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THE HUMAN HEALTH EFFECTS OF DDT (DICHLORODIPHENYL-TRICHLOROETHANE) AND PCBS (POLYCHLORINATED BIPHENYLS) AND AN OVERVIEW OF ORGANOCHLORINES IN PUBLIC HEALTH*

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ABSTRACT

Organochlorines are a diverse group of persistent synthetic compounds, some of which are detectable in nearly everyone. Many organochlorines are endocrine disruptors or carcinogens in experimental assays. p,p′-DDE (dichlorodiphenyl-dichloroethene) and PCBs (polychlorinated biphenyls) comprise the bulk of organochlorine residues in human tissues. We reviewed relevant human data cited in the 1991–1995 Medline database and elsewhere. High-level exposure to selected organochlorines appears to cause abnormalities of liver function, skin (chloracne), and the nervous system. Of more general interest, however, is evidence suggesting insidious effects of background exposure. Of particular concern is the finding of neonatal hypotonia or hyporeflexia in relation to PCB exposure. The epidemiologic data reviewed, considered in isolation, provide no convincing evidence that organochlorines cause a large excess number of cancers. A recent risk assessment

that considered animal data, however, gives a cancer risk estimate for background exposure to dioxin and dioxin-like compounds (e.g. some PCBs) with an upper bound in the range of 10^{-4} per year.

INTRODUCTION

Overview

The decades after World War II saw the large-scale production of cheap, long-lasting synthetic petrochemicals, e.g. pesticides, dielectrics, plasticizers, and fire retardants. The realization that persistent chemicals could be both uncontrollable and unexpectedly toxic is usually attributed to Rachel Carson, who published *Silent Spring* in 1962 (18).

The halogenated organic compounds that resist degradation, are lipophilic, and that tend to bioaccumulate are often considered as a group in toxicology and public health. Tables 1 and 2 list important examples of this diverse group of synthetic compounds; several of these have been widely distributed in the ecosystem, are frequently found at low levels in human tissue, and are toxic. Most organohalogens of public health importance are organochlorines. The exception is PBBs (see Tables 1 and 2 for definition of all acronyms used), manufactured as a flame retardant (11), which entered the food chain in Michigan in the 1970s when accidentally fed to livestock.

One way to broadly classify organochlorines is according to whether they are (Table 1) or are not (Table 2) pesticides. Most of the organochlorine pesticides are insecticides; hexachlorobenzene is a fungicide. Among the nonpesticide organochlorines is 2,3,7,8-TCDD (a PCDD), the most toxic synthetic chemical known. Throughout this review dioxin is defined as 2,3,7,8-TCDD, and PCDDs in general are called dioxins. Dioxin exerts most of its toxicity by occupying a receptor, the Ah receptor. Many specific compounds among the nonpesticide organochlorines exert toxicity by the same (dioxin-like) mechanism. For example, the "coplanar" PCBs (see Table 2, column 3) and 2,3,7,8-PCDF have dioxin-like activity. Most PCBs, however, do not have dioxin-like activity. PCBs were produced in large quantities until the 1970s for use in electrical equipment and other applications. When PCBs or other materials are subjected to extreme heat, such as in incinerators, PCDFs and PCDDs are produced. PCDFs and PCDDs also are produced as contaminants in chemical manufacturing; contamination of the herbicide Agent Orange with dioxin is an example.

Many organochlorine compounds can be detected in the blood of general population samples in the United States (Tables 1, 2) (99, 107). PCDDs and PCDFs are present at concentrations about one thousandth or one ten thousandth of p,p′-DDE and PCBs levels. The median concentration of p,p′-DDE in serum

Table 1 Salient characteristics of pesticide organochlorine compounds of importance in public health[a]

Class	Example: alternate name (specific examples within group, if applicable)	Endocrine disrupter	Percent of US population with detectable level in blood (level)	Carcinogen in animal models
Dichlorodiphenylethanes				
	DDT: dichlorodiphenyltrichloroethane	+		+
	(o,p′-DDT: o,p′-dichlorodiphenyltrichloroethane)	+	0.4	
	(p,p′-DDT: p,p′-dichlorodiphenyltrichloroethane)	+	35.7	
	(p,p′-DDE: p,p′-dichlorodiphenyldichloroethene)	+	99.5 (12.6 ppb)	
	Methoxychlor	+		±
Hexachlorocyclohexanes				
	Lindane: γ-hexachlorocyclohexane, γ-BHC		0.2	±
	β-Benzene hexachoride: β-BHC, β-HCH		17.2	±
Cyclodienes				
	Endrin			I
	Endosulfan	+		
	Aldrin		0.0	±
	Dieldrin	+	10.6	±
	Heptachlor		0.3	+
	Chlordane			+
	Toxaphene	+		
Other insecticides				
	Chlordecone: Kepone	+		+
	Mirex: Dechlorane		0.0	+
Hexachlorobenzene				
	Hexachlorobenzene: HCB		4.9	+

[a]Notes: Endocrine disrupter activity means either (*a*) estrogenic, (*b*), antiestrogenic, or (*c*) antiandrogenic. Classification as an endocrine disrupter was based on data in (64, 106). Percent of the general population with detectable levels (107) is affected by the detection limits of the assay, which is about 1 part per billion (ppb) for organochlorine pesticides in serum. Classification of compound according to carcinogenicity in animal models is based on the IARC Monographs (61); + means sufficient evidence of carcinogenicity, ± means limited (suggestive) evidence of carcinogenicity, and I means insufficient data. When no data were available for a given compound the classification was left blank.

Table 2 Salient characteristics of nonpesticide organobromine and organochlorine compounds of importance in public health[a]

Group acronym	Number of compounds in group (congeners)	Chemical name or description (important examples)	Dioxin-like toxicity	Endocrine disrupter	Percent of US population with detectable level in blood (level)	Carcinogen in animal models
PBBs	209	Polybrominated biphenyls	Y	+		+
PCBs	209	Polychlorinated biphenyls		+	100.0 (1.4 ppb)	+
		(the "coplanar" PCBs: mono-ortho and non-orthochloro-substituted PCBs)	Y			
PCDFs	75	Polychlorinated dibenzofurans			100.0 (0.5 ppt)	
		(TCDF: 2,3,7,8-tetrachlorodibenzofuran)	Y	+		
PCDD	135	Polychlorinated dibenzodioxin	Y		100.0 (5.0 ppt)	
		(TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin [dioxin], and OCDD: octachlorinated dibenzo dioxin)		+		+

[a]Notes: Footnotes for Table 1 apply: Reference 93 contains data on dioxin-like activity. General population blood levels are estimates based on measures in unexposed population groups (99; E DeVoto, personal communication). Serum concentrations are not expressed per unit lipid. ppb, parts per billion, ppt, parts per trillion.

(12.6 ppb = 37.7 nm/L) (107) is more than 100-fold greater than that of estradiol in premenopausal women on a molar basis and is about the same as that of testosterone in men. Many organochlorines have been shown to be carcinogenic in animal models (61).

Many organochlorines, most notably o,p′-DDT, are weakly estrogenic (Tables 1, 2) (64, 106), with estrogenic activity a thousandth or less than that of estradiol. Most exposure to o,p′-DDT is a consequence of direct exposure to pesticide application. In the general population, the less estrogenic p,p′-DDT, and its metabolite, p,p′-DDE, are present in blood in much higher concentrations than o,p′-DDT (107), reflecting their slower metabolism and the fact that the primary source of exposure is diet. p,p′-DDE was recently found experimentally to inhibit androgen binding to the androgen receptor (64). Because dioxin has antiestrogenic properties (94), the dioxin-like coplanar PCBs would also be expected to have antiestrogenic activity.

p,p′-DDE and PCBs comprise the bulk of organochlorine residues found in human adipose tissue, milk, or blood. In this review, we focus on DDT (and derivatives) and PCBs because of their higher levels in humans. We briefly review the health effects of dioxin because some PCBs have low-potency dioxin-like activity. In addition, although dioxins are present at much lower concentrations than p,p′-DDE and PCBs, their extreme potency make it biologically plausible that health effects could occur at ambient levels of exposure. We also briefly consider the health effects of PCDFs because some have dioxin-like activity and therefore assessment of the potential toxicity of dioxin-like compounds is informed by data on PCDF effects. Data on other organochlorine compounds are not considered here, because blood levels in humans are less often detectable and fewer human data on health effects are available. We note, however, a mass poisoning with hexachlorobenzene (46), and epidemics of seizures due to endrin-contaminated food (116).

Methods

We identified data for consideration in this review as follows: the WinSPIRS-Medline software (Silver Platter Software International, N.V., 1995) was used to search the Medline Express database covering 1991–1995; the search was executed in February 1996. For each medical subject heading (MESH) searched (DDT, DDE, polychlorinated biphenyls, and dioxins), the term was "exploded" and the scope was limited to human studies published in English. From the result of the search, we identified reports of cross-sectional, case-control, and cohort studies, and reviews. Other relevant data were identified from the reference lists in the publications so identified. In addition, other relevant materials were identified by consultation with subject matter experts. Data were considered supportive of a causal relation if findings of an effect were consistent and the

potential for bias limited. Along with human data, animal data are needed for a complete risk assessment, but are outside the scope of this review.

For each type of organochlorine reviewed, we provide a note on history and background exposure and then group the findings according to the type of outcome.

Chemistry

The persistent organochlorines have at least one ring in their structure. The chemical structure of the compounds considered in greatest detail in this review are shown in Figure 1. The dichlorodiphenylethanes and PCBs have two aromatic rings, and the PCDFs and PCDDs have three. The PCBs found in greatest quantity in human tissues have 6 or 7 chlorines. The PCBs with the most dioxin-like activity (coplanar PCBs) are chlorinated at both para positions (4,4′-chlorinated) and two or more meta positions (3,5,3′, and 5′- are meta positions). In fact, all the PCBs, PCDFs, and PCDDs with the greatest dioxin-like activity have chlorines at the far ends of the molecule and not elsewhere. The term congener is used to refer to a compound with a specific arrangement of chlorine.

