (Br. Ind. Biol. Res. Assoc., Carshalton/Surrey, Engl.). *Food Cosmet. Toxicol.* 1973, 11(4), 555–64 (Eng). Administration of *carrageenan* [9000-12-8] in either native or degraded form produced acute or chronic ulcerationin in the large intestine of guinea pigs and rabbits. Preulcerative changes consisted primarily of accumulations of macrophages in the lamina propria and were assocd. with the presence of carrageenan in the subepithelial tissues. None of these changes occurred in the rat, hamster, squirrel monkey, or ferret. Limited tests indicated that humans were also resistant to the material.

133437a **Intestinal effects of carrageenans in the rhesus monkey (Macaca mulatta).** Benitz, K. F.; Golberg, L.; Coulston, F. (Inst. Exp. Pathol. Toxicol., Albany Med. Coll., Albany, N. Y.). *Food Cosmet. Toxicol.* 1973, 11(4), 565–75 (Eng). Male and female rhesus monkeys given native *carrageenan* [9000-13-9] (from *Chondrus crispus*) at 1.2 g/kg/day in their drinking water for 7–14 weeks all gained wt. and remained in good condition, and microscopic exams. of their intestinal tract revealed little or no change. Monkeys given degraded carrageenan (from *Eucheuma spinosum*) at 2.9 g/kg/day showed considerable wt. losses, intestinal tract bleeding, and anemia. Patholog. changes in the colon ranged from shallow mucosal erosions to ulceration assocd. with cellular infiltration, granulation tissue in the lamina propria, and formation of multiple crypt abscesses. These changes reversed somewhat when the animals recovered on tap water for 14 weeks.

133438b **Toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin.** Greig, J. B.; Jones, Glenys; Butler, W. H.; Barnes, J. M. (Toxicol. Unit, Med. Res. Counc. Lab., Carshalton/Surrey, Engl.). *Food Cosmet. Toxicol.* 1973, 11(4), 585–95 (Eng).



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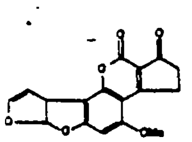
2,3,7,8-*Tetrachlorodibenzo-p-dioxin* (I) [1746-01-6] caused pericardial edema and death in chickens after a single oral dose of 25–50 μg/kg. The extreme toxicity of I for guinea pigs was confirmed. Female rats given I orally at 200 μg/kg had depressed food intake and wt. loss, and died in 40 days. Postmortem examn. revealed gastric hemorrhage and jaundice in many cases. The liver showed pathol. changes at later periods, in particular the formation of multinucleate parenchymal cells.

133439c **Excretion and metabolism of orally administered aflatoxin B, by rhesus monkeys.** Dalezios, J. L.; Hsieh, D. P. H.; Wogan, G. N. (Dep. Environ. Toxicol., Univ. California, Davis, Calif.). *Food Cosmet. Toxicol.* 1973, 11(4), 605–16 (Eng). Rhesus monkeys given ^{14}C-labeled *aflatoxin* B_1 (I)



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[1162-65-8] orally at 0.015 or 0.4 mg/kg excreted 40% of the radioactivity in the urine and 42% in the feces in 7 days. The blood and esp. the liver retained radioactivity for >5 weeks. The major urinary metabolite sepd. from a $CHCl_3$ extn. was *aflatoxin* [illegible] [6795-23-9], which accounted for 18–20% of the administered radioactivity during days 1–4. Four unidentified metabolites were also found in the $CHCl_3$ fraction. *Aflatoxin* P_1 [32215-02-4] in the urine represented 5% of the administered radioactivity, and was excreted as the glucuronide and the SO_4^{2-} conjugate. Only 15% of the fecal radioactivity was solvent extractable. Aflatoxins M_1 and B_1 in the feces accounted for 2.6 and [illegible] the dose, resp.

133440w **Pathology of liver necrosis and regeneration after administration of dimethylnitrosamine in massive [illegible].** Kuster, Gustavo G. R.; Woods, John E.; Ludwig, [illegible] (Mayo Clin. and Mayo Found., Rochester, Minn.). *J. Su[illegible] Oncol.* 1973, 5(1), 9–16 (Eng). Centrilobular and midzonal congestion and necrosis occurred in the livers of [illegible] given a lethal dose of *dimethylnitrosamine* [62-75-9], [illegible]. Auxilary liver transplants saved the animals' lives and lessened the hepatic damage. Cirrhosis of the liver did not occur in any case.

133441x **Physiological and ultrastructural effects of fluoride on tissues of Rubus cultivated in vitro.** Pilet, Paul E.; Roland, Jean C. (Inst. Biol. Physiol. Veg., Univ. Lausanne, Lausanne, Switz.). *Ber. Schweiz. Bot. Ges.* 1972, 82(3), 259–83 [illegible]. At high levels (10^{-3} and $10^{-4}M$ of NaF), *fluoride* [16984-48-8] inhibited growth (expressed in terms of changes in fresh wt. and total protein) of *R.* [illegible]. The ma[illegible] uptake of fluoride [illegible] with the [illegible] phase (about 10 days) of the tissues. [illegible] density of free ribosomes and altered the [illegible] and the endoplasmic reticulum.

133442y **Ozone interaction with [illegible]. II. Effects on oxygen consumption of [illegible].** [illegible] Mohammad G.; DeLucia, Anthony J.; [illegible] George K.; Aith Christopher; Cross, Carroll E. (Sch. Med., Univ. California, Davis, Calif.). *J. Lab. Clin. Med.* 1973, 82(3), 357–65 (Eng). Acute exposure of rats to the environmental pollutant *ozone* [10028-15-6] (2 ppm for 8 hr) decreased the O consumption of lung homogenates and mitochondria, as did in vitro ozone treatment of the homogenate or mitochondrial fractions. In contrast, subacute exposures (0.8 ppm for 10 or 20 days) increased O utilization. An increase in the specific activity of mitochondrial respiratory enz. [illegible] in the latter animals was not sufficient to account for the overall stimulation of respiration. Subacute ozone increased the abundance of Type II alveolar cells, however and these cells contain many mitochondria. An increased no. of mitochondria may therefore account for the enhancement of O consumption following subacute ozone exposure.

133443z **Elevated circulating renin activity in rats following doses of cadmium known to induce hypertension.** [illegible] H. Mitchell, Jr.; Erlanger, Margaret W. (Sch. Med., Washington Univ., St. Louis, Mo.). *J. Lab. Clin. Med.* [illegible], 399–405 (Eng). Blood *renin* [9015-94-5] activity was elevated in rats administered *cadmium acetate* [543-90-8] in amts. sufficient to induce hypertension but not overt toxicity or renal dysfunction. The animals recieved 1.8 μmoles of Cd i.p. or 5 [illegible] in their drinking water. The Cd-injected rats had simultaneous elevations of both blood pressure and renin activity, the increases in the two parameters being significantly correlated.

133444a **Determination of carbon monoxide and carbon dioxide in cigaret smoke.** Reif, H.; Kuhn, H. (Austria Tabakwerke A.-G., Vienna, Austria). *Fachliche Mitt. Oesterr. Tabakregie* 1973, 14, 239–51 (Ger). An app. is described for the complete and direct detn. of *carbon monoxide* [630-08-0], *carbon dioxide* [124-38-9], *oxygen* [7782-44-7], *nitrogen* [7727-37-9], and *methane* [74-82-8] in cigaret smoke. The one channel app. contains, in sequence, a smoking machine, smoke-collection balloon, electromagnetic valve, and gas chromatograph equipped with a 1 m column filled with a 5 Å mol. sieve. When tested oriental tobacco burned more slowly, and produced slightly less CO than Virginia, Burley, or cigar tobacco. CO prodn. was increased by addmixt. with puffed or sheet tobacco, but unaffected by addmixt. with synthetic tobacco. Increased paper porosity, or inclusion of a ventilation zone or selective filter in the cigaret also reduced CO prodn. Thus, CO in cigaret smoke may be controlled better by altering cigaret prepn. (paper, filter etc.), than the tobacco blend. However, synthetic tobacco can be used to lower the tar and nicotine content of cigarets without increasing CO prodn.

133445b **Toxicological, radioisotopic, and immunological study during the evaluation of the action of some detergents under experimental conditions.** Veldre, Ingeborg; [illegible]esaar, S.; Saliev, V. (USSR). *Gig. Tr. Prof. Patol. Est. SSR* 1972, No. 8, 115–19 (Russ). Rats given oral doses of the detergents *sulfonol* [12068-03-7] and *tipol* [39450-12-9] at 20% LD_{50}/day for 30 days showed no abnormal changes in appearance or behavior. Radioisotope hepatography showed that sulfonol slightly decreased the absorption-excretory function of the liver. Neither detergent affected skin microfloral levels or the phagocytic activity of blood neutrophils. Tipol induced a temporary decrease in erythrocyte no. and increase in neutrophil count. Wt. gain by the exptl. animals slightly lagged behind that of controls. Therefore, these detergents are of low toxicity for animals.

