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Human health effects of dioxins: cancer, reproductive and endocrine system effects

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Polychlorinated dioxins, furans and polychlorinated benzene constitute a family of toxic persistent environmental pollutants. In Europe, environmental concentrations increased slowly throughout this century until the late 1980s. Dioxins have been shown to be carcinogenic in animals and humans. In humans, excess risks were observed for all cancers, without any specific cancer predominating. In specific cohorts, excess risks were observed for reproductive cancers (breast female, endometrium, breast male, testis) but, overall, the pattern is inconsistent. In animals, endocrine, reproductive and developmental effects are among the most sensitive to dioxin exposure. Decreased sperm counts in rats and endometriosis in rhesus monkeys occur at concentrations 10 times higher than current human exposure. In humans, results are inconsistent regarding changes in concentrations of reproductive hormones. A modification of the sex ratio at birth was described in Seveso. There exist no data on effects such as endometriosis or time-to-pregnancy. Small alterations in thyroid function have occasionally been found. Increased risk for diabetes was seen in Seveso and a herbicide applicators cohort but, overall, results were inconsistent. Experimental data indicate that endocrine and reproductive effects should be among the most sensitive effects in both animals and humans. Epidemiological studies have evaluated only a few of these effects.

Key words: cancer/dioxin/endocrine diseases/reproductive effects

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Introduction

Tetrachlorodibenzo-*p*-dioxin (TCDD) is considered by the International Agency for Research on Cancer (IARC) as a human carcinogen. The World Health Organization (WHO, 1998) has recommended that human ingestion in adults should stay within the limits of 1–4 pg/kg weight/day. The critical effects used to define this tolerable daily intake (TDI) were effects on the reproductive, developmental and endocrine systems. In experimental animals, the endocrine system has been shown to be one of the critical targets for dioxins with multiple hormone systems affected. Several major reviews on the effects of TCDD and related compounds have been completed in the past few years. They include the US EPA's draft dioxin reassessment (Environmental Protection Agency, 1994), the IARC evaluation (IARC, 1997), and the WHO's consultation on the TDI (WHO, 2000). This review focuses on specific health effects of dioxins in adults, particularly cancer, reproductive and endocrine effects and is based, in part, on the conclusions of these major reviews. Effects in children are covered only briefly.

Sources of human exposure

The main sources of exposure in western Europe are nowadays waste incinerators and the reprocessing metal industry. Emissions from the paper and pulp industry, which was one of the main contaminants some years ago, and from the use of contaminated herbicides have been drastically reduced in industrialized countries. Historical trends indicate that exposure to dioxins has been increasing in Europe during this century, with a peak around the 1950–1960s and a gradual decrease thereafter (Figure 1). Two peaks of exposure in the 1980s-1990s were associated with the increased exposure from pulp and papers industries initially, and from poorly controlled emissions from waste incineration later.

Exposure to humans is nearly entirely through the diet, particularly milk and other dairy products, fish and meat. The

importance of specific dietary items may vary by region. For example, consumption of fish appears to be a more important source in north German and south Scandinavian populations than in other European populations.

There exist 210 polychlorinated dioxin and furan congeners. TCDD is the most toxic compound of this family of structurally related chemicals, which have a common mechanism of action and induce the same spectrum of effects. This has led to the development of a relative potency ranking scheme using toxic equivalent factors (TEQ). The total dioxin-like activity of a complex mixture is expressed as the weighted sum of all the dioxin-like chemicals (Ahlborg *et al*., 1994; van den Berg *et al*., 1998). This scheme includes 17 dioxins and furans and a small number of PCB which show dioxin-like activity. These compounds are the ones which are the most prevalent and show the most toxic activity in human populations.