Toxic Equivalency Factors and Other Mechanistic Considerations

Most, if not all, 2,3,7,8-TCDD toxicity and that of other compounds with dioxin-like activity is mediated through binding with the Ah receptor (113). To quantify the dioxin-like activity of a compound on a scale reflecting toxicologic activity relative to pure dioxin, the toxic equivalency factor (TEF) approach is used, where the concentration of the compound with dioxin-like activity is multiplied by a weight (TEF). TEFs are based on findings from a variety of experimental settings and species, and no specific set of TEFs has achieved universal acceptance. For a mixture of compounds, the product of the concentration and TEF for each compound (the toxic equivalence [TEq] for the compound) is summed across all compounds present to obtain a total toxic equivalency for the mixture. Because dioxin and dioxin-like compounds are often present as complex mixtures, expressing their toxicity as total TEq facilitates regulation and evaluation of effects. An example calculation follows: Suppose a subject was found to have a blood level of OCDD of 1×10^{-9} g/g, and of dioxin of 1×10^{-12} g/g (both expressed per gram of blood lipid). With a TEF for OCDD of 0.001, and a TEF for dioxin of 1 (93), the total TEq present is $1 \times 10^{-9} \times 0.001 + 1 \times 10^{-12} \times 1$, or 2 pg/g. TEq calculations based on analyses of dioxins and PCBs in samples of human milk from The Netherlands showed that about half the total TEq could be attributed to dioxins and the other half was from PCBs (67). Estimates of this type made in human samples from several other countries, however, suggest PCBs contribute the majority of total TEq (86).

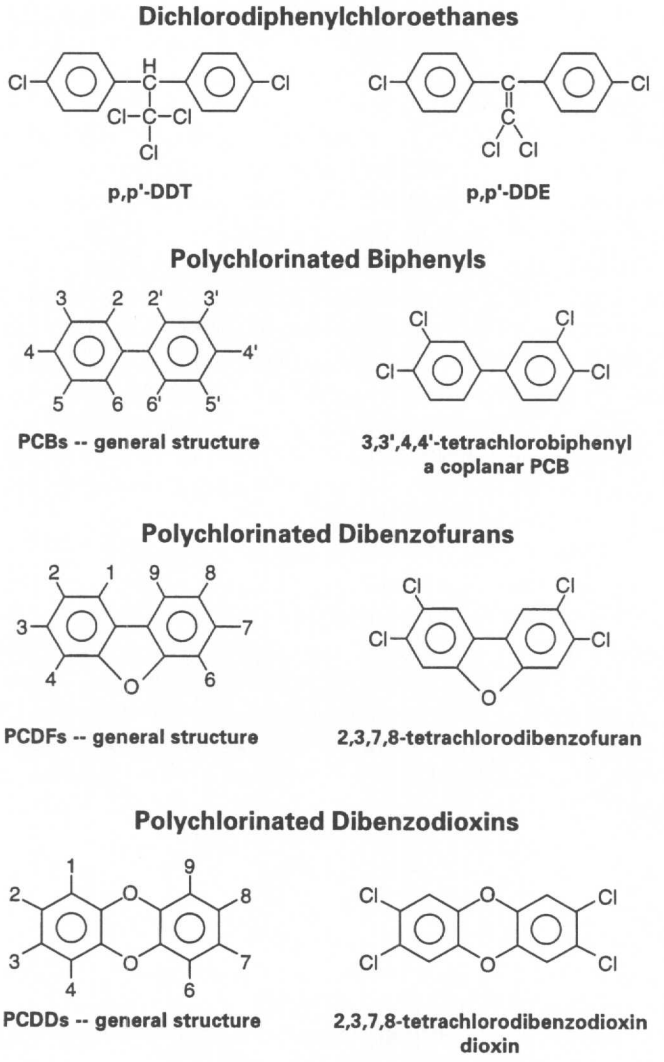

Figure 1 The chemical structures of the compounds considered in detail in this review.

Organochlorines in groups that include congeners with dioxin-like activity may affect health via mechanisms other than that comparable to dioxin. For example, several lower molecular weight PCBs with TEFs of 0 cause neurologic damage in rats and primates (93).

The Problem of Mixed Exposures

For many organochlorines, particularly the nonpesticides, exposure tends to be to a mixture of congeners of the same group, to mixtures of congeners from different groups, or to mixtures including other chemicals. In the case of Agent Orange, the health effects of the active ingredients (2,4-dichlorophenoxyacetic acid [2,4-D], 2,4,5-trichlorophenoxyacetic acid [2,4,5-T]) are hard to distinguish from that of the Agent Orange contaminant dioxin. In the Yu-Cheng incident in Taiwan, rice oil was accidentally contaminated with a mixture of PCBs, PCDFs, and other compounds. Occupational exposure to dioxin has been shown to be correlated with exposure to 4-aminobiphenyl, a known human carcinogen (22). Furthermore, background exposure to dioxins and PCBs appears to be highly correlated (67, 86). Thus, the available data on health effects of organochlorine exposure frequently cannot be readily interpreted as due to a specific compound.

The health effects of occupational and general population exposures to organochlorine compounds are often considered together in this review. We note, however, that the nature of exposure, apart from dose, in the two settings is often different, and so may be the effects. Exposure to DDT by pesticide applicators, for example, is primarily to p,p′-DDT, whereas it is the p,p′-DDE metabolite to which nearly all of the general population is exposed via diet. Similarly, occupational exposure to PCBs results in exposure to more lower molecular weight congeners than does the general population exposure, which also comes from diet.

DDT AND RELATED COMPOUNDS

A Note on History and Background Exposure

From the 1940s to the 1960s, organochlorine pesticides, including DDT, saw widespread use in the United States, especially in agriculture and forestry (27). Production and use of DDT in the United States has been banned since 1972, and similar policies regarding most other organochlorine compounds have been enacted (Lindane is a notable exception).

The DDT preparation typically used was technical grade DDT, a mixture made primarily of p,p′-DDT, with a lesser quantity of o,p′-DDT and related dichlorodiphenylchloroethanes. Although p,p′-DDT and o,p′-DDT have half-lives of about 7 years (125), the half-life of p,p′-DDE, a metabolite of p,p′-DDT, is much longer, accounting for its greater concentration in humans (Table 1).

With the decrease in use of DDT, blood levels of dichlorodiphenylchloroethanes have fallen; levels among those in the general population in the 1960s were about five times higher than at present. Nonetheless, exposure is ongoing because of accumulation in the biosphere. Meat and fish are the main sources of exposure for adults. Children also get organochlorines in their mother's milk.

Data on Human Health Effects

PANCREATIC CANCER Garabrant et al (42) found that among workers at a chemical manufacturing plant, exposure to technical grade DDT was associated with increased risk of pancreatic cancer (odds ratio for ever-exposed, 4.8, 95% CI 1.3–17.6). Risk increased with duration of exposure. Effects of exposure to related compounds, such as DDD [1,1-dichloro-2,2,-bis(p-chlorphenyl)ethane, a dichlorodiphenylethane] were also evaluated and were associated independently with increased risk. The findings were based on 28 cases, and associations with over 400 chemicals were studied. Other studies among cohorts of workers highly exposed to DDT in chemical manufacturing (26, 123) have been too small to be informative regarding an association with pancreatic or other specific cancers.

NON-HODGKIN'S LYMPHOMA In two large US case-control studies, agricultural exposure to DDT, as assessed by questionnaire, was associated with increased risk of non-Hodgkin's lymphoma (17, 126). Subjects who handled DDT without protective equipment when applying it to crops had an odds ratio of 2.0 (95% CI 1.3–3.1) in an analysis adjusted for exposure to other insectides and risk factors (17). In the other large study (126), use of DDT was associated with an odds ratio of 1.8 (95% CI 1.0–3.2). One (51) of two smaller Swedish case-control studies also suggested an increased risk with exposure [odds ratio 1.6 (no CI given)], whereas in the other (85) none of the cases had been exposed to DDT. Overall the data suggest an association between increased risk of non-Hodgkin's lymphoma and exposure to DDT in farming or related activities.

BREAST CANCER Data on the relation between p,p′-DDE levels and risk of breast cancer can be categorized into two groups, according to degree of informativeness. The first group of studies (25, 35, 82, 114, 117) is relatively uninformative. In the five studies, all with fewer than 50 cases, the level of p,p′-DDE in adipose tissue of cases and controls was compared. Controls were not carefully selected to represent exposure in the population where the cases originated. A summary measure of the association in the five studies, the average $\log_e$ ratio of mean p,p′-DDE levels in cases and controls (1), was 1.03 (95% CI 0.98–1.08). On the whole, the data from the five studies are not especially supportive of a p,p′-DDE-breast cancer relation.

Data from two larger studies of p,p′-DDE and breast cancer are more informative (Table 3) (70, 122). In each study, the cases and controls were from

Table 3 Results of two studies of serum DDE and PCB levels in relation to risk of breast cancer

Author	Number of cases	Number of controls	Mean serum levels in controls (μg/L) DDE	Mean serum levels in controls (μg/L) PCB	Adjusted Odds Ratio (95% CI) for high: low levels[a] DDE	Adjusted Odds Ratio (95% CI) for high: low levels[a] PCB
Wolff (122)	58	171	7.7	6.7	3.68 (1.01–13.50)	4.35 (0.90–22.0)
Krieger (70)	150	150	43.1	4.8	1.33 (0.68–2.62)	0.94 (0.48–1.84)
White	50	50	35.0	4.2	2.38 (0.54–10.64)	0.45 (0.09–2.20)
Black	50	50	43.4	4.5	3.85 (0.93–16.05)	2.21 (0.70–6.98)
Asian	50	50	50.8	5.6	0.71 (0.23–2.18)	0.78 (0.24–2.58)

[a]For the Wolff et al study (122) the contrast is between high and low quintiles; for the Krieger et al study (70) it is between high and low tertiles. The confidence interval for the PCB value from the Wolff et al study (122) was estimated from a graph.

the same well-defined population, and the results were adjusted for potential differences between subjects with high and low p,p′-DDE levels. The lower p,p′-DDE levels in the study by Wolff et al (122) are due to the samples being obtained after 1984, whereas those in the study by Krieger et al (70) were from the 1960s. Adami et al (1) calculated the odds ratio per standard deviation increase in p,p′-DDE level in the Wolff and Krieger studies; on that scale, the odds ratios for the Wolff results were markedly higher, possibly because of an anomalous relation of lactation with p,p′-DDE levels in the study subjects (74). The odds ratio per standard deviation increase in p,p′-DDE for both studies combined was 1.27 (95% CI 0.95–1.69). While the data from the study by Wolff et al (122) clearly support an association, the overall data from the study by Krieger et al (70) do not. Krieger et al (70) studied the p,p′-DDE-breast cancer association by race because of the higher organochlorine levels in some groups (107). Among the most highly exposed group (Asians), however, evidence of a direct p,p′-DDE-breast cancer relation was weakest. Although effect modification by race could account for the associations suggested among whites and blacks in the Kreiger study, the logic behind focusing on findings that support an association (96) rather than on the results as a whole is based on conjecture. Overall, the data on p,p′-DDE exposure and risk of breast cancer are inconclusive.

OTHER CANCERS Case-control studies using questionnaires to assess exposure to DDT in relation to risk of other cancers suggest that for soft-tissue sarcoma no association exists (34, 52, 126), and that for leukemia (15, 41) and Hodgkin's disease (51, 85) the results are mixed and inconclusive.