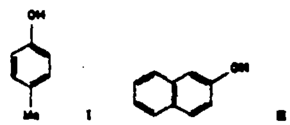
133446c **Effect of the structure and physicochemical qualities of some phenols on their biological activity.** Veldre, Ingaborg (USSR). *Gig. Tr. Prof. Patol. Est. SSR* 1972, No. 8, 146–54 (Russ). 3,4-*Dimethylphenol* (I) [95-65-8], 2,6-*dimethyl*=

K26195 K11257

Me I II

phenol (I) [576-26-1], and other methylphenols found in shale waste water showed little cumulative toxic properties when tested on exptl. animals. S survey of the literature showed that there was no clear relation between the biol. activity of these phenols and their chem. structure and phys. chem. properties.

133447d Combined effect of orally administered p-cresol and β-naphthol on a warm-blooded organism. Veldre, Ingeborg (USSR). *Gig. Tr. Prof. Patol. Est. SSR* 1972, No. 8, 155-64 (Russ). Rats receiving orally *p-cresol* (I) [106-44-5] at 0.0001

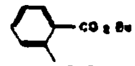


Me I II

mg kg day or *β-naphthol*(II) [135-19-3] at 0.44 mg/kg/day for 8 months showed abnormalities in nervous system functions, as indicated by changes in conditioned reflex formation in faulty regulation of blood pressure after *adrenaline* [51-43-4] administration. At 50% of these doses the compds. had no toxic effect. The 2 compds. upon combined administration were additive in their effects on the animals.

133448e Effect of chloroprene on embryogenesis. Sal'nikova, L. S.; Fomenko, V. N. (Inst. Gig. Tr. Profzabol., Moscow, USSR). *Gig. Tr. Prof. Zabol.* 1973, (8), 23-6 (Russ). Female rats inhaling *chloroprene* [126-99-8] at 3-4 mg/m³ (i.e., the max. permissible concns. in industrial establishment) four hrs daily throughout their pregnancy showed high embryonal mortality, reduced fetal wt., and abnormalities in fetal vascular permeability. The neonats showed deficient wt. gain and poor functioning of the parenchymatous organs. Chloroprene similarly administered at 10 times lower concns. still had an adverse effect on the offspring of the rats, and at 100 times lower concn. (0.56 mg/m³) had no effect on embryogenesis or on the offspring.

133449f Substantiation of the maximum permissible concentration of dibutyl phthalate in the air of industrial premises. Antonyuk, O. K.; Aldyreva, M. V. (Inst. Gig. Toksikol. Pestits., Polim. Plast. Mass., Kiev, USSR). *Gig. Tr. Prof. Zabol.* 1973, (8), 26-30 (Russ). Anal. of gases given off



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during heating of poly(vinyl chloride) materials plasticized with phthalates showed that the major component was *dibutyl phthalate* (I) [84-74-2]. Toxicol. studies of the effects of I on mice, rats, and rabbits were carried out, and extrapolations to the human organism indicated that the air inside industrial establishments should not contain more than 0.5 mg I/m³.

133450z Autoimmune processes in experimental benzene-induced hemopathy. Tikhachek, E. S.; Frash, V. N. (Med. Inst., Sverdlovsk, USSR). *Gig. Tr. Prof. Zabol.* 1973, (8), 30-3 (Russ). Rabbits poisoned with *benzene* [71-43-2] (0.5 ml/kg/day s.c. for 2 weeks) showed a reticuloplasmocytic reaction in their bone marrow and increased antibody titres to spleen and bone marrow antigens and to leukocytes and erythrocytes. C_6H_6 also had a no. of hematol. effects, i.e. erythrocyte, reticulocyte, and thrombocyte nos. decreased. During the recovery period, normalization of blood cell compn. paralleled the decrease in autoimmune antibodies.

133451a General toxic effect of perchloric acid. Selivanova, L. N.; Koltunova, I. G.; Vorob'eva, E. N. (Moscow, USSR). *Gig. Tr. Prof. Zabol.* 1973, (8), 33-5 (Russ). *Perchloric acid* [7601-90-3], given orally or s.c. to rats, mice, and dogs, showed in addn. to its irritating effect a specific antithyroid action, and also induced abnormalities in hepatic, renal, cardiovascular, and hemopoietic functions. These effects should be considered when evaluating the industrial toxicity of $HClO_4$.

133452b Effect of some food components on the met-and sulfhemoglobin-forming action of nitrates and nitrites. Rinna, M.; Lutsoya, Kh. I. (Tallin. Nauchno-Issled. Inst. Epidemiol., Mikrobiol. Gig., Tallin, USSR). *Sb. Dokl. Respub. S'ezda Epidemiol., Mikrobiol., Infek. Gig., 2nd* 1972, 301-5 (Russ). Edited by Yannus, [illegible] Tallin. Nauch.-Issled. Inst. Epidemiol., Mikrobiol. Gig.: Tallin, USSR. [illegible] (a yoghurt like drink), lactic acid [50-21-5], [illegible] [110-44-1], and *pyridoxine* [65-23-6] decreased the [illegible] methemoglobin and sulfhemoglobin in rat induced [illegible] *nitrate* [14797-55-8], when given along with NO_3^- [illegible] this protective effect when its lactic acid was pptd. as [illegible] salt. Sour milk made from unpasteurized milk [illegible] methemoglobin and sulfhemoglobin formation in [illegible] humans eating food contg. NO_3^-. Therefore [illegible] particular product should never be consumed together with NO_3^- [illegible] foods, e.g. vegetables.

133453c Tetratogenic and embryotoxic action of [illegible] nitrites and nitrates added to food products. Subbotin, [illegible] Volkova, N. V. (Leningr. Sanit.-Gig. Med. Inst., Le[illegible] USSR). *Sb. Dokl. Respub. S'ezda Epidemiol., Mikrobiol.* [illegible] *Gig., 2nd* 1972, 309-11 (Russ). Edited by Yannus [illegible] Tallin. Nauch.-Issled. Inst. Epidemiol., Mikrobiol. Gig.: T[illegible] USSR. *Na nitrite* [7632-00-0], and to a lesser extent [illegible] [7631-99-4], were strongly teratogenic and embryotoxic [illegible] chick embryos when added at 1 mg/egg in water soln. The livers of the fetal chicks showed a no. of protein and fat dystrophic changes.

133454d Toxicity of pyrocatechol as a primary product of phenol oxidation. Veldre, I.; Kim, U. (Inst. Eksp. Klin. [illegible] Tallin, USSR). *Sb. Dokl. Respub. S'ezda Epidem[illegible] Mikrobiol., Infek. Gig., 2nd* 1972, 345-7 (Russ). Edited [illegible] Yannus, A. E., Tallin. Nauch.-Issled. Inst. Epid. [illegible] Mikrobiol. Gig.: Tallin, USSR. The toxicity of a *pyrocatechol-phenol mixt.* [39450-16-3] varied directly with the pr[illegible] *pyrocatechol* [120-80-9] and was higher in female rats [illegible] males. The clin. pattern of pyrocatechol poisoning (administered by gastric gavage) in rats was somewhat different from that [illegible] *phenol* [108-95-2] itself and was characterized by a [illegible] period of increased motor activity (esp. running and jumping) starting 3-5 min postadministration, then clonic spasms, and finally death (usually within the 1st few hr.

133455e Experimental toxicological study of some nitroparaffins. 2. 1-Nitropropane. Dequidt, J.; Vasseur, P.; Potencier, J. (Lab. Toxicol. Hyg. Atmos., Fr.). *Bull. Soc Pharm. Lille* 1972, (4), 131-6 (Fr). Whether administered i.p. or by inhalation, *1-nitropropane* [108-03-2] induced lower levels of methemoglobin than those previously obsd. after 2-nitropropane treatment of rats. 1-Nitropropane, however, was more toxic (inducing death at lower doses) than 2-nitroprop[illegible] route, and less toxic than the latter by the pulmonary route.

133456f Experimental toxicological study of some nitroparaffins. 3. Nitroethane. Dequidt, J.; Vasseur, P., [illegible] (Lab. Toxicol. Hyg. Atmos., Fr.). *Bull. Soc. Pharm.* [illegible] (4), 137-41 (Fr). Whether administered to rats [illegible] inhalation, *nitroethane* [79-24-3] was considerably less [illegible] the previously studied 1- and 2-nitropropanes. Even [illegible] acute intoxication, only low levels of methemoglobin [illegible] induced by nitroethane.

133457g Experimental toxicological study of acetonitrile [illegible] rats. 1. Acute intraperitoneal intoxication. Dequidt [illegible] Haguenoer, J. M. (Lab. Toxicol. Hyg. Atmos., Fr.). *Bull.* [illegible] *Pharm. Lille* 1972, (4), 149-54 (Fr). In rats which had been given a single i.p. injection of *acetonitrile* [75-05-8] [illegible] concns. of the latter were similar in all organs [illegible] mg/100 g), concns. of free *hydrocyanic acid* [74-90-8] were negligible, and levels of dissimilated HCN ranged from [illegible] 359 μg/100 g in the liver to highs of 1327, 1757, and 1045 [illegible] in the spleen, stomach, and skin, resp.

