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CONTENTS

AUGUST 1972

SCIENTIFIC COMMUNICATIONS

Studies on Mutagen Exposure to Methyl Mercury Through Fish Consumption

Gunter Ekbo, MD; Alf G. Johansson, PhD; Lars-Olof Olsson, ME; Bernt Strand, ME;
Stefan Skerfving, MD; and Turbjörn Westermarck, Turku, Sweden

77

Absorption and Excretion of Cesium in Man

Kajander Niemi, MD, and Gunter F. Nordberg, MD, Stockholm

85

Effect of Metal-Binding Proteins of Tobacco Smoke on *In Vitro* Activity of Enzymes

Vincent N. Finkel, PhD, and Harold G. Poterang, PhD, Cincinnati

97

Pulmonary Infiltration Due to Aerosol Theomone

John M. Gandy, MD, Washington, DC, and Mary Jane Wagstaff, MD, Rockville, Md

101

Erythrocyte 2-aminolevulinic Acid Dehydratase in New Lead Exposure

Irene Hornberg, MD; Saberi Tobi, MD; Jorma Nihlman, MS;
and Mattias Vahlman, Helsinki

109

South-Alkaline Analysis in Chronic Bronchopulmonary Disease

Holbert Hest, MD, and James F. Morris, MD, Portland, Ore

114

Retention of Inhaled Formaldehyde, Propionaldehyde, and Acrolein in the Dog

John L. Egle, Jr., PhD, Richmond, Va

120

Toxicity of Chlorinated Hydrocarbons and Related Compounds

Ernie D. Ridd, MD, Chamblee, Ga

125

Respiratory Uptake of Gases in Dogs

Eiji Yokoyama, MD, and Robert Frank, MD, Seattle

131

Differences in Metal Axial Distribution Displayed by Trans-Surface Analysis

Richard K. Savers, PhD, and David A. Chambers, PhD, Winston

139

Pulmonary Function and Physical Conditioning in Latin and Chinese Subjects

James Kollias, PhD; Richard A. Bales, PhD; H. Larry Swartz;
and Kenneth R. Buehler, PhD, University Park, Pa

145

FEATURE SECTION

Books

151

Announcements and Comments

159

kw. Ecology-1972

PC13

ENVIRONMENT REPORTER

August 11, 1972

THE BUREAU OF NATIONAL AFFAIRS, INC.

Volume 3, Number 15

AIR POLLUTION		MICHIGAN	
Improved nitric oxide monitor developed	443	Sulfur dioxide, fuel standards now in effect	447
Information on airborne contaminants requested for OSHA system standards	445	MOTOR VEHICLES	
ATOMIC ENERGY		Export of uncertified cars allowed by EPA	438
Memorandum of understanding signed by AEC, TVA, Commonwealth Edison	437	Technical appendix available from EPA	447
CHEMICALS		NEW JERSEY	
EPA proposes amendments to FIFRA	438	Grants received for demonstration recycling programs	442
House subcommittee approves bill	439	NEW MEXICO	
Review group may be established by EPA	434	Air pollution regulations established	446
CONTRACTS		Environmental agency plans hearings on septic tank rules	442
ESSO Research receives EPA contract	440	NOISE	
EDUCATION		International conference to be held	443
Air pollution training courses scheduled	443	OCEANOGRAPHY	
College environmental dissertations listed	444	NOAA awards \$1.8 million sea grant	447
ELECTRIC POWER		OHIO	
Senate plant siting background report issued	444	Governor appoints director of environmental agency	442
ENERGY		PESTICIDES	
Bureau of Mines summarizes progress	447	EPA proposes amended regulations on shipment of test poisons	445
Problems reviewed before House subcommittee	432	PETROLEUM	
Impact of federal decisions studied	436	Aspen charges oil leak on North Slope existed for 18 months	445
ENFORCEMENT		Committee held exploration efforts inadequate	435
EPA issues 180-day notices	433	Interior Department sets hearing on proposed oil lease sale	446
New York City firms to halt toxic metal discharges	438	Witnesses support proposed Oil Pollution Act amendments	433
FEDERAL AID		POPULATION	
EPA sewage treatment construction aid	440	House Population Committee formed	441
HUD basic water, sewer program grants	440	PROCUREMENT	
FLORIDA		EPA awards research in solid waste reduction	439
Heated water discharges limited	445	SOLID WASTE	
GASOLINE		NASM set urges use of water soluble adhesives for new-papers	443
Termination of lead discharges recommended	436	NEPCO calls for market expansion of waste paper products	434
GENERAL POLICY		Proposal to use PVC containers brings opposition	443
CEO issues Third Annual Report	427	WATER POLLUTION	
Conferees approve bill to develop water, power resources	435	EPA recommends permit system to protect subsurface waters	437
Environmental statements listed	441	Halpern introduces bill to tax discharges	441
EPA appoints urban affairs director	446	House Public Works spokesman expects water quality action soon	438
Fourth environmental research center designated	435	WEATHER MODIFICATION	
House approves conference report on EPA appropriations	428	Regional administrator opposes Washington paper mill discharge permit	446
President Nixon asks Congress to act on pending bills	427	WEATHER MODIFICATION	
Senate approves funds for military construction of control facilities	435	Cloud seeding experiment to test rainfall augmentation	447
Senate passes bill to curb housekeeping	431		
ILLINOIS			
Deadlines on operating permits set back	442		
Water pollution seminars to be held	443		
INDUSTRY			
Ford agrees to obtain licenses for Stirling engines	438		
JOURNAL			
Brief coverage of government action and coming events	446		
LITIGATION			
Army to comply with Virginia regulations	430		
New book on environmental law published	445		