REPRODUCTIVE EFFECTS By modern standards, good data on the relation of DDT exposure to adverse reproductive outcomes are nearly nonexistent. The two most statistically powerful studies of this issue (72, 84) were case-control

studies of maternal blood DDT (primarily p,p′-DDE) levels in relation to spontaneous abortion. In neither study were case-control differences evident. Data from several small studies (88, 97, 98) showed cord tissue or cord blood DDT (mostly p,p′-DDE) levels were higher in premature infants than in term infants. The importance of these findings, however, is unclear owing to the possibility that the results are confounded by lipid levels or risk factors for prematurity, and because early fetal loss was not assessed in these studies.

IMPAIRED LACTATION Higher levels of p,p′-DDE in maternal milk have been associated with shorter duration of lactation (45, 92). In the first study (92), among women lactating for the first time, lactation was 0.9 week shorter (95% CI −1.7 to −0.1) for each 1 ppm increase in p,p′-DDE/g milk fat, and a similar association was observed for subsequent lactations. In the later study (45), done among a Mexican population where exposure to p,p′-DDE was higher, an association of milk p,p′-DDE with shorter duration of lactation was seen among women who had previously lactated, but not among women who were lactating for the first time. Because p,p′-DDE is excreted in milk and the duration of breast-feeding for each of a woman's children tend to be similar, a short first lactation, resulting in higher milk p,p′-DDE levels, is likely to be followed by a short second lactation, independent of a biologic effect of p,p′-DDE on duration of lactation. In a simulation done by Gladen & Rogan (45), however, the effects of breast-feeding duration and p,p′-DDE excretion via lactation were taken into account, and an independent effect of p,p′-DDE level on duration of lactation after the first child was evident in their data. At any rate, an association of p,p′-DDE with duration of first lactation is more directly interpretable than associations with later lactations. The absence of an association of p,p′-DDE with duration of first lactation in the Mexican population is a notable inconsistency with the findings in the first study, and thus overall the data on lactation duration and p,p′-DDE levels remain suggestive but inconclusive.

ANDROGEN RECEPTOR ANTAGONISM Recent concerns that environmental hormones might be related to falling sperm counts and disorders of the male reproductive tract (101) merit consideration. Increased rates of testicular cancer and cryptorchidism (43), and decreased sperm counts and quality (4) remain unexplained. Kelce et al (64) recently reported that p,p′-DDE binds to the rat androgen receptor, thereby antagonizing the effect of androgen, and noted that the levels of p,p′-DDE that had measurable effects in their in vitro system were comparable to those observed in humans in areas contaminated with DDT. Bush et al (16) found the levels of p,p′-DDE in the semen of men with and without fertility problems were similar. Due to hormonal regulation in the fully developed human, however, compensation for antagonism by p,p′-DDE could be

complete. But in the embryo or fetus, the absence of a mature endocrine system increases the possibility of adverse effects of androgen antagonists.

NEUROLOGIC EFFECTS DDT is an insecticide because it inhibits neuronal repolarization. Manifestations of DDT poisoning in humans arise by the same mechanism (27). Symptoms of poisoning include perioral and lingual paresthesia, apprehension, hypersensitivity to stimuli, irritability, dizziness, vertigo, tremor, and convulsions (28, 53). Workers who were highly exposed to DDT and monitored for neurologic abnormalities showed no consistent evidence of adverse sequelae (53). In North Carolina children with ambient exposure to p,p′-DDE, levels of exposure were not associated with neurologic or developmental abnormalities (44).

OTHER HEALTH EFFECTS Highly exposed workers have lower serum bilirubin and slightly elevated serum levels of selected liver function tests (81). The lower serum bilirubin levels are possibly due to activation of hepatic cytochrome oxidases. Levels of plasma p,p′-DDT showed a strong inverse correlation with natural killer lymphocyte levels in a small study including some frequent fish consumers (109), but levels of other organochlorine compounds were correlated with those of DDT, complicating interpretation.

Summary

Other than the long-recognized neurologic toxicity associated with DDT poisoning, and laboratory abnormalities in DDT-exposed workers, human health effects of DDT exposure are not established.

The data relating occupational exposure to DDT and pancreatic cancer, and questionnaire-assessed DDT exposure with non-Hodgkin's lymphoma are suspicious and worthy of follow-up. The report that exposure to p,p′-DDE at levels not much above background may antagonize androgen activity, coupled with the potential decline of sperm counts and normalcy, is of note. Many other factors, however, could be responsible for the decline, and rates of cryptorchidism appear to have been increasing when DDT levels were falling. Whether p,p′-DDE or related DDT compounds decrease duration of lactation remains unresolved. In developing countries where DDT is still in use, a concomitant decrease in lactation could contribute to infant mortality.

Many studies of serum p,p′-DDE levels and breast cancer are now under way. If a positive association is found, its interpretation may be difficult. For example, a recent study reported that central obesity, itself a potential breast cancer–risk factor, is associated with higher serum p,p′-DDE levels (24). Thus blood levels of this compound may reflect a subject's metabolism and p,p′-DDE levels themselves may not be responsible for an increased risk.

PCBs

A Note on History and Background Exposure

From the 1920s until 1977 PCBs were produced in the United States for use in capacitors, transformers, carbonless copy paper, and other applications (12). The PCB mixtures used varied according to the average level of chlorination and distribution of congeners. By far the best-selling PCB mixture was 42% chlorine by weight (Aroclor 1242), which consisted of 1% monochlorobiphenyls, 13% bichlorobiphenyls, 45% trichlorobiphenyls, 31% tetrachlorobiphenyls, and 10% pentachlorobiphenyls. The half-life of PCBs varies according to the specific congener and ranges from 1 day to 70 years (78). With few exceptions, extant epidemiologic data on health and PCBs address exposure to total PCBs, not congener-specific exposure.

Few good data exist on trends in levels of PCBs in humans. Over the past 25 years levels may have declined slightly. As with DDT, exposure is ongoing owing to accumulation in the biosphere. Meat and fish are the main sources of exposure for adults, and children get additional exposure from human milk.

Data on Human Health Effects

CANCER For the cancer sites shown in Table 4 (except breast), data from at least one study have suggested an association with occupational PCB exposure. For these sites (and breast), we have summarized all the data available from cohort studies of PCB-exposed workers. Most studies were of capacitor workers (8, 13, 48, 59, 83, 103; PR Taylor, unpublished manuscript), and two were of transformer workers (73, 127). The small number of expected cases for any given cancer site (Table 4) reflects that, in general, the cohorts were relatively small and had limited lengths of follow-up. Published results were supplemented via correspondence with investigators to complete the table where possible. The minimum length of employment required for inclusion in the studies ranged from one day (103) to six months (48), and the level of exposure varied widely among those included in the cohorts. The summary SMRs and their Poisson-based 95% confidence intervals (10) shown at the bottom of Table 4 therefore provide only a rough indication of overall association.

The SMR in Table 4 for skin cancer and occupational PCB exposure was 1.8. The association is driven almost entirely by the results from Sinks et al (103). All of the skin cancers observed in that study were melanomas. Risk of melanoma, however, was not related to estimated cumulative PCB exposure. An association between melanoma and occupational PCB exposure in an additional cohort was reported in a letter (5) (2 cases observed, 0.04 expected). Another finding of note from Table 4 was that the observed number of kidney cancers exceeded the number expected in all cohorts except one. In addition, a cluster of three

Table 4 Observed (O) and expected (E) cancer mortality among PCB-exposed workers in 8 cohorts, for selected sites[a]

First author	Rectum ICD-9: 154		Liver, biliary 155–156		Pancreas 157		Skin 172–173		Breast 174		Prostate 185		Kidney 189		Brain 191–192		Lymphoma 200–203[b]	
	O	E	O	E	O	E	O	E	O	E	O	E	O	E	O	E	O	E
Gustavsson (48)	0	0.22	1	0.23	0	0.36	0	0.08	NA[c]	NA	1	0.90	1	0.14	0	0.19	1	0.31
Bertazzi (8)	0	0.41	2	0.4	2	0.43	0	0.14	2	1.99	1	0.47	0	0.20	2	0.28	5	1.36
Brown (13)	4	1.9	5	1.9	2	3.7	1	1.49	9	11.56	1	1.48	2	1.52	0	2.73	5	4.44
Nicholson (83)	2	1.20	0	0.55	1	2.02	1	0.56	5	3.76	2	2.3	1	0.78	0	0.97	2	1.94
Taylor[d]	7	3.5	3	2.6	10	6.4	3	3.0	13	15.4	4	3.6	5	2.9	1	5.2	3	8.7
Liss (73)	NA	NA	0	0.5	1	1.37	0	0.38	1	0.23	5	1.2	3	0.6	4	0.8	3	1.3
Sinks (103)	1	1.2	1	0.8	2	2.8	8	2.0	2	3.97	1	2.3	2	1.5	5	2.8	5	4.35
Yassi (127)	0	0.82	0	0.70	8	1.21	2	0.66	0	0.01	0	1.24	1	0.73	9	2.92	7	4.4
Total	14	9.25	12	7.68	26	18.29	15	8.31	32	36.92	15	13.49	15	8.37	21	15.89	31	26.8
SMR	1.5		1.6		1.4		1.8		0.9		1.1		1.8		1.3		1.2	
(95% CI)	0.8–2.5		0.8–2.7		0.9–2.1		1.0–3.0		0.6–1.2		0.6–1.8		1.0–3.0		0.8–2.0		0.8–1.6	

[a]Data for males and females combined, except for cancer of the breast and prostate. The data for Liss (73) are for those known to be exposed. The data for Yassi et al (127) are for those employed for more than three months, with acceptance criteria 1, 2, and 3 (see 127).
[b]For Taylor, ICD-9 208 is included.
[c]NA: not available.
[d]PR Taylor, unpublished manuscript.

cases with kidney cancer among PCB-exposed utility company workers has been reported (100). The elevated summary SMR for pancreatic cancer reflects primarily the increase found by Yassi et al (127). In that study, the increase in pancreatic cancer was greatest among those who were most exposed—workers who assembled transformers for more than six months. In the largest of the PCB-exposed cohorts, a greater-than-expected number of deaths from pancreatic cancer was also observed (PR Taylor, unpublished manuscript). Overall, data on occupational PCB exposure and cancer risk are inconclusive.