Dioxins are lipophilic, are slowly metabolized and eliminated, and tend to bioaccumulate. The half-life of these compounds varies, but the TEQ of the mixtures to which humans are exposed are usually determined by just a few compounds. The half-life of TCDD has been estimated in humans to be between 7 and 8 years. This half-life may vary with dose, age, sex and body composition. Most of the effects of dioxins are believed to be mediated through the aryl hydrocarbon receptor, which is highly conserved in different species. The route of exposure to TCDD has little influence on the effects seen following dioxin treatment. Various dioxin effects, including enzyme induction, immunotoxicity, developmental effects, tend to be similar irrespective of whether the exposure is acute or chronic. This reflects the fact that it is the tissue concentration which is directly associated with the response.

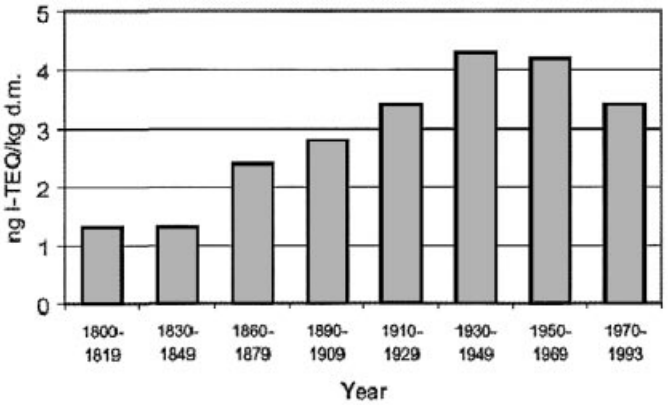

Figure 1. Time trends in dioxin concentrations in sediments in Loch Corienan Arr, Scotland (Rose and McKay, 1996). TEQ = toxic equivalent factors.

Effects in experimental animals

TCDD exposure has been associated with a wide spectrum of effects in experimental animals (IARC 1997; Birnbaum and Tuomisto, 2000). The LD_{50} dose differs markedly between species. The wide differences in LD_{50}, however, are not necessarily seen when examining other effects. For example, differences between species are much less pronounced for fetotoxicity. Current knowledge of mechanisms of action of dioxins does not indicate that humans are in any way more resistant than experimental animals to the effects of dioxins.

The endocrine system has been shown in experimental animals to be one of the critical targets for dioxins, with multiple hormone systems affected. A selected list of endocrine alterations described in experimental animals shown in Table I. Steroidogenesis has been shown to affect the male and female reproductive systems in monkeys and rats. Reproductive effects of exposure to TCDD have been identified in many species, in both high and low doses. A list of reproductive effects observed is shown in Table II. The occurrence of endometriosis in female Rhesus monkey (Rier *et al*., 1993) after chronic low dose exposure to TCDD has been one of the critical outcomes for the definition of the TDI in the 1998 WHO consultation (WHO, 1998). A wide range of developmental effects have been observed in multiple species (IARC, 1997; Birnbaum and Tuomisto, 2000).

Table I. Endocrine effects in experimental animals associated with dioxin exposure (modified from Birnbaum and Toovisto, 2000)

Decreased circulating melatonin concentrations due to enhanced metabolism
Decreased thyroxine concentrations
Decreased total thyroxine concentrations (may be associated with an increase in thyroid-stimulating hormone concentrations)
Thyroid follicular cell hyperplasia
Decrease in blood insulin and glucose
Reduction in glucose transporting activities in adipose tissue and the pancreas
Increase in serum gastrin concentrations
Disruption (pituitary) of the normal feedback mechanisms between plasma testosterone, dihydrotestosterone, oestradiol, and LH secretion
Increases in adrenocorticotrophic hormone resulting in altered concentrations of circulating glucocorticoids
Decrease in the number of glucocorticoid receptors in the liver of rats and mice, in the placenta of mice and in the muscle of rats
Up-regulation of the number of glucocorticoid receptors in the developing palate
Decrease of the number of oestrogen receptors in uterine, and liver tissue, as well as in certain breast cancer cell lines (effects dependent upon the age of the animal)
Alteration of the metabolism of oestrogens and androgens
Inhibition of the expression of growth factors and of vitamin A