Toxicity of Chlorinated Hydrocarbons and Related Compounds

A Review Including Chlorinated Dibenzodioxins and Chlorinated Dibenzofurans

Renate D. Kimbrough, MD, Chamblee, Ga

Various chlorinated technical compounds, namely, 2,4,5-trichlorophenol, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and European chlorinated biphenyls (Phenoclor DPS and Clophen A60), have been found to be contaminated with trace amounts of chlorinated dibenzofurans or chlorinated dibenzodioxins. Toxic fat which produces hydropericardium in chickens also contains chlorinated dibenzodioxins. These and other technical chlorinated compounds such as the technical pentachlorophenol have been implicated in causing chloracne, liver disease, teratogenicity, x-disease in cattle, and chick edema. The literature on the toxicity of the chlorinated technical compounds is reviewed. It is mentioned that 2,4,5-T and the chlorinated biphenyls also induce porphyria. Whether the various disease entities are caused by the contaminants, combinations of the chemical and its contaminants or by the chemicals themselves needs further evaluation.

RECENTLY several chlorinated compounds, such as the polychlorinated biphenyl and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), have received a great deal of attention. Polychlorinated biphenyls (PCB) are increasingly found in our environment and 2,4,5-T has been used extensively as an herbicide. Occasionally these and other chlorinated technical compounds have caused diseases that bear similarity to each other.

Some of these chemicals have been found to be contaminated with chlorinated dibenzofurans or chlorinated dibenzodioxins. The various diseases produced by one or more of the different technical compounds are discussed in this paper. Attention is focused on the various contaminants and their possible relationship to different diseases in a variety of species. The need for further well-coordinated epidemiological and experimental animal studies is pointed out.

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From the Chamblee Toxicology Laboratory, Environmental Protection Agency, Chamblee, Ga.

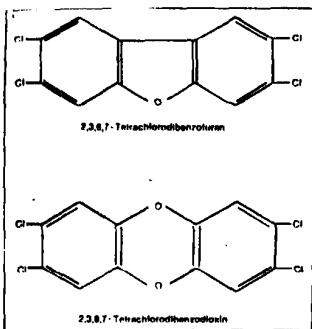
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Chloracne

This disease is described by the formation of comedones with or without cysts and pustules. The follicular orifices are filled with sebaceous and keratinous material. Melanosis and a secondary inflammatory reaction may exist. Chloracne was described for the first time by Herzheimer¹ in 1899 who thought it was produced by free chlorine. Wauer² in 1918 and Teleky³ in 1927 suggested the term "pernakrankheit." They felt that this skin disease was produced by certain chlorinated hydrocarbons. Jones and Alden⁴ were among the first to report a case of chloracne in a 26-year-old male Negro who worked for three years distilling chlorinated biphenyls. This patient also complained of lassitude, loss of appetite, and loss of libido.