BREAST CANCER Much of what was said above regarding p,p′-DDE and breast cancer applies to the data on PCBs and breast cancer. In the smaller, less informative case-control studies (4 had PCB data), the average $\log_e$ ratio of mean PCB levels in cases and controls (1) was 1.06 (95% CI 0.95–1.19). The results for PCBs presented in the study by Wolff et al study (122) suggest an association (Table 3), although the original authors noted that when the estimate was adjusted for p,p′-DDE the PCB effect was decreased by half (not shown). The results overall of the study by Kreiger et al (70) do not support an association. The odds ratio per μg/L increase in serum PCB level for both studies combined was 1.02 (95% CI 0.94–1.11) (1). The summary SMR for breast cancer (Table 4) for occupational PCB exposure does not support an association. Overall the data on PCB exposure and risk of breast cancer are inconclusive, but suggest no association.

REPRODUCTIVE EFFECTS Studies of pregnancy outcome in relation to PCB exposure have been prompted by the results of experiments among animals (80) and the experience in Taiwan and Japan with mixed PCB/PCDF exposure (discussed later). Women occupationally exposed to PCBs gave birth to children who were ~60 g lighter than children of women from the same plant who were less exposed (112). This difference was partially explained by a shorter gestation (1/3 of a day) among those exposed.

In populations less exposed to PCBs, the relation between birth weight, gestational age, and level of exposure has been inconsistent, with some studies showing lighter babies among those with greater exposure (36, 118), others showing no effect (91), and still others where increased exposure was associated with slightly heavier babies (23, 105).

With respect to effects on spontaneous abortion or stillbirth, exposure to PCBs was not found to increase risk among women living near the Great Lakes (23, 80). Blood PCB levels among women with miscarriage were found to be higher than in women with normal deliveries in one study (72), but the level of many potentially confounding factors were related to PCB levels and the analysis included no adjustment for these.

SPERM FUNCTION Among PCB-exposed workers sperm counts were nearly identical to those in a comparison group (32). In a study of men with background exposure, PCB levels in seminal fluid were unrelated to sperm count or motility (16). In a subgroup of infertile subjects in that study, however, sperm motility was inversely related to PCB level, but whether the reduction in motility was due to PCBs was unclear.

NEUROLOGIC DEVELOPMENT Neurologic and developmental status in children, as assessed at birth with the Brazelton Behavioral Assessment Scale and subsequently with other measures, has been examined in relation to PCB exposure among two US cohorts, one in North Carolina (89) and a second in Michigan (62, 63). In the North Carolina children, who were essentially a population cross-section, those whose level of prenatal exposure was among the highest 5–10% showed hypotonia (decreased muscle tone) and hyporeflexia at birth and slower motor development on serial examinations until 2 years of age. The PCB-hypotonia/hyporeflexia association was not confounded by other known determinants of neurologic or behavioral abnormalities at birth. The Michigan children were born to mothers who were frequent lake (PCB-contaminated) fish consumers, or lake fish abstainers. Among children whose mother ate the most fish, hyporeflexia at birth was observed more often. When level of prenatal PCB exposure in Michigan was based on measured values, as it was in North Carolina, however, the relation of exposure to this finding was less clear. Nonetheless, at various points during follow-up up to 4 years of age, slower cognitive development was found in those with the highest measured transplacental PCB exposure.

In a more recent study, neurologic "optimality" in newborns was examined in relation to PCB levels in The Netherlands (57). Among those with greater PCB exposure the prevalence of hypotonia was increased and prevalence of neurologic optimality was reduced—findings like of those in the US studies. In the Dutch study, however, the levels of PCBs were highly correlated with those of dioxins (67). Thus, whether the associations observed were attributable to PCBs is unclear. Despite the occurrence of ambiguous or inconsistent findings within and across studies of neurologic development and PCB exposure, the data overall indicate that high prenatal PCB exposure encountered in general populations in developed countries may be adversely affecting children. The greater but later exposure from the mothers' milk, however, is so far without consistent effect (89).

LIVER FUNCTION ABNORMALITIES A relation between occupational exposure to PCBs and abnormal findings on routine physical and laboratory examination has been reported in a number of cross-sectional studies (20, 30, 71, 76, 104). A

frequent finding was subtle elevations of serum enzymes of hepatic origin, especially γ-glutamyl transferase (GGT). The particular PCB mixture used, the level of exposure, the degree of contamination with PCDFs, and the concurrent exposure to other compounds, however, varied across studies. In addition, the number of exposed subjects was generally less than 100 and a rudimentary analysis of data obtained. These obfuscating factors aside, the data suggest that exposure to large amounts of PCBs causes alteration of liver function. Whether this alteration merely reflects induction of liver metabolizing enzymes or whether it has clinical significance is not clear. Because of the relatively small size of the occupational cohorts exposed to PCBs, few investigators have reported findings for death from liver cirrhosis. SMRs for cirrhosis of 107 (95% CI 39–233) (14), 50 (95% CI 10–146) (PR Taylor, unpublished manuscript), and 9 (95% CI 0–50)(103), however, have been observed. Background exposure to PCBs, slightly higher than average due to frequent fish consumption, was found to be associated with GGT level in a survey of 458 people in Alabama (69).

INDUCTION OF THE P450 SYSTEM Experimental data from animal studies clearly show that PCBs induce P450 metabolizing enzymes (93). The half-life of antipyrine, a drug metabolized by this enzyme system like phenobarbital, was studied in PCB-exposed workers and controls, and was found to be 50% shorter among the exposed (2). A less dramatic, but similar decrease was found in a second group of workers exposed to higher-molecular-weight PCBs (30).

THYROID In men occupationally exposed to PCBs (31), thyroid hormone levels bore no clear relation to measured PCB levels. In mothers and their children from Rotterdam, background levels of PCB exposure, as assessed in breast milk, was associated with lower maternal T_3 and T_4 levels and higher infant TSH levels (68). The hormone levels observed, however, were within normal limits, and the associations observed may have been due to dioxins (PCB and dioxin levels were highly correlated in that population). In addition, gender or pregnancy-related effects, or differences in PCB composition may account for the discrepancy between the results of the occupational and background-exposure studies.

IMMUNOLOGIC Among workers with high-level exposure to PCBs, the cutaneous delayed hypersensitivity response to mumps and trychophyton was examined and found to be no different than in a control group (32). In another group of workers, PCB levels were related to higher lymphocyte counts when PCB exposure was ongoing; in addition, the composition of the white cell population was related to exposure but in an inconsistent manner (71). Studies of background-level exposure to PCBs have had mixed results with respect to clinical outcomes. In a Dutch study, the frequency of infectious illnesses

among breast-fed infants in the first 18 months of life were unrelated to PCB levels (120). In Wisconsin, however, PCB exposure was associated with the frequency of infectious illness in the first four months of life (105). Additional data from background-exposed populations suggest that PCBs may account for alterations in levels of lymphocyte subtypes (109, 120), but these findings are in populations where dioxins or fatty acids from fish might confound the PCB-lymphocyte relation.

DERMATOLOGIC Several skin abnormalities in addition to chloracne appear to be caused by occupational exposure to PCBs. For example, 10% of capacitor manufacturing workers had hyperpigmentation (39), a prevalence presumably higher than in the general population. Studies of skin abnormalities in relation to occupational exposure to PCBs have been supportive of a relation, but often weakened by lack of control groups (39, 76), or small sample size (20). Fischbein et al (39) showed, however, that workers with skin abnormalities had higher plasma PCB levels than did those without abnormalities. In another report, a causal relation between PCB exposure and chloracne was especially convincing because after PCBs were used to replace another heat exchange material, the exposed workers developed the characteristic skin lesions (79). Given the consistency of data that implicate aromatic chlorinated compounds as a cause of chloracne, there seems little reason to doubt that PCBs cause chloracne.

OTHER HEALTH EFFECTS Background exposure to PCBs, in a community where some people had high levels due to fish consumption (69), was associated with increased blood pressure. The association has not been replicated elsewhere.

Summary

Occupational exposure to PCBs has been consistently associated with abnormal liver function tests and chloracne. We also found that occupational exposure to PCBs was associated with a consistent increase in kidney cancer, though the number of cases in any single study was, at most, five. Although the potential for substantial occupational exposure is ongoing due to handling of transformers, modern workplace practices probably limit this. Additional follow-up of established cohorts may be the best option available to investigate the potential association with risk of kidney and other cancers.

The data relating occupational exposure to decreased weight of offspring at birth and shorter gestational age are suggestive but investigations of this association from other plants have not been reported.

Background exposure to PCBs may have subtle effects on neurologic development, immune function, and, in susceptible groups, thryoid function. The

finding in three of three studies that hypotonia or hyporeflexia at birth is greater among those with higher PCB levels in particular supports an effect that may have other more serious manifestations. Few data exist on the correlation between PCBs and dioxins in samples from subjects with background exposure, but where available (67, 86), a high correlation was found. Future investigations of background PCB effects may be especially informative, therefore, if confounding by dioxin can be ruled out.

MIXTURES OF PCBs AND PCDFs

The Asian Mass Poisonings

In two Asian communities, in incidents about 10 years apart, people consumed rice oil contaminated with a mixture of PCBs, PCDFs, polychlorinated terphenyls (PCTs), and polychlorinated quaterphenyls (PCQs) (55, 77). In both instances, the rice oil was contaminated during processing by machines that used PCBs as heat exchangers. The PCBs, subjected to high temperatures, formed the other polychlorinated hydrocarbon compounds, and leaks within the processors mixed the organochlorine contaminants with the rice oil. Thus, about 1700 people in western Japan (1968) and 2000 in western Taiwan (1979) were poisoned. Because the toxicity of PCTs and PCQs are not well characterized and tissue levels among the exposed were generally less than for PCBs, the effects of exposure to the mixture have been attributed primarily to PCBs and PCDFs, the latter being recognized for its dioxin-like activity. The total amounts of organochlorine mixture consumed among the exposed in both incidents were similar (55), as were the manifestations of exposure. The average total intake of PCBs in contaminated rice oil was about 1 gram. During the Asian incidents the intake of PCBs exceeded average US intake (65) by more than a thousand-fold. In both locations, exposure to PCBs was much greater than for PDCFs, but in terms of TEqs, PCDFs contributed the majority. In Japan, the epidemic illness resulting from consumption of the contaminated food was dubbed Yusho, or oil disease; in Taiwan, it was called Yu-Cheng. A systematic health survey among the exposed was not conducted in either location. Much of the available data are from case series and may reflect the findings in the most severely afflicted.

Data on Human Health Effects

The primary manifestation of Yusho and Yu-Cheng was dermatologic: chloracne and hyperpigmentation of the skin, gingiva, and nails were frequent. Ocular abnormalities such as hypersecretion and swelling of the sebaceous glands of the eyelids were also common. Slowed nerve conduction, especially of sensory nerves, was documented in many cases (55, 77). Altered

immunoglobulin levels were documented in both populations, and white cell changes were reported in Yu-Cheng patients. Increases in serum triglycerides and decreased bilirubin were found in both populations, and abnormalities in other liver function tests were also evident, although the pattern of abnormality varied between populations.