133458h Order deeming certain spray adhesives to be banned hazardous substances due to finding of imminent hazard to the public health. Anon. (Consum. Prod. Saf. Comm., Washington, D. C.). *Fed. Regist.* 22 Aug 1973, 38(162), 22569 (Eng). There is a causal connection between exposure to specified spray adhesives and chromosome damage leading to genetic birth defects. Distribution of these products for household use is banned under the Federal Hazardous Substances Act. W. Horwitz

133459j Quantitative determination of lead in the hair of Thai children. Kritalugsana, Sompool; Sommayura, S[illegible]; Pringsulaka, Prapa (Siriraj Hosp., Bangkok, Thailand). *Siriraj Hosp. Gaz.* 1973, 25(5), 743-50 (Thai). Levels of 2-8[illegible] μg lead [7439-92-1]/g were detd. in hair samples from [illegible] children, compared to levels of 139-2358 μg Pb/g in hair samples from 4 cases of chronic Pb intoxication. Hair samples are easier to collect from children than blood or 24-hr urine samples. [illegible] the detn. of Pb in hair samples may be used to diagnose poisoning, esp. in children.

133460c Acute oral toxicity of 2-alkyl- and 2,6-dialkylanilines. Correlation with lipophilicity. Durden, John A., Jr. [illegible] Plast. Div., Union Carbide Corp., South Charleston, W[illegible] *J. Med. Chem.* 1973, 16(11), 1316 (Eng). Acute oral [illegible] rats of a series of alkylanilines I (R, R' = H or alkyl) appear to depend primarily on the lipophilicity of the derivs., with [illegible] lipophilic compds. being the least toxic. The [illegible]

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a level of 10–25 ppm to less than 1 ppm about 6 months before the survey was undertaken, but in addition an increased awareness among workers of the necessity for safety precautions may also have played a part.

2230. TETRACHLORODIBENZODIOXIN—INTIMATIONS OF CARCINOGENICITY?

Buu-Hoï, N.P., Hien, D.-P., Saint-Ruf, G. & Servoin-Sidoine, Jacqueline (1971). Propriétés cancéromimétiques de la tétrachloro-2,3,7,8 dibenzo-p-dioxine ("dioxine"). C.r. hebd. Séanc. Acad. Sci., Paris 272, 1447.

The teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin ('dioxin') present as a contaminant in some commercial samples of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) is well established (BIBRA Bull. 1971, 10, xiv), though the situation regarding 2,4,5-T itself is less clear. The above authors have now described certain hepatic effects of dioxin linking its activity with that of known carcinogens.

Dioxin injected intraperitoneally into rats at dose levels of 0.005–10 mg/kg reduced the duration of paralysis induced by zoxazolamine by 33–95%, being far more potent in this respect than benzo[a]pyrene. No such activity was shown by unsubstituted dibenzo-p-dioxin or its 2-nitro, 2,6- or 2,7-dichloro or octachloro derivatives, by 2,4,5-trichlorophanol or by 2,4,5-T. Mice injected intraperitoneally with 20 mg dioxin/kg also showed a significant shortening of phenobarbitone-induced sleep. In addition to this induction of microsomal hydroxylating enzymes, dioxin injected into rats in a dose of 20 μg/kg followed by a second dose of 100 μg/kg 7 days later caused a gradual decrease in the level of hepatic arginase during the ensuing 3 wk. A marked reduction in liver arginase has also been reported in rats fed with the carcinogen, p-dimethylaminoazobenzene (Sato, Tohoku med. J. 1963, 67, 597).

[Although such effects may be produced by carcinogens, the relationship is by no means exclusive. In particular, the stimulation of hydroxylating enzymes can be induced by many compounds, including HMT whose freedom from carcinogenicity has been demonstrated in conventional long-term feeding studies. Tests such as those described above have little or no predictive value and cannot be used as a substitute for present methods of long-term toxicity testing.]

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cited above) that a patie
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the manufacturers (Gesla
in fact, DEEP, which is
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However concern is
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absence of a liver. Und
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PROCESSING AND PACKAGING CONTAMINANTS

2231. PHTHALATE PLASTICIZERS AND PVC BLOOD PACKS

Marcel, Y.L. & Noel, S.P. (1970). Contamination of blood stored in plastic packs. Lancet i, 35.

Jaeger, R.J. & Rubin, R.J. (1970). Plasticizers from plastic devices: Extraction, metabolism, and accumulation by biological systems. Science, N.Y. 170, 460.

During the past year it has become apparent that significant quantities of di-(2-ethylhexyl) phthalate (DEHP) can be detected in blood that

2232. IRON DEXTRAN AGAINS

Ferm, V.H. (1970). Prote
pathic action of indium.

Zinc is known to p
of cadmium in hamsters (
while selenium protects a
and arsenic (Holmberg & F
example is now given of
action of another. Ferm
its ability to suppress t
by indium, whose teratoge
demonstrated (BIBRA Bull.

Table I. Numbers of CDD and CDF Isomers as a Function of the Number of Chlorine Substituents

Number of Chlorine Atoms	Number of CDD Isomers	Number of Isomers
1	2	4
2	10	16
3	14	28
4	22	38
5	14	28
6	10	16
7	2	4
8	1	1

Table II. Physical Properties of Two Chlorinated Dioxins

	2,3,7,8-TCDD	OCDD[a]
Empiric Formula	$C_{12}H_4Cl_4O_2$	$C_{12}Cl_8O_2$
Percent by Weight		
C	44.7	31.3
O	9.95	7.0
H	1.25	
Cl	44.1	61.7
Molecular Weight	322	459.8
Melting Point (°C)	305	330
Decomposition Temperature (°C)	>700	>700
Solubilities (g/l)		
o-Dichlorobenzene	1.4	1.83
Chlorobenzene	0.72	
Anisole		1.73
Xylene		1.58
Benzene	0.57	
Chloroform	0.37	0.56
n-Octanol	0.048	
Methanol	0.01	
Acetone	0.11	
Dioxane		0.38
Water	2×10^{-9}	

[a] Octachlorodibenzo-*p*-dioxin.

Table III. Toxicities of Selected Poisons[a]

Substance	Molecular Weight	Minimum Lethal Dose (mol/kg)
Botulinum Toxin A	9.0×10^5	3.3×10^{-17}
Tetanus Toxin	1.0×10^5	1.0×10^{-17}
Diphtheria Toxin	7.2×10^4	4.2×10^{-12}
2,3,7,8-TCDD[b]	322	3.1×10^{-9}
Saxitoxin	372	2.4×10^{-8}
Tetrodotoxin	319	2.5×10^{-8}
Batrotoxin[c]	757	5.2×10^{-7}
Curare	696	7.2×10^{-7}
Strychnine	334	1.5×10^{-6}
Muscarin[c]	210	5.2×10^{-6}
Diisopropylfluorophosphate	184	1.6×10^{-5}
Sodium Cyanide	49	2.0×10^{-4}

Source: Pland and Kende [4]. These data were compiled by Mosher et al. [5], and the values indicate only relative toxicity. It should be noted that the values deal with different species, routes of administration, survival times and, in one case, mean lethal dose rather than minimum lethal dose. Except where noted, administration was by the intraperitoneal route in mice.

[b] On oral administration in the guinea pig.

[c] Intravenous injection in the cat.

Table IV. Acute Toxicities of Chlorodibenzodioxins [1]

r and Positions rine Substituents	LD_{50} (μg/kg)[a] Guinea Pigs	Mice
	>300,000	
ri-	29,444	>3,000
Tetra-	0.6–2.0	284
8 Penta-	3.1	114
8 Penta-	1,125	>5,000
7,8 Hexa-	72.5	823
7,8-Hexa-	70–100	1,250
8,9 Hexa-	60–100	>1,440
6,7,8 Hepta-	>600, 7,150	
6,7,8,9 Octa-		1×10^6

[a] Rate for oral doses; test period is 30 days.

Summary of Toxic Effects of 2,3,7,8-TCDD on Several Animal Species[a] [1,6]

	Mice	Guinea Pigs	Monkeys (Female)
ns Involution	+++	+++	+++
Reduction (white pulp)	+	+	+
marrow Hypoplasia	±	++	+
Megalocytosis/ Degeneration	+++	-	-
uct Hyperplasia	±	±	+++
ular Degeneration	++	+++	N/A
-pelvis Hyperplasia	-	++	+
ry-bladder Hyperplasia	-	++	-
al-cortical Atrophy			
na Glomerulys)	-	++	-
norhage			
stinal	+	+	-
renal	-	++	-
s	++	-	+
eous lesions	-	-	+++

[a] ± effects; + mildly affected; ++ moderately affected; +++ severely affected.