Chloracne is one of the most frequent forms of occupational dermatitis, and many cases have been reported in the United States as well as in Europe, particularly Germany and England.

Teleky³ reported in 1940 that he personally had seen at least "150 to 280 workers" in four different factories with chloracne. He stated that liver disease occurs independently from chloracne, and usually manifests itself after an exposure time of four to six months, but may occur in as short a time as seven weeks. Occasionally loss of appetite, nausea, and edema of the face and hands are the first symptoms. Abdominal pain and vomiting follow, and then jaundice develops. At autopsy, acute yellow atrophy of the liver is found. He cites Flinn and Jarvik⁵ who reported cases of acute yellow atrophy with fatal outcome following exposure to Halowaxes. Halowaxes, which are chlorinated naphthalenes, as well as the PCB (Aroclors) were increasingly used after 1930 to insulate cables. Teleky³ cites many other case reports (Drinker et al,⁶ Jones,⁴ Greenburg et al,⁷ Cotter,¹⁰ McLachlan and Robertson,¹¹ and Collier¹²). Von Oetting



Chemical structure of a chlorinated dibenzodioxin and a chlorinated dibenzofuran.

gins¹⁵(p368-319) describes the occurrence of chloracne in workers exposed to these chemicals. He cites several references which indicate that dermatitis is the result of the local effect or direct contact with the chemical, while the toxic hepatitis results from absorption.

Chloracne has been reported in workers exposed to chloronaphthalenes, chlorobiphenyls, chlorodiphenyloxides, certain petroleum products, and solid chlorophenols.¹⁴ More recently Meigs et al¹⁶ and Hofman and Meneghini¹⁷ reported 14 and 13 cases of chloracne, respectively. Exposure to chlorinated biphenyls was established in most of these cases. Birmingham¹⁷ observed chloracne in 15 employees who had painted flat sections of glass with enamel and then baked it. The enamel had Aroclor (a PCB) incorporated in it. Flewig¹⁸ produced chloracne experimentally on the upper back of eight male adults by applying Halowax 1014, pentachloronaphthalene, and hexachloronaphthalene.

Bauer et al¹⁹ reported chloracne in workers that handled technical 2,4,5-trichlorophenol. In some of these workers neuromuscular weakness, psychopathological changes, blepharocconjunctivitis, and liver involvement also occurred. Kimmig and Schulz²⁰ found that pure 2,4,5-trichlorophenol did not produce hyperkeratosis when applied to

the rabbit ear. (The rabbit ear test is used as a screening test to determine whether a compound is likely to produce chloracne. The chemical, dissolved in propylene glycol, is painted on the rabbit ear. If the test is positive, erythema occurs within two days and in a few weeks hyperkeratosis develops.) The rabbit skin offers us an experimental method that will indicate the ability of substances to produce acneiform dermatitis in man.²¹ Pure 2,4,5-trichlorophenol did not affect the rabbit ear, and neither did 1,2,4,5-tetrachlorobenzene, the starting material in the manufacture of 2,4,5-trichlorophenol. However, technical 2,4,5-trichlorophenol which was used in the production of 2,4,5-T did produce hyperkeratosis of the rabbit ear. It was concluded that by-products which had resulted during alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene were the causative agents.

Kimmig and Schulz²⁰ isolated several contaminants and found that some of them, namely tetrachlorodibenzofuran (Figure) at a concentration of 0.05% as well as tetrachlorodibenzodioxin (Figure) at a concentration of 0.005%, produced hyperkeratosis in the rabbit ear. A hepatotoxic effect was also observed with these compounds. They also found that pure pentachlorophenol did not produce hyperkeratosis of the rabbit ear. Chloracne was observed in workers of a West German plant who produced technical pentachlorophenol from hexachlorobenzene.²² The technical material also induced hyperkeratosis in the rabbit ear. It is possible that technical pentachlorophenol contains toxic impurities, particularly since pentachlorophenol is produced by alkaline hydrolysis from hexachlorobenzene. Dibenzodioxin and dibenzofuran themselves do not cause liver necrosis or hyperkeratosis when applied to the rabbit ear; however, they become highly toxic when they contain three or more chlorine atoms.²⁰ Some of the workers with chloracne also develop eye irritation, hepatotoxicity, intolerance to alcohol, neuromuscular symptoms, porphyria cutanea tarda, and psychologic alterations.²³ According to Braun,²⁴ chloracne seems to result from direct contact with the chemicals producing it. Crow,²⁵ on the other hand, points out that chloracne can also be produced by systemic absorption.