Mortality 15 years after the poisoning in Japan was increased for cancers of the respiratory tract in males [SMR = 3.3 (95% CI 1.4–6.4)] and liver in males [SMR = 5.6 (95% CI 2.6–10.6)]; in females the SMR for liver cancer was 3.0 (95% CI 0.4–11.0) (10, 58). Both men and women had an SMR for liver disease of 2.7; among both men and women combined, the SMR was 2.7 (95% CI 1.2–5.3)]. Mortality 4 years after poisoning in Taiwan was remarkable for one half of the 24 deaths observed being due to liver cancer or liver disease (54).

Children born to mothers who had consumed the contaminated rice oil in Taiwan were followed carefully with respect to mortality, growth, cognitive development, behavior, and activity. The children also showed many of the same physical and laboratory abnormalities as adults. Among 39 children in utero while their mothers were consuming the contaminated rice oil, risk of death was 0.21 within four years after birth (54). The exposed children had lower body weights relative to controls for about ten years after the exposure, and they never attained comparable stature (47). The exposed children also had lower scores on intelligence tests (21, 90) and did not get better. In addition, exposed children showed disordered behavior and were hyperactive. The level of growth, cognitive deficit, and disordered behavior and activity were not correlated, suggesting independent causal pathways from exposure to outcome. The myriad abnormalities present in the Yu-Cheng children raise the possibility that children may be more sensitive than adults to the adverse effects of organochlorine exposure.

DIOXIN AND RELATED COMPOUNDS

A Note on History and Background Exposure

With the exception of the mass poisoning incidents in Asia, sources of PCDFs and PCDDS are similar and are discussed together in this paragraph, as PCDD/Fs. Levels of PCDD/Fs in environmental samples increased markedly over the historical baseline in the 1940s and increased to a peak in the 1970s (119). Thereafter a modest decrease ensued. This pattern parallels the activity of modern chlorine chemistry. PCDD/Fs were never produced for commercial purposes and are made inadvertently during many processes such as combustion, paper bleaching, and production of chlorine and organochlorine chemicals. The congeners that contain a chlorine at the 2,3,7, and 8 positions are persistent

and tend to bioaccummulate in animals. The half-life of dioxin is about eight years. As with other environmentally persistent organochlorine residues, exposure is ongoing due to accumulation in the biosphere. Meat, fish, milk, dairy products, fats, and oils are the main sources of exposure for adults, and children get additional exposure from human milk.

Data resulting from the industrial accident in Seveso, Italy (6), in 1976, are cited repeatedly in the following section; thus a brief description of that incident is given here. A runaway chemical reaction caused an explosion that created a cloud of ~3000 kg of organic material, including an unknown but substantial amount of dioxin. About 600 people lived in the area most contaminated by the plume, and the blood levels of dioxin in that group were in a range that equaled or exceeded that of chemical manufacturing workers exposed to dioxin (102). Because of the relatively small number of highly exposed people in Seveso, the statistical power to detect effects in that population is limited.

Data on Human Health Effects

The human health effects of herbicide exposure have been reviewed recently by the National Academy of Science's Institute of Medicine (IOM) (Table 5) (60). As mentioned earlier, dioxin is a contaminant of the herbicide 2,4,5-T. The effects of 2,4-D and 2,4,5-T and other herbicides were considered along with those of dioxin in the IOM review. Because the herbicides considered are relatively nontoxic and have short half-lives, the question arises whether the IOM review is informative primarily about dioxin. In several instances, however, the effects noted in Table 5 could be due to the herbicides themselves and not to dioxin. An example is non-Hodgkin's lymphoma, for which increased risk was observed in studies of agricultural workers exposed to 2,4-D (50), which is less contaminated with dioxin than 2,4,5-T (50).

In this section, we briefly consider selected conditions for which dioxin is known or suspected to increase risk, with special attention to whether the evidence supports dioxin itself as the causal factor. The IOM report (60) serves as the frame of reference.

SOFT-TISSUE SARCOMA The evidence that exposure to herbicides or their contaminant, dioxin, is carcinogenic in humans is strongest for soft-tissue sarcoma (STS) (60). The most statistically powerful data addressing this association are from Swedish case-control studies in which questionnaires were used to assess exposure (50). Although the strength of the association is impressive (Table 6), the potential confounding by 2,4,5-T exposure is intractable, and dioxin exposure was not documented with measured levels. Data from the largest prospective studies of workers occupationally exposed to dioxins, either in the chemical manufacturing industry (38), or in manufacturing or application

Table 5 Summary table from the Update 1996 Veterans and Agent Orange Institute of Medicine review (60) of findings in occupational, environmental, and veterans studies regarding the association between specific health problems and exposure to herbicides (revised)[a]

Sufficient evidence of an association
Soft-tissue sarcoma
Non-Hodgkin's lymphoma
Hodgkin's disease
Chloracne
Limited/suggestive evidence of an association
Respiratory cancers (lung, larynx, trachea)
Prostate cancer
Multiple myeloma
Acute and subacute peripheral neuropathy
Spina bifida
Porphyria cutanea tarda
Inadequate insufficient evidence to determine whether an association exists
Hepatobiliary cancers
Nasal/nasopharyngeal cancer
Bone cancer
Female reproductive cancers (cervical, uterine, ovarian)
Breast cancer
Renal cancer
Testicular cancer
Leukemia
Spontaneous abortion
Birth defects (other than spina bifida)
Neonatal/infant death and stillbirths
Low birthweight
Childhood cancer in offspring
Abnormal sperm parameters and infertility
Cognitive and neuropsychiatric disorders
Motor/coordination dysfunction
Chronic peripheral nervous system disorders
Metabolic and digestive disorders (diabetes, changes in liver enzymes, lipid abnormalties, ulcers)
Immune system disorders (immune suppression and autoimmunity)
Circulatory disorders
Respiratory disorders
Skin cancer
Limited/suggestive evidence of no association
Gastrointestinal tumors (stomach cancer, pancreatic cancer, colon cancer, and rectal cancer)
Bladder cancer
Brain tumors

[a]Note: "Herbicides" refers to the major herbicides used in Vietnam: 2,4-D (2,4-dichlorophenoxyacetic acid); 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and its contaminant TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin); cacodylic acid; and picloram. The evidence regarding association is drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

Table 6 Mantel-Haenszel adjusted odds ratios (OR) and 95% confidence intervals (CI) for soft-tissue sarcoma among persons exposed to all dioxins, TCDD, and dioxins other than TCDD in four case-control studies involving 434 cases and 948 controls[a]

	Unexposed	Exposed < 1 year	Exposed ≥ 1 year
All dioxins			
Cases (n)	352	58	24
Controls (n)	865	74	9
OR	1	2.4	6.4
CI		1.6–3.6	3.1–13.3
TCDD			
Cases (n)	352	40	6
Controls (n)	865	39	2
OR	1	3.0	7.2
CI		1.9–4.9	2.1–24.3
Other dioxins			
Cases (n)	352	18	18
Controls (n)	865	35	7
OR	1	1.7	6.2
CI		0.9–3.2	2.5–15.1

[a]Adapted from (50). All subjects were exposed for at least 1 day and a minimum latency period of 5 years was used. Odds ratios are adjusted for study.

of herbicides (66), also support an association. In the National Institute of Occupational Safety and Health (NIOSH) occupational cohort (38), among a subcohort with mortality examined in a period 20 years after first exposure and who had a year or more of exposure, the relative risk was more than six (after excluding a case found on pathologic review not to have soft-tissue sarcoma). A subsequent study showed, however, that exposure to 4-aminobiphenyl, a known human carcinogen, was correlated with dioxin exposure in one of the factories contributing cases (22), thus raising the possibility that the results of the NIOSH study were confounded. In a case-control study nested within the International Agency for Research on Cancer (IARC) cohort (66), exposure to several chemicals was assessed, and while exposure to dioxins or furans was associated with increased risk (OR = 5.6, 95% CI 1.1–27.7), distinguishing among the effects of the other chemicals with highly correlated exposure was not possible. While the available data in general support an herbicide/dioxin-STS association, notable unsupportive studies exist (126). The lack of support of the hypothesis in data from a US case-control study (126) has been postulated (50) as being due to the primary phenoxyacetic acid exposure being 2,4-D, whereas in the Scandinavian studies, herbicides containing 2,4,5-T (dioxin-contaminated) were more often used. Additional questions about classification of STS in epidemiologic

studies complicate interpretation of the data (108). Overall, the epidemiologic data are consistent with dioxin being a cause of STS, but are inconclusive.

RESPIRATORY CANCER For respiratory cancers, the "limited/suggestive evidence of an association" with herbicides (Table 5) is primarily data that support dioxin exposure as increasing risk. The IOM report (60) cites four studies of heavily exposed chemical production workers in which the relative risk was about 50–100% higher than in the comparison group, and for whom the increased risk was probably not attributable to differences in smoking or other exposures. In the NIOSH study (38), among workers with 20 or more years since first employment in the plant, those with one year or more of exposure had a greater SMR [142 (95% CI 103–192)] than those with less than one year of exposure (SMR = 103 [95% CI 62–161]). The absence of direct data on potentially confounding factors in the exposed and comparison groups, and the large number of small studies of lesser-exposed groups where no association was evident, however, accounts for the "limited/suggestive" evidence category for this group of cancers.

HEPATOBILIARY CANCER The potential relation of dioxin exposure with risk of hepatobiliary cancer merits consideration because in animal models of dioxin carcinogenesis liver cancer is a frequent finding (56). The embryologic origin of the liver and biliary tree are sufficiently close that grouping these cancers as a single outcome in humans may be justifiable. Most of the human data on dioxin exposure and cancer risk have been in male populations, and in those data the results on hepatobiliary cancer are mixed (60), although the number of exposed cases even in the largest studies (38, 95) was at most six. In the Seveso population, however, hepatobiliary cancers were increased, especially among females (7). Dioxin is a hepatic carcinogen in rats, but only among females (75). The potential for a confluence of animal and human findings exists regarding sex-specific carcinogenic effects of dioxin in the hepatobiliary system.

OTHER CANCERS In the most recent follow-up in Seveso, excess cases of lymphoreticulosarcoma, multiple myeloma, and myeloid leukemia were found among the subgroup that was highly exposed (7). Because dioxin is an estrogen antagonist in laboratory experiments (94), epidemiologic data on endometrial and breast cancer are of interest, but existing studies are too small to provide meaningful data.