2,3,7,8-TCDF + 2,3,4,7,8-PeCDF
LD_{50} 1–100 μg/Kg for most sensitive animal species

K-3067-(100) K-66681-(100) ⇒ DR-15-0526
K-3166-(100) DD-525-(100)
[1982] DR-99-6281-(100)
DR-115-9224-(100) DR-188-4748-(100)
DR-120-7405-(100) DR-188-5252-(100)
DR-148-9129-(100) DD-685-(100)
DR-82-9209-(100) DR-184-9129-(100)
DR-53-3664-(100) K-84763-(100)
DR-188-4737-(100)
K-54762-(100)

DOW215883

81

Table VI. Accidents in Chemical Plants Manufacturing TCP [7]

Date	Manufacturer	Country	Personnel Injured	Cause of Accident
1949	Monsanto	U.S.	117	Overheating leading to explosion
1952, 1953	Boehringer	W. Germany	37	Exposure during manufacturing process
1953	Badische Anilin und Soda Fabrik AG (BASF)	W. Germany	55	Overheating leading to explosion
1953, 1971	Rhone Poulenc	France	97[a]	Exposure during manufacturing process
1956	Hooker	U.S.	Staff employees	Overheating
1960	Diamond Shamrock	U.S.	Figure unknown	Overheating
1963	Philips Duphar	Holland	30	Overheating leading to explosion
1964	Spolana	Czechoslovakia	72	Exposure during manufacturing process
1964	Dow Chemical	U.S.	30	Exposure during manufacturing process
1968	Coalite and Chemical Products	U.K.	79	Overheating leading to explosion
1970(?)	Bayer	W. Germany	5	Exposure during manufacturing process
1972, 1973	Chemie, Linz	Austria	50	Exposure during manufacturing process
1976	Icmesa (Givaudan)	Italy	106 children	Overheating
Before 1976	Thompson Hayward	U.S.		Overheating leading to explosion

[a] Including 17 injured in a 1956 explosion and 21 in 1966. Source: A. Hay, "Accidents in Trichlorophenol Plants: A Need For Realistic Surveys to Ascertain Risks to Health", in "Health Effects of Halogenated Aromatic Hydrocarbons", W. J. Nicholson and J. A. Moore, Eds. *Ann. N.Y. Acad. Sci.* 320:1–730 (1979).

Table VII. Higher Chlorodibenzodioxins CDD and Chlorodibenzofurans CDF Detected in Chlorophenols and Related Pesticides

Product	CDD Detected[a]					CDF Detected[a]				
	Tetra-	Penta-	Hexa-	Hepta-	Octa-	Tetra-	Penta-	Hexa-	Hepta-	Octa-
TCP	-	-	-	-	-	+	+	+	+	
Tetrachlorophenol	+	+	+	+	+	+	+	++	++	
PCP	-	-	+	++	++			++	++	++
2,3,5-T	++	ND	++	-	-	ND	ND	ND	ND	ND
Silvex	+	ND	-	-		ND	ND	ND	ND	ND
2,4-D[b]	-	ND	+	-						
Erbon	-	ND	-	-	++	ND	ND	ND	ND	ND
Sesone	-	ND	+	-	-	ND	ND	ND	ND	ND

[a] Concentration ranges: ++ = >10 ppm; + = 0.5–10 ppm; - = <0.5 ppm; ND = not determined.
[b] Recent analyses by Wright State University.

Table VIII. Levels of TCDD in Various Environmental and Biological Samples Analyzed by the Brehm Laboratory of Wright State University

Sample Description	Native TCDD D
Hazardous waste landfill soil/sludge, New York state	300–199,000
Trichlorophenol manufacturing waste, still bottom, Arkansas	22,000
Blood sample from workers involved in cleanup of *ortho*-chlorophenol spill in tank car derailment, missouri	7–28 pp
Blood sample from Vietnam veteran	41
Bovine	10
Municipal refuse-fired incinerator, New York state (on particulate emissions)	15 mg hr
Soot from wood-burning fireplace	0.65 ppb
Agent Orange	0.1–60 ppm
2,4-D (several manufacturers)	0.2–1.3 ppt

Table IX. TCDD Levels in Wildlife in Seveso, Italy, Area Following TC

Animal	No. of Samples Analyzed	Tissue	Positive	TCDD I Average
Field Mouse	14	Whole body	14/14	4.5
Hare	5	Liver	3/5	7.7
Toad	1	Whole body	1/1	0.2
Snake	1	Liver	1/1	2.7
		Adipose tissue		16.0
Earthworm[b]	2	Whole body	1/2	12.0

Source: Fanelli et al. [9], referenced in Esposito et al. [1].
[b] Each sample represents a 5-g pool of earthworms.

Table X. Results of HRGC/LRMS Analysis of Wipe Sample from Area Contaminated by Transformer Fire for Tetra- Through Octachlorinated Dibenzo-*p*-dioxins and Dibenzofurans

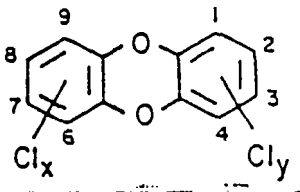
CDD/CDF[a]	Apparent Isomers[b]	Quantity of CDD/CDF Detected (ng/wipe)	Minimum Detectable Quantity (ng per isomer)
TCDD	ND	ND	0.10
	$^{37}Cl_4$-2,3,7,8		
PCDD	ND	ND	0.10
HxCDD	ND	ND	0.20
HpCDD	1,2,3,4,6,7,8-	0.65	0.20
	1,2,3,4,6,7,9-	0.45	0.20
	Total	1.1	0.20
	$^{37}Cl_4$ 1,2,3,4,6,7,8		
OCDD	1,2,3,4,6,7,8,9-	1.0	0.20
	$^{37}Cl_8$-OCDD		
TCDF	1,2,4,8-	2.0	0.10
	2,3,6,8-	3.1	0.10
	2,3,7,8-	9.6	0.10
	Other isomers (8)	35.8	0.10
	Total	50.4	0.10
PCDF	1,2,4,7,8-	5.2	0.10
	Other isomers (13)	11.8	0.10
	Total	17.0	0.10
HxCDF	1,2,4,6,7,9-	1.6	0.20
	Other isomers (12)	43.6	0.20
	Total	45.2	0.20
HpCDF	1,2,3,4,6,8,9-	2.7	0.20
	Other isomers (4)	4.6	0.20
	Total	7.3	0.20
OCDF	1,2,3,4,6,7,8,9-	7.3	0.20

[a] PCDD = penta-CDD; HxCDF = hexa-CDF; HpCDF = hepta-CDF; OCDF = octa-CDF.
[b] See text for discussion.

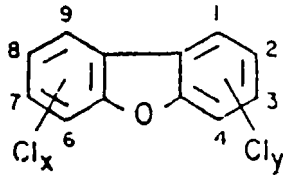
Table XI. HRGC/LRMC Analytical Results for CDD/CDF in Ash Sample from Incineration of Wastes Containing PCP*

CDD/CDF	Total Number of Apparent Isomers	Total Detectd (ng/g)	Minimum Detectable Concentrated (ng/g)
MCDF	3	75	0.1
DCDF	8	25	0.3
TrCDF	8	15	0.6
TCDF	7	7	0.5
PCDF	5	8	1
HxCDF	5	5	1
HpCDF	2	6	1
OCDF	1	2	1
MCDD	1	1	0.1
DCDD	4	5	0.3
TrCDD	5	2	0.6
TCDD	4	4	0.2
PCDD	5	32	1
HxCDD	5	81	1
HpCDD	2	117	1
OCDD	1	198	1

*Recent analyses by Wright State University.