This disease in a Olson²⁶ in 1947. . . dence was published chlorinated naphthalene case.²⁷ Cattle with decline in vitamin A of poisoning in ion, diarrhea, poly and discharge from cough, poor appetite maculae in the buccal hyperkeratosis of the scopic examination shows central lobule cells with bile duct tion of the glands in bladder. Cystic dilata tubules of the renal : degree of fibrosis and pancreas, was also of crisis and cirrhosis : the nephrons, and e the endometrium were after ingestion of 1 chlorinated naphtha Link²⁸ fed hexachlor swine and produced the liver and kidneys vaginal epithelium a A depression of the was also observed.

Drinker and co-w liver of rats was a male were fed high naphthalene, pentachloronaphthalene, pentachloronaphthalene phenyls. When Scho chloronaphthalene to to moderate fatty de with centrilobular cells. Degenerative ch the kidneys and the : tosis.

It can be concluded that highly chlorine duce liver changes cows, x-disease of the drop in the vitamin A the leading manifests is possible that the represents a manifest liver disease.

Slkes et al²⁹ found produced in cattle w

This disease in cattle was described by Olafson²² in 1947. A few years later evidence was published showing that highly chlorinated naphthalenes caused the disease.²³ Cattle with x-disease show a rapid decline in vitamin A plasma levels. Symptoms of poisoning include excessive lacrimation, diarrhea, polyuria, marked salivation, and discharge from the nostrils. A chronic cough, poor appetite, and numerous red maculae in the buccal mucosa develop, and hyperkeratosis of the skin follows. Microscopic examination of autopsy material shows central lobular degeneration of liver cells with bile duct proliferation and dilation of the glands in the wall of the gallbladder. Cystic dilation of the collecting tubules of the renal cortex, with a moderate degree of fibrosis and degenerated cells in the pancreas, was also observed.²⁴ In sheep, necrosis and cirrhosis of the liver, damage to the nephrons, and squamous metaplasia of the endometrium were the principle findings after ingestion of feed containing highly chlorinated naphthalenes.²⁵ Huber and Link²⁶ fed hexachloronaphthalene to young swine and produced degenerative lesions of the liver and kidneys and hyperplasia of the vaginal epithelium with keratin formation. A depression of the vitamin A plasma level was also observed.

Drinker and co-workers⁷ found that the liver of rats was affected when the animals were fed high doses of tetrachloronaphthalene, pentachloronaphthalene, and hexachloronaphthalene or chlorinated biphenyls. When Schoettle et al.²¹ fed hexachloronaphthalene to rats, they observed mild to moderate fatty degeneration of the liver with centrilobular vacuolation of hepatic cells. Degenerative changes were observed in the kidneys and the skin showed hyperkeratosis.

It can be concluded from these reports that highly chlorinated naphthalenes produce liver changes in several species. In cows, x-disease of the skin, together with a drop in the vitamin A plasma level, is one of the leading manifestations of the disease. It is possible that the vitamin A deficiency represents a manifestation of concomitant liver disease.

Sikes et al.²⁷ found that x-disease could be produced in cattle with highly chlorinated

naphthalenes, but also with petroleum products such as crank case oil. The toxic products were excreted in the milk and produced x-disease in the calves drinking the milk. They cited other authors who were able to produce the disease with a complex wood preservative and a lubricant.

Bell²⁸ tested the ability of various compounds of the chlorinated naphthalene group to produce x-disease. He discovered that dichlorinated and trichlorinated naphthalenes did not produce the disease while tetrachloronaphthalene had an effect, and the higher chlorinated naphthalene, pentachloronaphthalene, hexachloronaphthalene, heptachloronaphthalene, and octachloronaphthalene, caused severe disease. Octachloronaphthalene was less toxic than hexachloronaphthalene and heptachloronaphthalene.