SPINA BIFIDA A 1995 paper about birth defects among children of Vietnam veterans (121) was the stimulus for putting spina bifida in the category of "Limited/Suggestive Evidence of Association" in the Veterans and Agent Orange Update 1996 (60), whereas previous assessments had considered evidence about reproductive outcomes and dioxins to be inconclusive (e.g. 110). The IOM

Table 7 Selected results from studies on spina bifida among children of Vietnam veterans[a]

Study	Exposure category	Proportion affected per 1000 births	Relative risk (95% CI)
Ranch Hand Study (121)			
	Reference	0	
	Exposed-low	4.1	
	Exposed-high	7.5	
Birth Defects Study (33)			
	Reference		1
	Exposed-1 (low)		1.2 (1.0–1.4)
	Exposed-2		1.5 (1.1–2.1)
	Exposed-3		1.8 (1.1–3.0)
	Exposed-4		2.2 (1.2–4.3)
	Exposed-5 (high)		2.7 (1.2–6.2)
Vietnam Experience Study (19)			
	Reference		1
	Exposed (Vietnam)		1.7 (0.6–5.0)

[a]The number of exposed cases in the Ranch Hand Study is 3; in the Birth Defects Study is 19; and in the Vietnam Experience Study is 9. Some data used to make this table were drawn from Reference 60.

report (60) was influenced most by the three studies (19, 33, 121) judged to be of the highest overall quality, summarized in Table 7. Despite their relative strength, the validity of the findings in the three studies remains open to question, and the statistical power is limited. Further questions about the association of exposure to herbicides or dioxin with spina bifida are due to an association with anencephaly being less clear. If exposure to herbicides or Agent Orange causes one type of neural tube defect (spina bifida), it might be expected to cause another (anencephaly).

PERIPHERAL NEUROPATHY Evidence that exposure to dioxin causes a subacute transient peripheral neuropathy derives mainly from a study of Seveso residents examined within two years of the accident (37). Nerve conduction velocity and other electrophysiological measures were used to make the diagnosis of peripheral neuropathy. The prevalence of peripheral neuropathy among Seveso residents with chloracne or elevated liver function tests suggestive of high exposure was 2.8-fold higher (95% CI 1.2–6.5) than in Seveso residents without such evidence of exposure. Studies of peripheral neuropathy much longer after exposure in Seveso do not support an association, nor is there evidence that dioxin causes a chronic neuropathy in heavily exposed workers (111).

LIVER FUNCTION TEST ABNORMALITIES The greater prevalence of liver function abnormalities among Seveso victims with chloracne, as compared with a

control group (6), is a good example of the evidence that dioxin causes this condition. Of note is that in this Seveso study, elevated GGT and evidence of alterations in porphyrin metabolism were among the changes found.

INDUCTION OF THE P450 SYSTEM Induction of selected P450 metabolizing enzymes has been used as evidence of detectable effects of exposure to dioxin-like compounds in humans (124). Among workers who previously were heavily exposed to dioxin, however, evidence of induction of a P450 enzyme (P4501A2) was not evident (49). The failure to detect enzyme induction in that study was possibly due to insensitivity of the assay or inadequate sample size.

ENDOCRINE Male workers who had been highly exposed to dioxin were found to have subtle, but statistically significant, elevated levels of the gonadotropins LH and FSH, and a similar decrease in testosterone (29). In rats, dioxin decreases testosterone synthesis and levels (29). In the much less exposed Vietnam ranch hands, lower testosterone levels were also found, but these were not significantly different than from a control group (29).

THYROID In two European studies (68, 87), the relation of dioxin levels in breast milk among breast-fed infants has been examined in relation to thyroid function. In both studies, higher dioxin levels in breast milk were associated with a higher TSH level in the infant. Findings regarding thyroid hormone levels, however, were inconsistent. In addition, the high correlation among levels of PCBs and dioxins in the Dutch study (67) complicate interpretation of the findings.

CHLORACNE The epidemic of chloracne among those highly exposed in the Seveso incident (6) is an especially good example of the evidence that dioxin causes this condition.

CORONARY HEART DISEASE Occupational exposure to PCDDs and PCDFs, as estimated with blood measures on a subset of subjects and expressed as total TEq, increased in proportion to mortality from cardiovascular disease and ischemic heart disease among workers in the Boehringer-Ingelh plant in Hamburg, Germany (40). In other studies of highly exposed people, however, heart disease (38) or ischemic heart disease (9) was not elevated.

Summary

The epidemiologic data that high-level dioxin exposure causes liver function abnormalities and chloracne are incontrovertible.

Epidemiologic data are consistent with high-level dioxin exposure causing soft-tissue sarcoma, but potential confounding by other exposures precludes certainty. A similar situation obtains for several cancers, e.g. lung cancer. In

the case of hepatobiliary cancer, the possibility that dioxin increases risk, more so in females than males, is supported by findings in Seveso; this observation is consistent with animal, especially rat, findings.

Male workers studied long after their dioxin exposure were found to have subtle alterations in gonadotropin and testosterone levels. Neuropathy was associated with dioxin exposure in Seveso; the absence of subsequent confirmation in the Seveso population suggests that the affliction was transient.

Findings in two Dutch studies suggest the possibility that background dioxin exposure may have a subtle effect on thyroid function. As noted previously, however, the result may be confounded by PCB exposure.

OVERALL DISCUSSION AND CONCLUSIONS

Viewed individually, studies finding an association between background organochlorine exposure and health effects are not impressive. The possibility that bias accounts for the association cannot be ruled out, and the abnormalities found are subclinical. Across studies, results are often inconsistent. Endogenous defenses may well be effective against synthetic toxins, as has been suggested by Ames and colleagues (3). The data viewed as a whole, however, raise suspicion that a portion of the population may be experiencing subtle effects.

In particular, the finding of hypotonia or hyporeflexia at birth in relation to PCB exposure suggests that ambient exposure can have detectable effects. High-level exposure to a mixture of PCBs and PCDFs causes neurobehavioral abnormalities, thus increasing the plausibility of subtle low-level effects. With only three studies of PCBs and abnormal findings at birth, however, the relation is far from established. Further, the ability to discriminate between PCB and dioxin and dioxin-like effects in the future will be an advance, as present data leave as an open question whether findings associated with background PCB exposure, if real, are confounded by mixed exposure with dioxin.

Understanding the subclinical effects, if any, of organochlorine exposure might serve to guide investigations of possible clinical effects, and inform risk assessments. For example, if men highly exposed to p,p′-DDE show evidence of androgen receptor blocking with increased levels of luteinizing hormone or follicle stimulating hormone, studies of reproductive effects of in utero p,p′-DDE exposure in males might be better justified. If sensitive assays of Ah receptor–mediated P4501A1 induction show no effect of ambient levels of dioxin exposure, then suspicion of health effects would decrease. Such an approach might help avoid committing our limited research resources to studies of diseases with poorly understood etiology in relation to ambient organochlorine exposure unless a strong biologic rationale is delineated.

The effect, if any, of exposure to a specific organochlorine compound may depend on the presence of other compounds (organochlorines, or otherwise). For example, the effect of a dioxin-like compound might depend on whether indole carbinol (derived from broccoli and other foods) is present—because both bind the Ah receptor (3). Thus simultaneous measurement of several organochlorine compounds, diet, or other factors might be needed to fully characterize effects.

The statistical power of epidemiologic studies to detect cancer risks related to organochlorine exposure, if any, have been limited by small populations of highly exposed people and the low level of exposure in the general population. Where associations have been detected, e.g. soft-tissue sarcoma and dioxin, potential confounding due to other exposures precludes conclusions regarding causality. The existing epidemiologic data, considered in isolation, provide no convincing evidence that organochlorines cause a large excess number of cancers. Several associations, however, merit more study, such as p,p′-DDE and breast cancer. Absence of convincing evidence, however, does not mean absence of risk.

The Environmental Protection Agency (EPA) recently characterized the cancer risk associated with background exposure to dioxin and dioxin-like compounds (115). Their assessment gives great weight to the animal data, where dioxin is a potent carcinogen. They assumed that the results of cohort studies of dioxin-exposed workers reflect dioxin effects, and found the animal and human data to be consistent with respect to dose-response. The EPA, using a conservative (worst case) model, estimated that background exposure to dioxin and dioxin-like compounds is associated with an upper-bound cancer risk in the range of 10^{-4} per year. The true average risk, if any, may be much lower.

The health effects of the foreign substances within us are not fully known. Given the persistence of organochlorine residues and our closed global ecosystem, mankind has ample motivation and opportunity to comprehensively characterize their toxicity.

Literature Cited

1. Adami HO, Lipworth L, Titus-Ernstoff L, Hsieh CC, Hanberg A, et al. 1995. Organochlorine compounds and estrogen-related cancers in women. *Cancer Causes Control* 6:551–66
2. Alvares AP, Fischbein A, Anderson KE, Kappas A. 1977. Alterations in drug metabolism in workers exposed to polychlorinated biphenyls. *Clin. Pharmacol. Ther.* 22:140–46
3. Ames BN, Profet M, Gold LS. 1990. Nature's chemicals and synthetic chemicals: comparative toxicology. *Proc. Natl. Acad. Sci. USA* 87:7782–86