Chlorinated Dibenzo-p-dioxin



Chlorinated Dibenzofurans

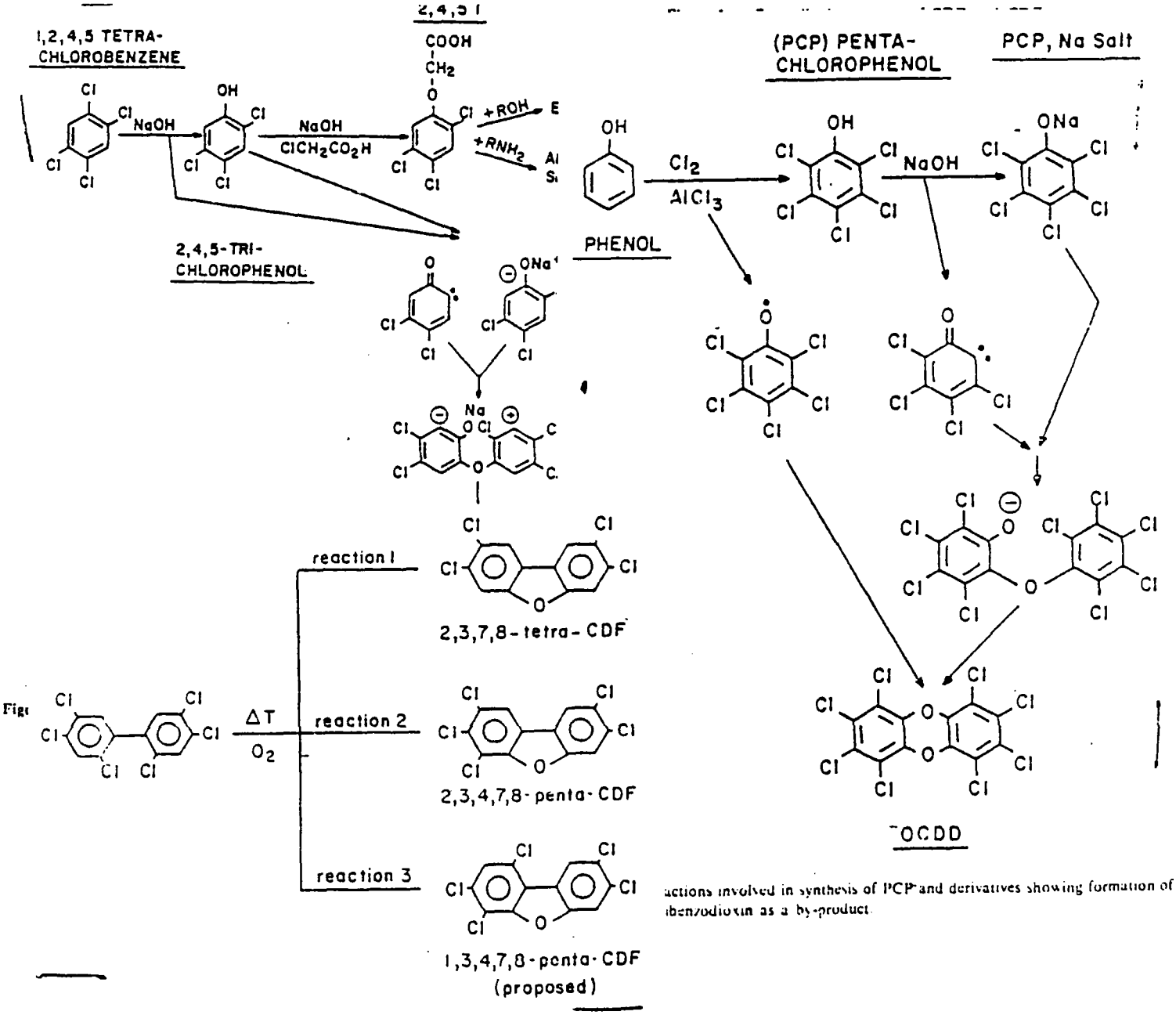


Figure 4. Reactions leading to formation of CDF from pyrolysis of 2,2',4,4',5,5'-hexachlorobiphenyl.

actions involved in synthesis of PCP and derivatives showing formation of ibenzodioxin as a by-product

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Detoxication of hazardous waste. Ann Arbor Sci. Pub., Exner, J.H. ed. 1982

CHAPTER 15

CHLORODIBENZODIOXINS AND CHLORODIBENZOFURANS: AN OVERVIEW

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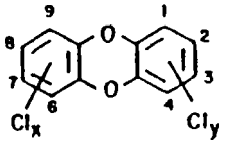
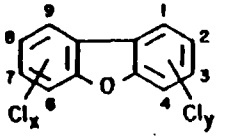
Chlorodibenzodioxins (CDD) and chlorodibenzofurans (CDF) are two series of tricyclic aromatic compounds that exhibit similar physical and chemical properties and that apparently induce similar biological effects. Generalized structures of the CDD and CDF and the numbering according to the position of chlorine substituents on the rings are shown in Figure 1. The number of chlorine atoms in the molecule can range from one to eight; therefore, a large number of positional isomers are possible. The total number of CDD is 75, and there are 135 CDF. The numbers of CDD and CDF isomers as a function of the number of chlorine atom substituents are indicated in Table 1.

In the past few years, widespread concern has arisen with respect to contamination of the environment by CDD and CDF. This concern has been prompted in part by observations, principally based on animal studies, that indicate that certain of the CDD and CDF exhibit potent toxicity. In addition, it has been recognized that, since the CDD and CDF are present as contaminants in numerous commercial chemicals that have been or are being produced and used in large quantities [1], the potential for extensive environmental contamination by these compounds is very great. Moreover, CDD and CDF generally are quite stable chemically and thermally, and are reasonably soluble in several common organic solvents (selected physical properties of two representative chlorinated



Chlorinated Dibenzo-p-dioxin



Chlorinated Dibenzofurans

Figure 1. Generalized structures of CDD and CDF.

Table I. Numbers of CDD and CDF Isomers as a Function of the Number of Chlorine Substituents

Number of Chlorine Atoms	Number of CDD Isomers	Number of Isomers
1	2	4
2	10	16
3	14	28
4	22	38
5	14	28
6	10	16
7	2	4
8	1	1

dioxins are shown in Table II). There is some evidence to suggest that the CDD and CDF are accumulating in the environment, and that these compounds persist for considerable periods.

The purpose of this chapter is to give a concise overview of the present status of knowledge of the CDD and CDF, as a prelude to discussions of

Table II. Physical Properties of Two Chlorinated Dioxins

	2,3,7,8-TCDD	OCDD[a]
Empiric Formula	$C_{12}H_4Cl_4O_2$	$C_{12}Cl_8O_2$
Percent by Weight		
C	44.7	31.3
O	9.95	7.0
H	1.25	
Cl	44.1	61.7
Molecular Weight	322	459.8
Melting Point (°C)	305	330
Decomposition Temperature (°C)	>700	>700
Solubilities (g/l)		
o-Dichlorobenzene	1.4	1.83
Chlorobenzene	0.72	
Anisole		1.73
Xylene		3.58
Benzene	0.57	
Chloroform	0.37	0.56
n-Octanol	0.048	
Methanol	3.01	
Acetone	0.11	
Dioxane		0.18
Water	2×10^{-9}	

[a]Octachlorodibenzo-*p*-dioxin.

various methods of destroying these compounds or detoxifying wastes in which they are contained, which are presented in other chapters in this book. More comprehensive reviews of this subject can be consulted for additional details [1-3].

TOXICITY AND HEALTH EFFECTS OF CDD AND CDF

The toxicity of chemical compounds is usually assessed on the basis of tests with animals. Frequently, in these tests, large doses of the material being tested are administered in an attempt to compress the time scale for response. This testing may result in misleading conclusions, because such massive doses are usually unrealistic in terms of the doses that would be encountered in typical real-world exposures. Moreover, since toxic response is a function of the pharmacokinetics and the adaptive charac-

teristics of each particular animal system, the response of different animal species to a given chemical may, and frequently does, vary markedly. All of these considerations lead one to conclude that it is extremely difficult, if not impossible, to extrapolate toxicologic data from one animal species to another, particularly to humans. Still, animal tests are one measure of the toxicity of chemicals, and some CDD and CDF have been tested in this manner. On this basis, as shown by the comparison in Table III [4,5], the acute toxicities of at least some CDD [in particular, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)] are comparable to or exceed the toxicities of several well known poisons, and these rank among the most lethal chemical compounds known to man. It has also been observed that the LD_{50} doses for various CDD isomers, based on tests with guinea pigs and mice, differ substantially, depending on the number and location within the molecule of the chlorine atom substituents (Table IV). Of the CDD isomers tested, the 2,3,7,8-TCDD is recognized to be the most toxic. The acute toxicities of CDF have been less extensively investigated, but the LD_{50} values for 2,3,7,8-tetrachlorodibenzofuran (2,3,7,8-TCDF) and 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PCDF) appear to be similar to those for the more toxic CDD, that is, 1–100 μg/kg for the most sensitive animal species.

Table III. Toxicities of Selected Poisons[a]

Substance	Molecular Weight	Minimum Lethal Dose (mol/kg)
Botulinum Toxin A	9.0×10^3	3.3×10^{-17}
Tetanus Toxin	1.0×10^5	1.0×10^{-11}
Diphtheria Toxin	7.2×10^4	4.2×10^{-12}
2,3,7,8-TCDD[b]	322	3.1×10^{-9}
Saxitoxin	372	2.4×10^{-8}
Tetrodotoxin	319	2.5×10^{-8}
Bufotoxin[c]	757	5.2×10^{-7}
Curare	696	7.2×10^{-7}
Strychnine	334	1.5×10^{-6}
Muscarin[c]	210	5.2×10^{-6}
Diisopropylfluorophosphate	184	1.6×10^{-5}
Sodium Cyanide	49	2.0×10^{-4}

[a] Source: Pland and Kende [4]. These data were compiled by Mosher et al. [5], and the values indicate only relative toxicity. It should be noted that the values deal with different species, routes of administration, survival times and, in one case, mean lethal dose rather than minimum lethal dose. Except where noted, administration was by the intraperitoneal route in mice.
[b] LD_{50} on oral administration in the guinea pig.
[c] Intravenous injection in the cat.

Table IV. Acute Toxicities of Chlorodibenzodioxins [1]

Number and Positions of Chlorine Substituents	LD_{50} (μg/kg)[a] Guinea Pigs	Mice
2,8-Di-	>300,000	
2,3,7 Tri-	29,444	>3,600
2,3,7,8 Tetra-	0.6 2.0	284
1,2,3,7,8 Penta-	3.1	338
1,2,4,7,8 Penta-	1,125	>5,000
1,2,3,4,7,8 Hexa-	72.5	825
1,2,3,6,7,8 Hexa-	70 100	1,250
1,2,3,7,8,9 Hexa-	60 100	>1,440
1,2,3,4,6,7,8 Hepta-	>600; 7,100	
1,2,3,4,6,7,8,9 Octa-		>4 × 10^4

[a] All values are for oral doses; test period is 30 days.