Chick Edema

In 1987,^{24,25} a disease occurred in a large number of chickens which, at first glance, seemed to represent an epidemic. It was soon discovered that the residues of certain distilled animal fats produced the condition when they were added to the chicken diet.^{26,27} The disease was called chick edema because it manifests itself with hydropericardium and ascites in chickens. Ducks and turkeys experience a reduction in growth.

Allen and Lalich²⁸ produced hydropericardium and ascites in chickens when enough toxic fat was given to kill most of the birds in five weeks. ("Toxic fat" is a term used for fat found in chicken feed that induces chick edema.) When the concentration of toxic fat was reduced and fed to the chickens for 150 days, hydropericardium and ascites developed less frequently, but testicular hypoplasia became apparent. Simpson et al.²⁹ described proliferation and hypertrophy of the vascular endothelium and possible necrosis of hepatic and bile duct tissue in chickens and turkeys. When monkeys (*Macaca mulatta*) were fed toxic fat, alopecia, subcutaneous edema, decreased total serum protein (with a reversal in the albumin-globulin ratio), and reduced hematopoiesis and spermatogenesis developed. Gastric ulcers occurred in 66% of the animals. Focal areas of necrosis and degeneration were observed in the liver; and the bile duct epithelium was found to be affected when it was examined under the electron microscope. Dilata-

Table 1.—Disease Resulting From Exposure

Chloracne	Pathological Findings of the Liver	Birth Defects and Lethal Factor	X-Disease in Cattle
Certain petroleum products Chloronaphthalenes (mainly pentachloro- benzene, and hepta- chlorobiphenyls Chlorodiphenyloxides Chlorophenols (technical 2,4,5-trichlorophenol, pentachlorophenol) Technical 2,4,5-T	Chlorinated naphthalenes Chlorinated biphenyls Technical 2,4,5-T and other chlorophenols	Certain technical 2,4,5-T Purified material from toxic fat Polychlorinated biphenyls	Highly chlorinated naphthalenes Petroleum products

* "Toxic fat" is a term used for fat found in chicken feed that induces chick edema.

tion of the heart and hypertrophy of the cardiac muscle were also present.¹⁰

Toxic fat is not the only product capable of producing the chick edema syndrome. Chlorinated biphenyl products, used as a plasticizer in a paint, have caused hydropicardium and ascites in chickens,¹¹ and two of seven Bangalese finches fed PCB developed hydropicardium.¹² The seven finches of a total of 56 birds died during the course of the experiment. A mixture of pentachloronaphthalene and hexachloronaphthalene, when fed to chickens, resulted in chick edema.¹³ The toxic fat which contained the chick edema factor was studied intensively. Flick et al¹⁴ separated a purified crystalline concentrate which produced chick edema and decreased the hatchability of injected eggs. Embryonic deformities were also produced. Flick et al¹⁵ were not able to produce testicular hypoplasia in cockerels when they fed low doses of toxic fat (0.6% and 1.0%) to the cockerels for 12 weeks, as had been reported by Allen and Lalich.¹⁶

In 1967, Cantrell et al¹⁷ reported that 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin was one of the toxic compounds producing chick edema. Tomita et al¹⁸ had shown earlier that the heating of pentachlorophenol produced octachlorodibenzo-*p*-dioxin. Higginbotham et al¹⁹ showed that the chick edema factor represented chlorinated dibenzo-*p*-dioxin. The two principal compounds isolated were 2,3,7-trichlorodibenzo-*p*-dioxin and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. The authors suggested, as a possible source of contamination, fats and fatty acids containing commercial chlorophenols. When crude fats and tallow are heated to produce fatty acids chlorophenol residues might be converted to a chick edema factor.