4. Auger J, Kunstmann JM, Czyglik F, Jouannet P. 1995. Decline in semen quality among fertile men in Paris during the past 20 years. *N. Engl. J. Med.* 332:281–85
5. Bahn AK, Rosenwaike I, Harrmann N, Grover P, Stellman J, O'Leary. 1976. Melanoma after exposure to PCB's. (Letter). *N. Engl. J. Med.* 295:450
6. Bertazzi P, di Domenico A. 1994. Chemical, environmental, and health aspects of the Seveso, Italy, accident. See Ref. 98a, pp. 587–632
7. Bertazzi PA, Pesatori AC, Consonni D, Tironi A, Landi MT, Zocchetti C. 1993. Cancer incidence in a population accidentally exposed to 2,3,7,8–tetrachlorodibenzo-para-dioxin. *Epidemiology* 4:398–406
8. Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C. 1987. Cancer mortality of capacitor manufacturing workers. *Am. J. Ind. Med.* 11:165–76
9. Bertazzi PA, Zocchetti C, Pesatori AC, Guercilena S, Sanarico M, Radice L. 1989. Ten-year mortality study of the population involved in the Seveso incident in 1976. *Am. J. Epidemiol.* 129:1187–200
10. Breslow NE, Day NE. 1987. *Statistical Methods in Cancer Research.* Vol. 2. *The Design and Analysis of Cohort Studies*, pp. 69–72. IARC Sci. Publ. No. 82. IARC, Lyon. 406 pp.
11. Brilliant LB, Wilcox K, Van Amburg G, Eyster J, Isbister J, et al. 1978. Breast-milk monitoring to measure Michigan's contamination with polybrominated biphenyls. *Lancet* 2(8091): 643–46
12. Brinkman UAT, de Kok, A. 1980. Production, properties and usage. In *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, ed. R Kimbrough, pp. 1–40. New York/Oxford: Elsevier. 406 pp.
13. Brown DP. 1987. Mortality of workers exposed to polychlorinated biphenyls–an update. *Arch. Environ. Health* 42:333–39
14. Brown DP, Jones M. 1982. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. *Arch. Environ. Health* 36:120–29
15. Brown LM, Blair A, Gibson R, Everett GD, Cantor KP, et al. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res.* 50:6585–91
16. Bush B, Bennett AH, Snow JT. 1986. Polychlorobiphenyl congeners, p,p′-DDE, and sperm function in humans. *Arch. Environ. Contam. Toxicol.* 15:333–41
17. Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, et al. 1992. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res.* 52:2447–55
18. Carson R. 1962. *Silent Spring.* Boston: Houghton Mifflin.
19. Centers for Disease Control. 1989. *Health Status of Vietnam Veterans. Vietnam Experience Study.* Atlanta: US DHHS. Vol. 1, Synopsis
20. Chase KH, Wong O, Thomas D, Berney BW, Simon RK. 1982. Clinical and metabolic abnormalities associated with occupational exposure to polychlorinated biphenyls (PCBs). *J. Occup. Med.* 24:109–14
21. Chen YCJ, Guo YL, Huse CC, Rogan WJ. 1992. Cognitive development of Yu-Cheng ("Oil Disease") children prenatally exposed to heat-degraded PCBs. *JAMA* 268:3213–18
22. Collins JJ, Strauss ME, Levinskas GJ, Conner PR. 1993. The mortality experience of workers exposed to 2,3,7,8–tetrachlorodibenzo-p-dioxin in a trichlorophenol process accident. *Epidemiology* 4:7–13
23. Dar E, Kanarek MS, Anderson HA, Sonzogni WC. 1992. Fish consumption and reproductive outcomes in Green Bay, Wisconsin. *Environ. Res.* 59:189–201
24. Demark-Wahnefried W, Schildkraut J, Hamilton M, Laseter Jl, Hughes C. 1996. *Correlates of serum organochlorine levels in women undergoing weight loss.* Annu. Meet. Am. Soc. Prev. Oncol., 20th, March 20–23, Bethesda, MD. Abstr. 37.
25. Dewailly E, Dodin S, Verreault R, Ayotte P, Sauve L, et al. 1994. High organochlorine body burden in women with estrogen receptor-positive breast cancer. *J. Natl. Cancer Inst.* 86:232–34
26. Ditraglia D, Brown DP, Namekata T, Iverson N. 1981. Mortality study of workers employed at organochlorine pesticide manufacturing plants. *Scand. J. Work Environ. Health* 7(Suppl. 4):140–46
27. Ecobichon DJ. 1991. Toxic effects of pesticides. In *Casarett and Doull's Toxicology: the Basic Science of Poisons*, ed. MO Amdur, J Doull, CD Klaassen, pp. 565–80. New York: Pergamon. 1033 pp. 4th. ed.
28. Ecobichon DJ, Davies JE, Doull J, Ehrich M, Joy R, et al. 1990. Neurotoxic effects of pesticides. In *The Effect of Pesticides on Human Health*, ed. SR Baker, CF Wilkinson, pp. 131–99. Princeton: Princeton Sci. 438 pp.

29. Egeland GM, Sweeney MH, Fingerhut MA, Wille KK, Schnorr TM, Halperin WE. 1994. Total serum testosterone and gonadotropins in workers exposed to dioxin. *Am. J. Epidemiol.* 139: 272–81
30. Emmett EA. 1985. Polychlorinated biphenyl exposure and effects in transformer repair workers. *Environ. Health Perspect.* 60:185–92
31. Emmett EA, Maroni M, Jefferys J, Schmith J, Levin BK, Alvares A. 1988. Studies of transformer repair workers exposed to PCBs: II. Results of clinical laboratory investigations. *Am. J. Ind. Med.* 14:47–62
32. Emmett EA, Maroni M, Jefferys J, Schmith J, Levin BK, Jefferys J. 1988. Studies of transformer repair workers exposed to PCBs: I. Study design, PCB concentrations, questionnaire, and clinical examination results. *Am. J. Ind. Med.* 13:415–27
33. Erickson JD, Mulinare J, McClain PW, Fitch TG, James LM, et al. 1984. Vietnam veterans' risks for fathering babies with birth defects. *JAMA* 252:903–12
34. Eriksson M, Hardell L, Berg NO, Moller T, Axelson O. 1981. Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. *Br. J. Ind. Med.* 38:27–33
35. Falck F Jr, Ricci A, Wolff MS, Godbold J, Deckers P. 1992. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch. Environ. Health* 47:143–46
36. Fein GG, Jacobson JL, Jacobson SW, Schwartz PM, Dowler JK. 1984. Prenatal exposure to polychlorinated biphenyls: effects on birth size and gestational age. *J. Pediatr.* 105:315–20
37. Filippini G, Bordo B, Crenna P, Massetto N, Musicco M, Boeri R. 1981. Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8-tetrachlorodibenzodioxin. *Scand. J. Work Environ. Health* 7:257–62
38. Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, et al. 1991. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N. Engl. J. Med.* 324:212–18
39. Fischbein A, Thornton J, Wolff MS, Bernstein J, Selikoff IJ. 1982. Dermatologic findings in capacitor manufacturing workers exposed to dielectric fluids containing polychlorinated biphenyls (PCBs). *Arch. Environ. Health* 37:69–74
40. Flesch-Janys D, Berger J, Gurn P, Manz A, Nagel S, et al. 1995. Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. *Am. J. Epidemiol.* 142:1165–75
41. Flodin U, Fredriksson M, Persson B, Axelson O. 1988. Chronic lymphatic leukemia and engine exhaust, fresh wood, and DDT: a case-referent study. *Br. J. Ind. Med.* 45:33–38
42. Garabrant DH, Held J, Langholz B, Peters JM, Mack TM. 1992. DDT and related compounds and risk of pancreatic cancer. *J. Natl. Cancer Inst.* 84:764–71
43. Giwercman A, Skakkebaek NE. 1992. The human testis–an organ at risk? *Int. J. Androl.* 15:373–75
44. Gladen BC, Rogan WJ. 1991. Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development. *J. Pediatr.* 119:58–63
45. Gladen BC, Rogan WJ. 1995. DDE and shortened duration of lactation in a northern Mexican town. *Am. J. Public Health* 85:504–8
46. Gocmen A, Peters HA, Cripps DJ, Bryan GT, Morris CR. 1989. Hexachlorobenzene episode in Turkey. *Biomed. Environ. Sci.* 2:36–43
47. Guo YL, Lambert GH, Hsu CC. 1995. Growth abnormalities in the population exposed in utero and early postnatally to polychlorinated biphenyls and dibenzofurans. *Environ. Health Perspect.* 103(Suppl. 6):117–22
48. Gustavsson P, Hogstedt C, Rappe C. 1986. Short-term mortality and cancer incidence in capacitor manufacturers workers exposed to polychlorinated biphenyls (PCBs). *Am. J. Ind. Med.* 10:341–44
49. Halperin W, Kalow W, Sweeney MH, Tang BK, Fingerhut M, et al. 1995. Induction of P-450 in workers exposed to dioxin. *Occup. Environ. Med.* 52:86–91
50. Hardell L, Eriksson M, Axelson O, Hoar Zahm S. 1994. Cancer epidemiology. See Ref. 98a, pp. 525–47
51. Hardell L, Eriksson M, Lenner P, Lundgren E. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br. J. Cancer* 43:169–76
52. Hardell L, Sandstrom A. 1979. Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br. J. Cancer* 39:711–17
53. Hayes WJ Jr. 1982. *Pesticides Studied in Man*, pp. 195–205. Baltimore/London: Williams & Wilkins. 672 pp.

54. Hsu-ST, Ma-CI, Hsu-SK, Wu-SS, Hsu-NH, et al. 1985. Discovery and epidemiology of PCB poisoning in Taiwan: a four-year followup. *Environ. Health Perspect.* 59:5–10
55. Hsu CC, Yu MLM, Chen YCJ, Guo YLL, Rogan WJ. 1994. The Yu-cheng rice oil poisoning incident. See Ref. 98a, pp. 661–84
56. Huff J. 1994. Dioxins and mammalian carcinogenesis. See Ref. 98a, pp. 389–407
57. Huisman M, Koopman-Esseboom C, Fidler V, Hadders-Algra M, van der Paauw CG, et al. 1995. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. *Early Hum. Dev.* 41:111–27
58. Ikeda M, Kuratsune M, Nakamura Y, Hirohata T. 1986. A cohort study on mortality of Yusho patients–a preliminary report. *Fukuoka Acta Med.* 78:297–300
59. Industrial Disease Standards Panel. 1987. *Report to the Workers Compensation Board on Occupational Exposure to PCBs and Various Cancers*, IDSP Rep. No. 2, Toronto, Canada
60. Institute of Medicine (US). 1996. *Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. Veterans and Agent Orange: Update 1996.* Washington, DC: Natl. Acad. Press
61. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Lyon, France: WHO, IARC
62. Jacobson JL, Jacobson SW, Humphrey HEB. 1990. Effects of exposure to PCBs and related compounds on growth and activity in children. *Neurotoxicol. Teratol.* 12:319–26
63. Jacobson JL, Jacobson SW, Humphrey HEB. 1990. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *J. Pediatr.* 116:38–45
64. Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, Wilson EM. 1995. Persistent DDT metabolite p,p′-DDE is a potent androgen receptor antagonist. *Nature* 375:581–85
65. Kimbrough RD. 1995. Polychlorinated biphenyls (PCBs) and human health: an update. *Crit. Rev. Toxicol.* 25:133–63
66. Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, et al. 1995. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. *Epidemiology* 6:396–402
67. Koopman-Esseboom C, Huisman M, Weisglas-Kuperus, Van der Paauw CG, Tuinstra LGMT, et al. 1994. PCB and dioxin levels in plasma and human milk of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant's exposure to PCBs and dioxins. *Chemosphere* 28:1721–32
68. Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, Lutkeschipholt IJ, Van der Paauw CG. 1994. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatr. Res.* 36:468–73
69. Kreiss K, Zack MM, Kimbrough RD, Needham LL, Smrek AL, Jones BT. 1981. Association of blood pressure and polychlorinated biphenyl levels. *JAMA* 245:2505–9
70. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. 1994. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. *J. Natl. Cancer Inst.* 86:589–99
71. Lawton RW, Ross MR, Feingold J, Brown JF Jr. 1985. Effects of PCB exposure on biochemical and hematologic findings in capacitor workers. *Environ. Health Perspect.* 60:165–84
72. Leoni V, Fabiani L, Marinelli G, Puccetti G, Tarsitani GF, et al. 1989. PCB and other organochlorine compounds in blood of women with or without miscarriage: a hypothesis of correlation. *Ecotoxicol. Environ. Saf.* 17:1–11
73. Liss GM. 1989. Mortality and cancer morbidity among transformer manufacturing workers, Ferranti-Packard Ltd., St. Catherines. Toronto: Ontario Min. Labor, Health Stud. Serv.
74. Longnecker MP, London SJ. 1993. Re: Blood levels of organochlorine residues and risk of breast cancer. *J. Natl. Cancer Inst.* 85:1696–97
75. Lucier GW, Clark G, Tritscher A, Foley J, Maronpot R. 1992. Mechanisms of dioxin tumor formation: implications for risk assessment. *Chemosphere* 25:177–80
76. Maroni M, Columbi A, Arbosti G, Cantoni S, Foa V. 1981. Occupational exposure to polychlorinated biphenyls in electrical workers. II. Health effects. *Br. J. Ind. Med.* 38:55–60
77. Masuda Y. 1994. The Yusho rice oil poisoning incident. See Ref. 98a, pp. 633–59
78. Matthews HB, Dedrick RL. 1984. Phar-