Table V. Summary of Toxic Effects of 2,3,7,8-TCDD on Several Animal Species[a] [1,6]

	Mice	Guinea Pigs	Monkeys (Female)
Thymus Involution	•••	•••	•••
Spleen Reduction (white pulp)	•	•	•
Bone-marrow Hypoplasia	±	••	•
Liver, Megalocytosis/Degeneration	•••	-	
Bile-duct Hyperplasia	±	±	•••
Testicular Degeneration	••	•••	N/A
Renal-pelvis Hyperplasia	-	••	•
Urinary-bladder Hyperplasia		••	-
Adrenal-cortical Atrophy (Zona Glomerulys)		••	
Hemmorhage			
Intestinal	•	•	
Adrenal	-	••	
Ascites	••		•
Cutaneous lesions			•••

[a] Key: no effects; • mildly affected; •• moderately affected; ••• severely affected.

A summary of the observed biological effects of 2,3,7,8-TCDD on mice, guinea pigs and monkeys is presented in Table V [1,6]. While the effects and their severity vary to some extent among these species, as already noted, in general the major organs affected are the thymus, liver and spleen, along with the reticuloendothelial system. Reproductive functions are also affected in some animals, and pronounced developmental effects in offspring have been observed. In some animal species,

2,3,7,8-TCDD is fetotoxic (or embryotoxic), teratogenic and even carcinogenic [1]. A particularly apparent response to this compound observed in rabbits, monkeys and man is an acnegenic eruption (termed chloracne in man).

TCDD causes marked alteration of normal enzyme activity in certain laboratory animals. It is a highly potent inducer of aryl hydrocarbon hydroxylase (AHH), as well as the mixed-function oxidases and the cytochrome P_1-450 (P-448) enzymes of the liver, lung, placenta and kidney, in mice and rats [1]. It also appears that TCDD may potentiate the adverse action of other toxic materials, or even cause another seemingly innocuous agent to exhibit toxicity [1].

There are relatively few data concerning the distribution of CDD and CDF within animal tissues and organs or excretion of these compounds following administration. Some studies with TCDD indicate that in rats, excretion is largely via the feces, and that accumulation occurs principally in the fat and liver, with smaller amounts in the spleen, bone, heart, lungs, testes and kidney [1]. Most TCDD is apparently not metabolized by the rat, or at least metabolism of this compound occurs very slowly, and the metabolites have not been identified reliably.

Information on the effects of human exposure to CDD has been obtained principally from epidemiological studies of persons exposed as a result of accidents in chemical plants or by exposure to contaminated foods, materials or areas. A summary of the major accidents occurring in trichlorophenol (TCP) plants in the past several years is given in Table VI [7]. The most notable episode involving CDD contamination in recent years was the explosion that occurred at the Icmesa trichlorophenol plant located in Seveso, Italy, where TCP and 2,3,7,8-TCDD were dispersed over a wide area. Approximately 5000 persons were exposed in this accident [1,2]. Shortly after the accident, chloracne (a well-known symptom of acute CDD toxicity) was observed in some 134 persons. Other disorders reported included hepatic and coronary insufficiency, chronic bronchitis, muscular weakness, irritability and nervousness, urinary and pancreatic disorders, porphyria cutanea tarda, hyperpigmentation and hirsutism and chromosomal damage. A later followup study detected peripheral nerve damage and polyneuropathy in some of the exposed individuals [2].

TCDD is also known to be an inducer of delta-aminolevulinic acid (d-ALA) and AHH in man. Probably this accounts for stimulation of production of certain porphyrins, which are ultimately excreted in the urine. The distribution of CDD and CDF within the human body and the modes of elimination have not been established, nor are the metabolic pathways or metabolites (if any) known. Reproductive effects of CDD

Table VI. Accidents in Chemical Plants Manufacturing TCP [7]

Date	Manufacturer	Country	Personnel Injured	Cause of Accident
1949	Monsanto	U.S.	117	Overheating leading to explosion
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1953/1971	Rhone Poulenc	France	97[a]	Exposure during manufacturing process
1956	Hooker	U.S.	Staff employees	Overheating
1960	Diamond Shamrock	U.S.	Figure unknown	Overheating
1963	Philips Duphar	Holland	30	Overheating leading to explosion
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1964	Dow Chemical	U.S.	30	Exposure during manufacturing process
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and CDF in humans also have not been determined, in part because of the complicating factors caused by the many other hazardous organic compounds to which man is exposed.

The most notable reported episode involving human exposure to CDF occurred in Japan in 1968 as a consequence of the accidental contamination of rice oil used for cooking with polychlorinated biphenyls (PCB); subsequently, CDF were shown to be present in small quantities in the PCB [8]. This incident, which has come to be known as the "yusho" incident, involved more than 1200 persons. There were several near-term symptoms, including chloracne. Many of these symptoms were similar to those cited above for CDD [2]. By the end of 1977, some 51 of the exposed population had died; 11 of these were identified as resulting from malignant neoplasms of the stomach, lung, liver, breast or lymphatic system, or combinations of these [2]. Tissues (principally from the livers) of the victims of this accident were analyzed for CDF, as were samples of the PCB contaminant in the rice oil. A comparison of the results showed that many of the same CDF isomers were present in both the PCB contaminant and the liver tissues, and further indicated that certain CDF isomers, particularly those having all the lateral (2-, 3-, 7- and 8-) positions chlorinated, were preferentially retained in human tissues [8]. This is one of the few instances in which such compounds have been implicated unquestionably in severe human health effects.

In several animal studies, PCB have been implicated as inducing toxic effects in animals, but in some of these investigations, it has not been clear to what extent PCB were contaminated with CDF, and the causative agent or agents are therefore uncertain.

SOURCES AND ACCUMULATION OF CDD AND CDF IN THE ENVIRONMENT

As mentioned earlier, major sources of CDD and CDF detected in the environment are industrial chemicals. More recently, however, it has been recognized that these compounds are present in the effluents from various combustion processes. The principal environmental sources of CDD/CDF thus far identified include [1]:

1. chemical products for which the normal manufacturing process generates these compounds as by-products, and which are widely used in the environment (pesticides, wood-treating products, etc.);
2. uncontrolled manufacturing processes, which result in releases of CDD and CDF (explosions of reactors);

3 improper disposal of chemical manufacturing wastes or products containing CDD and CDF (landfills, waterways);
4 incineration of municipal, commercial and industrial wastes;
5 ordinary combustion processes (wood-burning and others); and
6 accidents (fires, spills, etc.).

Perhaps most important among the mass-produced chemicals which are known to be contaminated with CDD and CDF are the *ortho*-chlorophenols, particularly TCP and pentachlorophenol (PCP). TCP has been used widely as a preservative, bactericide, fungicide and algicide in many industrial products, and is the starting material used in the manufacture of a series of industrial and agricultural chemicals, notably the herbicide 2,4,5-T, and the related products, silvex, ronnel and hexachlorophene, a bactericide. PCP is extensively utilized in wood-preserving processes. CDD and CDF that have been detected in various chlorophenols and related pesticide products are listed in Table VII. The probable mechanism by which chlorodioxins are formed in the synthesis of *ortho*-chlorophenols is a thermally induced condensation reaction of two molecules of the sodium or potassium chlorophenate, such as that exemplified in Figure 2 for the production of 2,3,7,8-TCDD in the manufacture of 2,4,5-TCP. A so-called "predioxin," a phenoxyphenate or substituted diphenyl ether, may be an intermediate in this reaction. Similar condensation reactions can account for the formation of hexa- (HxCDD), hepta- (HpCDD) and octachlorodibenzo-*p*-dioxins (OCDD) in the manufacture of PCP (Figure 3).

The extensive occurrence of CDD and/or CDF in such widely used commercial chemicals as chlorophenols, their derivatives and PCB provides a clear indication of the need for adequate methods for destruction of chemical wastes and related materials that result from manufacture of these chemicals. Obviously, improper disposal of such chemical wastes can lead to extensive environmental contamination. Prominent examples of this that have received recent attention are the Love Canal area in Niagara Falls, New York, where several major chemical dumps are located, and a 2,4,5-T/2,4-D manufacturing plant site located in Arkansas. Levels of TCDD typically found in environmental samples from these sites are shown in Table VIII. Applications of excessive quantities of herbicides contaminated with TCDD, as in South Vietnam during the conflict there and at various military sites in the United States during this period, or the contamination of the environment resulting from such events as the TCP reactor explosion at Seveso, Italy, can also result in elevated levels of TCDD in plants and animals (including humans) present at such sites (Table IX [9]).