It was mentioned earlier in this article

that the Aroclors can produce chick edema. The Aroclors (PCB) are used primarily as dielectric fluids for capacitors and transformers, as industrial fluids for hydraulic, for gas turbine and for vacuum pumps, and as heat transfer fluids. They are also used as plasticizers and are widely distributed in the environment.²⁰ Aroclor is a trade name under which these compounds are marketed in the United States. They can be found in synthetic resins, synthetic and natural rubbers, cellulose resins, paint varnish, wax, asphalt, and in allyl starch. They have been employed for dust prevention, moisture proofing, sealing, impregnation, and vapor suppression to prolong the residual life of insecticides. They increase the toxicity of dieldrin and DDT in insects.²⁰ Depending on the amount of chlorine they contain they are assigned certain numbers. Aroclor 1260 for instance, contains 60% chlorine, while Aroclor 1242 has an approximate chlorine content of 42%. Miller,²¹ in 1944, tested a commercial chlorinated biphenyl with 42% chlorine and observed liver damage in rabbits, guinea pigs and rats. Skin changes were observed in the animals who received subcutaneous injections and application of the material to the skin. The skin lesions produced by subcutaneous injection were histologically similar to those of chloracne in man. Direct application to the skin produced inconsistent lesions compatible with low-grade irritation. Von Oettingen^{12 (p. 99-101)} discusses some of the earlier work on the toxicity of the Aroclors in his book *The Halogenated Hydrocarbons, Toxicity and Potential Dangers*. Nishizumi²² observed changes in the livers of mice and monkeys after feeding them chlorinated biphenyls. The author undertook this work because of an outbreak of poisoning that involved at

to Technical Compounds

Chick Edema

Toxic fat*
Chlorinated biphenyls
Mixture of pentachloro-
naphthalene
and hexachloro-
naphthalene

least 600 people in ingested rice bran as inated with chlor PCB (Kanechlor 40) leaked into the rice holes in a pipe used manufacturing process mentation and ab brown pigment dogs born and newborn Stillbirths were use of the mother. Adult orexin, fatigue, excre like discharge from and dark-brownish p Vos and Koeman²³ several polychlorinated, quail and rats. the toxicity of two polychlorinated biphenyls and Clophen A60) which was produced The European Commission toxicity and produce edema. Chick edema with European Commission Aroclor 1260. All duced porphyria. Chu three compounds: benzofuran, pentachloronaphthalene the European sample from the United States edema occurred on Aroclor 1260, the most indicative of small quantities in this preparation

Tetraz

Recently, Bionette Bethesda, Md (unpubl

to Technical Compounds

Chick Edema

Toxic fat*

Chlorinated biphenyls
Mixture of pentachloro-
naphthalene
and hexachloro-
naphthalene

Table 2.—Toxic Contaminants Found in Some Technical Compounds*

2,4,5-trichlorophenol

2,4,5-T

Toxic fat

European chlorinated
biphenyls (Phenoclor
DP6 and Clophen A 60)

Tetrachlorodibenzofuran
Tetrachlorodibenzodioxin

Tetrachlorodibenzofuran
Tetrachlorodibenzodioxin

1,2,3,7,8,9 hexachlorodibenzo-p-dioxin
2,3,7 trichlorodibenzo-p-dioxin
2,3,7,8 tetrachlorodibenzo-p-dioxin

Tetrachlorodibenzofuran
Pentachlorodibenzofuran
Hexachloronaphthalene

* Listed in Table 1.

least 600 people in Western Japan who had ingested rice bran oil that had been contaminated with chlorobiphenyls, a Japanese PCB (Kanechlor 400). The chlorobiphenyls leaked into the rice bran oil through pinholes in a pipe used for heat exchange in the manufacturing process. An increase in pigmentation and abnormal grayish dark-brown pigment deposits in the skin of still-born and newborn infants was observed.²² Stillbirths were unrelated to PCB poisoning of the mother. Adults showed chloracne, anorexia, fatigue, edema of the eyelids, cheese-like discharge from the meibomian glands, and dark-brownish pigmented nails.²⁴

Vos and Koeman²⁵ studied the toxicity of several polychlorinated biphenyls in chickens, quail and rats. The authors compared the toxicity of two European commercial polychlorinated biphenyls (Phenoclor DP6 and Clophen A60) and one (Aroclor 1260) which was produced in the United States. The European compounds showed higher toxicity and produced centrilobular liver necrosis. Chick edema was a common finding with European compounds and rare with Aroclor 1260. All three compounds produced porphyria. Chemical analysis of these three compounds revealed tetrachlorodibenzofuran, pentachlorodibenzofuran, and hexachloronaphthalene as a contaminant in the European samples but not in the sample from the United States.²⁶ Since hydroperticardium occurred occasionally in chicks fed Aroclor 1260, the authors felt that this was indicative of small quantities of a toxic factor in this preparation.