macokinetics of PCBs. *Annu. Rev. Pharmacol. Toxicol.* 24:85–103
79. Meigs JW, Albom JJ, Kartin BL. 1954. Chloracne from an unusual exposure to arochlor. *JAMA* 154:1417–18
80. Mendola P, Buck GM, Vena JE, Zielezny M, Sever LE. 1995. Consumption of PCB-contaminated sport fish and risk of spontaneous fetal death. *Environ. Health Perspect.* 103:498–502
81. Morgan DP, Lin LI. 1978. Blood organochlorine pesticide concentrations, clinical hematology and biochemistry in workers occupationally exposed to pesticides. *Arch. Environ. Contam. Toxicol.* 7:423–47
82. Mussalo-Rauhamaa H, Hasanen E, Pyysalo H, Antervo K, Kauppila R, Pantzar P. 1990. Occurrence of beta-hexachlorocyclohexane in breast cancer patients. *Cancer* 66:2124–28
83. Nicholson WJ, Seidman H, Selikoff IJ. 1987. Mortality experience of workers exposed to polychlorinated biphenyls during manufacture of electrical capacitors. *Prelim. Rep. Ind. Dis. Stand. Panel, Toronto, Ont.*
84. O'Leary JA, Davies JE, Feldman M. 1970. Spontaneous abortion and human pesticide residues of DDT and DDE. *Am. J. Obstet. Gyn.* 108:1291–92
85. Persson B, Dahlander AM, Fredriksson M, Brage NH, Ohlson CG, Axelson O. 1989. Malignant lymphomas and occupational exposures. *Br. J. Ind. Med.* 46:516–20
86. Peterson DG Jr, Todd GD, Wayman ET, Maggio V, Alexander LR, Needham LL. 1994. Levels of non-ortho-substituted (coplanar), mono- and di-ortho-substituted polychlorinated biphenyls, dibenzo-p-dioxins, and dibenzofurans in human serum and adipose tissue. *Environ. Health Perspect.* (Suppl. 1):102:195–204
87. Pluim HJ, de Vijlder JJM, Olie K, Kok JH, Vulsma T, et al. 1993. Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations. *Environ. Health Perspect.* 101:504–8
88. Procianoy RS, Schvartsman S. 1981. Blood pesticide concentration in mothers and their newborn infants: relation to prematurity. *Acta Paediatr. Scan.* 70:925–28
89. Rogan WJ, Gladen BC. 1992. Neurotoxicology of PCBs and related compounds. *Neurotoxicol.* 13:27–35
90. Rogan WJ, Gladen BC, Hung KL, Koong SL, Shih LY, et al. 1988. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. *Science* 241:334–36
91. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, et al. 1986. Neonatal effects of transplacental exposure to PCBs and DDE. *J. Pediatr.* 109:335–41
92. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, et al. 1987. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects on growth, morbidity, and duration of lactation. *Am. J. Public Health* 77:1294–97
93. Safe SH. 1994. Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. *Crit. Rev. Toxicol.* 24:87–149
94. Safe S, Astroff B, Harris M, Zacharewski T, Dickerson R, et al. 1991. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related compounds as antioestrogens: characterization and mechanism of action. *Pharmacol. Toxicol.* 69:400–9
95. Saracci R, Kogevinas M, Bertazzzi PA, Bueno de Mesquita BH, Coggon D, et al. 1991. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet* 338:1027–32
96. Savitz DA. 1994. Re: Breast cancer and serum organochlorines: a prospective study among white, black and Asian women. *J. Natl. Cancer Inst.* 86:1255–56
97. Saxena MC, Siddiqui MKJ, Bhargava AK, Seth TD, Krishnamurti CR, Kutty D. 1980. Role of chlorinated hydrocarbon pesticides in abortions and premature labor. *Toxicology* 17:323–31
98. Saxena MC, Siddiqui MKJ, Seth TD, Krishna Murti CR, Bhargava AK, Kutty D. 1981. Organochlorine pesticides in specimens from women undergoing spontaneous abortion, premature or full-term delivery. *J. Anal. Toxicol.* 5:6–9
98a. Schecter A, ed. 1994. *Dioxins and Health.* New York: Plenum. 710 pp.
99. Schecter A, Papke O, Ball M, Lis A, Brandt-Rauf P. 1995. Dioxin concentrations in the blood of workers at municipal waste incinerators. *Occup. Environ. Med.* 52:385–87
100. Shalat SL, True LD, Fleming LE, Pace PE. 1989. Kidney cancer in utility workers exposed to polychlorinated biphenyls (PCBs). *Br. J. Ind. Med.* 46:823–24
101. Sharpe RM, Skakkebaek NE. 1993. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 341:1392–95

102. Scheuplein RJ, Bowers JC. 1995. Dioxin–an analysis of the major human studies: comparison with animal-based cancer risks. *Risk Anal.* 15:319–33
103. Sinks T, Steele G, Smith AB, Watkins K, Shults RA. 1992. Mortality among workers exposed to polychlorinated biphenyls. *Am. J. Epidemiol.* 136:389–98
104. Smith AB, Schloemer J, Lowry LK, Smallwood AW, Ligo RN, et al. 1982. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. *Br. J. Ind. Med.* 39:361–69
105. Smith BJ. 1984. P.C.B. levels in human fluids: Sheboygan case study. *Tech. Rep. WIS-SG-83-240, Univ. Wisc. Sea Grant Inst.*, Madison, WI
106. Soto AM, Sonnenschein C, Chung KL, Fernandez MF, Olea N, Serrano FO. 1995. The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants. *Environ. Health Perspect.* 103(Suppl. 7):113–22
107. Stehr-Green PA. 1989. Demographic and seasonal influences on human serum pesticide residue levels. *J. Toxicol. Environ. Health* 27:405–21
108. Suruda AJ, Ward EM, Fingerhut MA. 1993. Identification of soft tissue sarcoma deaths in cohorts exposed to dioxin and to chlorinated naphthalenes. *Epidemiology* 4:14–19
109. Svensson BG, Hallberg T, Nilsson A, Schutz A, Hagmar L. 1994. Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds. *Int. Arch. Occup. Environ. Health* 65:351–58
110. Sweeney A. 1994. Reproductive epidemiology of dioxins. See Ref. 98a, pp. 549–85.
111. Sweeney MH, Fingerhut MA, Arezzo JC, Hornung RW, Connally LB. 1993. Peripheral neuropathy after occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Am. J. Ind. Med.* 23:845–58
112. Taylor PR, Stelma JM, Lawrence CE. 1989. The relation of polychlorinated biphenyls to birth weight and gestational age in the offspring of occupationally exposed mothers. *Am. J. Epidemiol.* 129:395–406
113. Tritscher AM, Clark GS, Lucier GW. 1994. Dose-response effects of dioxins: species comparison and implications for risk assessment. See Ref. 98a, pp. 525–47
114. Unger M, Kiaer H, Blichert-Toft M, Olsen J, Clausen J. 1984. Organochlorine compounds in human breast fat from deceased with and without breast cancer and in a biopsy material from newly diagnosed patients undergoing breast surgery. *Environ. Res.* 34:24–28
115. United States Environmental Protection Agency. 1996. *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds.* Washington, DC: Off. Health Environ. Assess., Off. Res. Dev., US EPA
116. Waller K, Prendergast TJ, Slagle A, Jackson RJ. 1992. Seizures after eating a snack food contaminated with the pesticide endrin. The tale of the toxic toquitos. *West. J. Med.* 157:648–51
117. Wasserman M, Nogueira DP, Tomatis L, Mirra AP, Shibata H, et al. 1976. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. *Bull. Environ. Contam. Toxicol.* 15:478–84
118. Wasserman M, Ron M, Bercovici B, Wasserman D, Cucos S, Pines A. 1982. Premature delivery and organochlorine compounds: polychlorinated biphenyls and some organochlorine insecticides. *Environ. Res.* 28:106–12
119. Webster T, Commoner B. 1994. Overview: the dioxin debate. See Ref. 98a, pp. 1–50
120. Weisglas-Kuperus N, Sas TCJ, Koopman-Esseboom C, Van der Zwan CW, De Ridder MAJ, et al. 1995. Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants. *Pediatr. Res.* 38:404–10
121. Wolfe WH, Michalek JE, Miner JC, Rahe AJ, Moore CA, et al. 1994. Paternal serum dioxin and reproductive outcomes among veterans of Operation Ranch Hand. *Epidemiology* 6:16–22
122. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. 1993. Blood levels of organochlorine residues and risk of breast cancer. *J. Natl. Cancer Inst.* 85:648–52
123. Wong O, Brocker W, Davis HV, Nagle GS. 1984. Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB, and DDT. *Br. J. Ind. Med.* 41:15–24
124. Wong TK, Sloop T, Lucier GW. 1986. Nondetectable concentrations of human placental Ah receptors are associated with potent induction of microsomal benzo[a]pyrene hydroxylase in individuals exposed to polychlorinated biphenyls, quaterphenyls, and dibenzofurans. *Toxi-*

col. Appl. Pharmacol. 85:60–68
125. Woodruff T, Wolff MS, Davis DL, Hayward D. 1994. Organochlorine exposure estimation in the study of cancer etiology. *Environ. Res.* 65:132–44
126. Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. 1987. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J. Natl. Cancer Inst.* 78:899–910
127. Yassi A, Tate R, Fish D. 1994. Cancer mortality in workers employed at a transformer manufacturing plant. *Am. J. Ind. Med.* 25:425–37