As already noted, CDF are also present as contaminants in some PCB

Table VII. Higher Chlorodibenzodioxins CDD and Chlorodibenzofurans CDF Detected in Chlorophenols and Related Pesticides [1,3]

Product	CDD Detected[a]					CDF Detected[a]				
	Tetra-	Penta-	Hexa-	Hepta-	Octa-	Tetra-	Penta-	Hexa-	Hepta-	Octa-
TCP	-	-	-	-	-	+	+	+	+	-
Tetrachlorophenol	+	+	+	+	+	+	+	↔	↔	+
PCP	-	-	+	↔	↔	-	-	↔	↔	↔
2,3,5-T	↔	ND	↔	-	-	ND	ND	ND	ND	ND
Silvex	+	ND	-	-	-	ND	ND	ND	ND	ND
2,4-D[b]	-	ND	+	-	-	-	-	-	-	-
Erbon	-	ND	-	-	↔	ND	ND	ND	ND	ND
Sesone	-	ND	+	-	-	ND	ND	ND	ND	ND

[a]Concentration ranges: ↔ = >10 ppm; + = 0.5–10 ppm; - = <0.5 ppm; ND = not determined.
[b]Recent analyses by Wright State University.

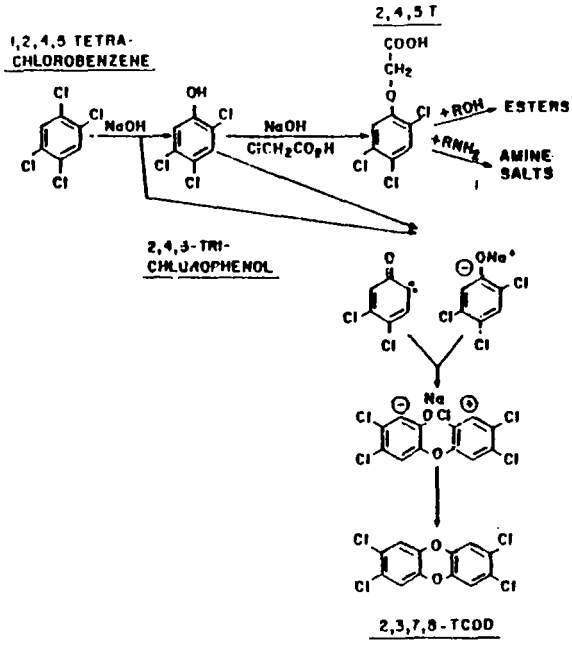

Figure 2. Reactions involved in synthesis of 2,4,5-trichlorophenol and related products (2,4,5 T and derivatives) showing formation of 2,3,7,8 TCDD as a by-product

formulations [2]. In addition, it is known that pyrolysis of PCB at certain temperatures (obviously lower than the temperatures required for complete destruction) yields CDF as products [3]. The reaction scheme for formation of CDF from pyrolysis of 2,2',4,4',5,5'-hexachlorobiphenyl, for example, is as shown in Figure 4. An instance in which a PCB formulation (also containing hexachlorobenzene) was incinerated under conditions leading to formation of substantial quantities of CDD and CDF occurred in Binghamton, New York. This episode occurred as a

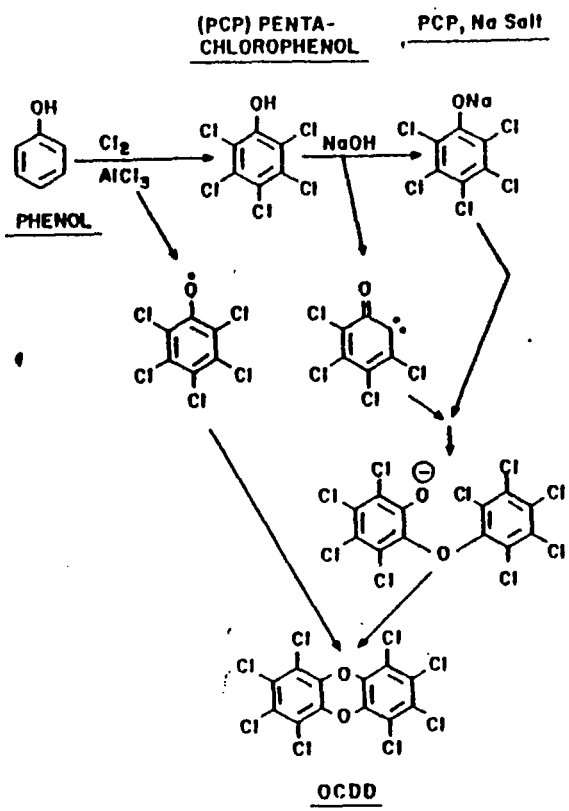

Figure 3. Reactions involved in synthesis of PCP and derivatives showing formation of octachlorodibenzodioxin as a by-product.

result of a transformer fire in the basement of a large office building. Soot samples and wipes of surfaces in nearby areas showed rather large concentrations of CDD and CDF, as indicated by the data shown in

Table VIII. Levels of TCDD in Various Environmental and Biological Samples Analyzed by the Brehm Laboratory of Wright State University

Sample Description	Native TCDD Detected
Hazardous waste landfill soil/sludge, New York state	300–199,000 ppt
Trichlorophenol manufacturing waste, still bottom, Arkansas	22,000 ppt
Blood sample from workers involved in cleanup of *ortho*-chlorophenol spill in tank car derailment, missouri	7–28 ppt
Blood sample from Vietnam veteran	41 ppt
Bovine	10 ppt
Municipal refuse fired incinerator, New York state (on particulate emissions)	15 ng/hr
Soot from wood-burning fireplace	0.65 ppb
Agent Orange	0.1–60 ppm
2,4-D (several manufacturers)	0.2–1.3 ppb

Table IX. TCDD Levels in Wildlife in Seveso, Italy, Area Following TCP Accident[a]

Animal	No. of Samples Analyzed	Tissue	Positive	TCDD Level (ng/g) Average	Range
Field Mouse	14	Whole body	14/14	4.5	0.07–49
Hare	5	Liver	3/5	7.7	2.7–11
Toad	1	Whole body	1/1	0.2	
Snake	1	Liver	1/1	2.7	
		Adipose tissue		16.0	
Earthworm[b]	2	Whole body	1/2	12.0	

[a]Source: Fanelli et al. [9], referenced in Esposito et al. [1].
[b]Each sample represents a 5-g pool of earthworms.

Table X for a wipe sample [10]. In still another instance, incineration of wood-treatment wastes containing PCP, and probably related CDD/CDF or precursors of these, in an incinerator that apparently provided less-than-optimum conditions for destruction, yielded ash residues containing relatively large quantities of CDD/CDF (see Table XI). Another chapter in this book [11] presents a more detailed discussion of the recent assessment of destruction of PCB by incineration under conditions where

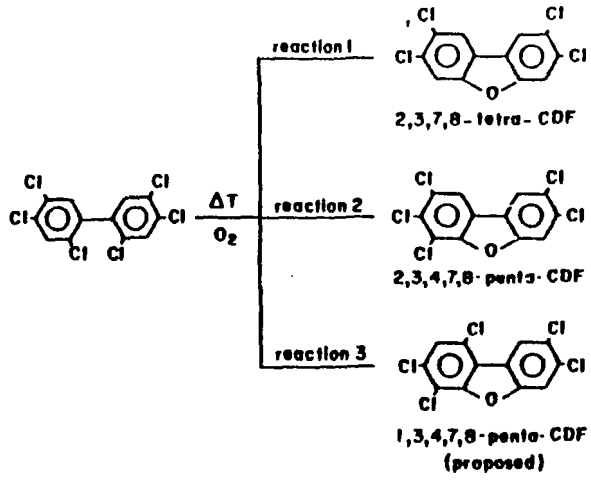

Figure 4. Reactions leading to formation of CDF from pyrolysis of 2,2',4,4',5,5'-hexachlorobiphenyl.

high destruction efficiency was achieved and the level of CDD/CDF in the combustion effluents were within limits which the U.S. Environmental Protection Agency (EPA) deemed acceptable.

ANALYSES OF CDD/CDF IN ENVIRONMENTAL SAMPLES

The extraordinary toxicity of some CDD and CDF dictates the need for analytical capabilities that can detect and quantify picogram quantities of CDD and CDF. At the same time, great analytical methods specificity is required, because several other prominent contaminants that persist in environmental samples (e.g., PCB and DDE) can interfere with the determination of CDD and CDF. The analytical capability described has only been realized within the past 3–4 years, and it is now possible to reliably determine parts-per-trillion levels of CDD and CDF in many

Table X. Results of HRGC/LRMS Analysis of Wipe Sample from Area Contaminated by Transformer Fire for Tetra- Through Octachlorinated Dibenzo-p-dioxins and Dibenzofurans

CDD/CDF[a]	Apparent Isomers[b]	Quantity of CDD/CDF Detected (ng/wipe)	Minimum Detectable Quantity (ng per Isomer)
TCDD	ND $^{37}Cl_4$-2,3,7,8	ND	0.10
PCDD	ND	ND	0.10
HxCDD	ND	ND	0.20
HpCDD	1,2,3,4,6,7,8	0.65	0.20
	1,2,3,4,6,7,9-	0.45	0.20
	Total	1.1	0.20
	$^{37}Cl_4$ 1,2,3,4,6,7,8-		
OCDD	1,2,3,4,6,7,8,9	1.0	0.20
	$^{37}Cl_8$-OCDD		
TCDF	1,2,4,8-	2.9	0.10
	2,3,6,8-	3.1	0.10
	2,3,7,8-	9.6	0.10
	Other isomers (8)	35.8	0.10
	Total	50.4	0.10
PCDF	1,2,4,7,8-	5.2	0.10
	Other isomers (13)	11.8	0.10
	Total	17.0	0.10
HxCDF	1,2,4,6,7,9-	1.6	0.20
	Other isomers (12)	43.6	0.20
	Total	45.2	0.20
HpCDF	1,2,3,4,6,8,9-	2.7	0.20
	Other isomers (4)	4.6	0.20
	Total	7.3	0.20
OCDF	1,2,3,4,6,7,8,9	7.3	0.20