Teratogenesis

Recently, Bionetics Research Laboratory, Bethesda, Md (unpublished data), as cited

by Emerson et al²⁷ found a teratogenic effect of technical 2,4,5-T in rats. Apparently, the technical 2,4,5-T was contaminated with 27 ppm of 2,3,7,8-tetrachlorodibenzo-p-dioxin. In the study published by Courtney et al,²⁸ it was stated that the technical 2,4,5-T which was found to be teratogenic in two strains of mice and one strain of rats was contaminated with 30 ppm 2,3,7,8-tetrachlorodibenzodioxin. Emerson et al²⁷ tested 2,4,5-T that only contained 1 ppm 2,3,7,8-tetrachlorodibenzo-p-dioxin at comparable dosage levels and did not elicit a teratogenic effect. This finding was substantiated by Sparacu et al²⁹ who studied teratogenic effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. A slight effect was observed at a dose of 0.125 µg/kg/day when the material was given by gavage from day 6 through day 15 of gestation. At the level of 0.5 µg/kg/day, the effect was quite pronounced. Courtney and Moore²⁹ were able to produce cleft palates and kidney malformations in three strains of mice with high doses (100 mg/kg subcutaneously daily from day 6 to 15 of pregnancy) of analytical grade 2,4,5-T that contained less than 0.05 ppm 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Keplinger et al³¹ reported a decreased survival of pups in rat reproduction studies when fed 100 ppm of Aroclor 1242 and 1254, and poor hatchability of eggs from chickens fed 10 or 100 ppm of Aroclor 1242 or 100 ppm of Aroclor 1254. It has been said³² that a purified crystalline concentrate from toxic fat led to the development of embryonic deformities in chickens.

Comment

In some instances, the same chemical compounds are responsible for the occurrence of

chloracne in people, liver disease in several species, x-disease in cattle, chick edema, and teratologic or other effects on the fetus. Not all of the disease entities have thus far been produced by all of the compounds (Table 1). Some of the compounds in question have been shown to be contaminated with chlorinated dibenzo-p-dioxins or chlorinated dibenzofurans (Table 2). The degree of contamination seems to vary with different compounds. Some companies manufacturing these compounds have instituted clean-up procedures which remove the greatest part of the contaminants. Improved hygiene among the workers and improved ventilation of the working area have, in many instances, reduced the incidence of chloracne. Whether all disease entities described are caused by the chlorinated dibenzodioxins or the chlorinated dibenzofurans is not yet known. Some of these chemicals are highly toxic, as illustrated by the fact that two applications of 10 µg of 2,3,6,7-tetrachlorodibenzo-p-dioxin applied to human skin²² produced chloracne-like symptoms. Single oral doses of 20 µg to 50 µg/kg/body weight resulted in fatal liver necrosis in rabbits.²³ There is no readily available information on the metabolism of these compounds in animals and their breakdown in the environment.²⁴ It is probable that they are stable. Crosby et al.²⁴ found that 2,3,7,8-tetrachlorodibenzo-p-dioxin and its homologues decomposed rapidly in alcohol solution under artificial light and natural light. However, photodecomposition was negligible in aqueous suspensions and on wet or dry soil. It is unknown whether the disease entities discussed are the result of one or several contaminants or the combined effect of the chemical compound and its contaminant.

Another unsolved problem is the observation that some of these compounds such as technical 2,4,5-T induce porphyria.²⁵ The chlorinated biphenyls also cause porphyria.²⁶ Whether porphyria is the result of the chemicals themselves or of the contaminants, or both, is not known. Crow²⁶ suggests that the porphyria produced by technical 2,4,5-T may have been caused by contamination of the chemical with crude chlorobenzenes, which were used to produce the chlorophenols from which the 2,4,5-T was made. Better awareness of the possible

contamination of the technical chemicals with various highly toxic substances, well coordinated epidemiological studies, and additional experimental studies in animals are needed to clarify these problems.

Chloracne has been produced experimentally in men by Shelley and Klignan (*Arch Derm* 75:689, 1957). The authors cite additional references on experimental dermal exposure of animals and men to chlorinated naphthalenes.

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