[a]PCDD = penta-CDD; HxCDF = hexa CDF; HpCDF = hepta CDF; OCDF = octa CDF.
[b]See text for discussion.

types of environmental and biological samples, hazardous chemical wastes, and chemical formulations. The Brehm Laboratory, Wright State University, has been one of the major contributors to the development of this highly sophisticated analytical methodology. In general, the analytical procedures now applied for definitive determinations of CDD and CDF isomers entail the following:

Table XI. HRGC/LRMC Analytical Results for CDD/CDF in Ash Sample from Incineration of Wastes Containing PCP*

CDD/CDF	Total Number of Apparent Isomers	Total Detected (ng/g)	Minimum Detectable Concentration (ng/g)
MCDF	3	75	0.1
DCDF	8	25	0.3
TrCDF	8	15	0.6
TCDF	7	7	0.5
PCDF	5	8	1
HxCDF	5	5	1
HpCDF	2	6	1
OCDF	1	2	1
MCDD	1	1	0.1
DCDD	4	5	0.3
TrCDD	5	2	0.6
TCDD	4	4	0.2
PCDD	5	32	1
HxCDD	5	81	1
HpCDD	2	117	1
OCDD	1	198	1

*Recent analyses by Wright State University.

1. extraction of CDD and CDF from the sample matrix using organic solvents,
2. preliminary separation of CDD and CDF from other constituents of the matrix, which also have been extracted (including other chlorinated materials) using acid-base treatments and liquid chromatography with alumina, silica gel and/or other suitable columns;
3. further fractionation of the CDD and CDF using normal and reverse-phase high-performance liquid chromatography (HPLC); and
4. analyses of the prepared extracts containing CDD and CDF using capillary-column gas chromatography/mass spectrometry (GC/MS). Both low- and high-resolution mass spectrometry may be used in this analysis, depending on the sample.

The application of this complex analytical procedure is tedious and costly, but such a procedure is necessary to obtain definitive data on the CDD and CDF isomers at the extremely low (parts-per-trillion) concentration levels at which these must be detected. The results of such an analysis are well illustrated by data obtained from analysis of the ash sample resulting from incineration of PCP wood-preserving process wastes, which are shown in Table XI. Interestingly, the TCDD isomers detected in this sample were 1,3,6,8,- 1,3,7,9-, 1,3,7,8- and 1,2,3,4-TCDD.

No 2,3,7,8-TCDD was found. Similar analyses have recently been accomplished by the Brehm Laboratory on stack effluents from incineration of municipal refuse, and on effluents from incineration of wastes containing PCB. The latter work is discussed more fully and the detailed analytical techniques are also described in another chapter in this book [11].

ENVIRONMENTAL TRANSPORT AND NATURAL DEGRADATION OF CDD

Considerable work has been done in an effort to assess the extent of degradation and transport of CDD in the environment [1], although the conclusions from these studies are not entirely clear. Although biodegration of TCDD does not seem to be a particularly important process, both TCDD and OCDD appear to be effectively photodegraded by both natural sunlight and artificial ultraviolet (UV) radiation [1]. Transport of TCDD in soil, water and air has been investigated, but since the results depend on so many environmental factors (e.g., type of soil and organic content, temperatures and organic content of water, and method of dispersal in air), the conclusions are not straightforward. It appears, however, that TCDD can migrate to some extent in soils, especially porous, sandy soils. Transport of CDD/CDF can occur in the air, especially if these compounds are sorbed on airborne particulates. It is also clear that transport of CDD/CDF can occur by runoff of surface waters and or leaching into groundwaters, which ultimately may contaminate lakes, rivers and streams. In the latter instance, TCDD appears to accumulate largely in sediments, although the content of other organic compounds in natural waters also affects the concentration of CDD/CDF therein. Finally, as discussed earlier, CDD/CDF can bioaccumulate in some plants, animals and fish exposed to these compounds; obviously, this may also result in transport and, ultimately, dispersion of these compounds in the environment. There are few baseline data on concentrations of CDD/CDF in the environment, however, except where high levels of CDD/CDF are anticipated because of massive contamination episodes such as those described earlier

DESTRUCTION OR DETOXICATION OF CHEMICAL PRODUCTS AND WASTES CONTAINING CDD/CDF

Among the methods applied in attempts to destroy or detoxicate wastes containing CDD and/or CDF are conventional incineration, photolysis,

radiolysis, ozonolysis, catalytic dechlorination and biological treatment. Several of these techniques and their application to such chlorinated compounds are discussed in more detail in several other chapters in this book. These chapters clearly demonstrate that considerable success has been achieved in devising environmentally acceptable methods for destroying or detoxifying hazardous wastes containing CDD and/or CDF.

REFERENCES

1. Esposito, M. P., T. O. Tiernan and F. E. Dryden. "Dioxins," U.S. EPA Report EPA-600/2-80-197, Industrial Environmental Research Laboratory, Office of Research and Development, Cincinnati, OH (1980).
2. Nicholson, W. J., and J. A. Moore, Eds. "Health Effects of Halogenated Aromatic Hydrocarbons," *Ann. N.Y. Acad. Sci.* 320:1-730 (1979).
3. Joint NIEHS/IARC Working Group. "Long-Term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans," World Health Organization/International Agency for Research on Cancer, Lyon, France (1978).
4. Pland, A., and A. Kence. "2,3,7,8-Tetrachlorodibenzo-p-Dioxin: Environmental Contaminant and Molecular Probe," *Fed. Proc.* 35(12):2404 (1976).
5. Mosher, H. S., F. A. Fuhrman, H. D. Buchwald and H. G. Fischer. *Science* 144:1160-1110 (1964).
6. Moore, J. A., and R. E. Faith. "Immunologic Response and Factors Affecting Its Assessment," *Environ. Health Persp.* 18:125 (1976).
7. Hay, A. "Accidents in Trichlorophenol Plants: A Need for Realistic Surveys to Ascertain Risks to Health," *Ann. N.Y. Acad Sci.* 320:321-324 (1979).
8. Rappe, C., H. R. Buser, H. Kuroki and Y. Masuda. "Identification of Polychlorinated Dibenzofurans (PCDFs) Retained in Patients with Yusho," *Chemosphere* 4:259-266 (1979).
9. Fanelli, R. "Presence of 2,3,7,8-Dibenzo-p-Dioxin in Wildlife Living Near Seveso, Italy: A Preliminary Study," Institute de Ricerche Farmacologiche "Mario Negri," Milan, Italy (1980).
10. "Determination of Chlorinated Dibenzo-p-Dioxins and Dibenzofurans in Surface Wipes and Related Specimens from Broome County Facilities, Binghamton, NY, Contaminated as a Result of a Transformer Fire," Brehm Laboratory, Wright State University (1981).
11. Tiernan, T. O., M. L. Taylor, J. G. Solch, G. F. Vanness, J. H. Garrett and M. D. Porter. "Incineration of Chemical Wastes Containing Polychlorinated Biphenyls: Assessment of Tests Conducted at Rollins Environmental Services, Deer Park, Texas, and Energy Systems Company, El Dorado, Arkansas," Chapter 9, this volume.

CHAPTER 16

SELECTED LEGAL ASPECTS OF A DIOXIN DETOXICATION PROJECT

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On a summer afternoon in 1974, Godfrey Moll, Plant Manager of the Syntex Agribusiness chemical production facility in Verona, Missouri, rapped on the side of an old 20-foot-tall steel tank, which had been sitting idle on the premises for many years. Syntex had purchased the plant, including the steel tank, in 1969. Moll assumed that the tank was empty because Syntex had never used it, but his knocking on the tank wall was inconclusive. Consequently, he carefully lowered a small flask into the tank and, to his surprise, it came up filled with a dark sludge material. Moll calculated from the size of the tank that it contained approximately 4300 gallons of this material, which was the consistency of heavy motor oil. Laboratory analysis of the sludge increased his surprise considerably: the 4300 gallons of sludge contained approximately 343 ppm of dioxin.

It soon became evident what had happened. In the late 1960s North Eastern Pharmaceutical and Chemical Company, Inc. (NEPACCO) leased a portion of the Verona plant from the company that then owned it. Under this lease, NEPACCO was entirely responsible for disposing of its own wastes and trash, and agreed to operate at all times in conformity with applicable laws and regulations. NEPACCO's activities at the plant included the production of hexachlorophene. One step of that manufacturing process, which involved the purification of trichlorophenol (TCP), apparently produced dioxin as an unwanted by-product.