The 1998 WHO consultation

The WHO consultation for the re-evaluation of the TDI was based on the Lowest Observed Adverse Effect Levels (LOAEL) for the most sensitive adverse responses reported in experimental animals (WHO, 2000). The critical effects used were: decreased sperm count in offspring of rats; immune suppression in offspring of rats; increased genital malformations in offspring of rats; neurobehavioural (object learning) effects in offspring of monkeys; endometriosis in monkeys.

The LOAEL for these effects corresponded to an estimated daily intake of 14–37 pg TCDD/kg body weight. A safety factor of 10 was applied to this interval to deduce the final TDI of 1–4 TEQ pg/kg body weight per day (the TDI provided is for toxic equivalents of dioxin and related compounds rather than only TCDD). These limits were based on experiments administering both acute gavage exposure to rats and also prolonged dietary exposure to monkeys, which resemble more the conditions of human intake.

Epidemiological studies examining effects of dioxin exposure

The epidemiological studies on dioxins and health include studies of industrial exposures in workers producing phenoxy herbicide and chlorophenols; studies of the population exposed in the industrial accident in Seveso; studies of subjects exposed during herbicide application; in particular, application cohorts of military personnel of the US army in Vietnam, commercial application cohorts, and community based studies (case–control studies).

The most informative epidemiological studies are those examining the population of Seveso, accidentally exposed to dioxins in 1976; those examining workers producing chlorophenols and chlorophenoxy herbicides contaminated with dioxins; and the Ranch Hand cohort of US army applicators. These populations have been exposed to 10-1000 times higher concentrations of TCDD than the general population. A summary of the populations included in these studies is shown in Table III.

Cancer in humans

Cancer mortality was invariably increased in all industrial cohorts examined (Table IV). Statistically significant increases of the order of 50% were observed among the exposed subcohorts of these populations. Positive linear trends in risk were found with increasing exposure for all cancers combined in all the studies (Figure 2). Increased risks with time since first exposure were observed in those studies that evaluated latency (Kogevinas *et al*., 1997; Steenland *et al*., 1999).

The results of the 15 year cancer incidence and 20 year mortality follow-up in Seveso have recently been reported (Bertazzi and Pesaton, 1999). The area in Seveso was subdivided into zones A, B and R in descending order of TCDD contamination (Table III). There was no overall increase in cancer risk, although an increase in cancer risk was seen for the last 5 years of follow-up. Mortality and cancer incidence from neoplasms of the lymphatic and haematopoietic system was higher in zones A and B ($RR = 1.8$, $P < 0.001$) in both sexes. Mortality from hepatobiliary cancer increased in women in zones A and B, while mortality from lung and rectal cancer increased in men in zones A and B.

In the IARC international cohort of workers (Kogevinas *et al*., 1997), elevated risks were observed for breast cancer in both women and men, endometrial cancer and testicular cancer (Table V). The increased mortality from breast cancer was confined to female workers in the Boehringer cohort in Germany [nine deaths, standardized mortality rate (SMR) = 2.84, 95% confidence interval (CI) 1.30–5.39]. Two of three deaths from endometrial cancer similarly occurred in this plant. Finally, an excess risk was seen for cancer of 'other endocrine organs', both deaths being from tumours of the suprarenal glands. No increase in breast cancer incidence or mortality was observed in Seveso. The excess risks for breast and endometrial cancers are in contrast with results from some of the chronic bioassays in which TCDD inhibited the development of spontaneous mammary and uterine tumours in female rats (Kociba *et al*., 1978).

Findings on cancer risk among subjects evaluated in community-based studies and spray applicator studies are contradictory. The large discrepancies observed are probably due to exposure misclassification, since most subjects classified as exposed in those studies had probably very similar or only slightly elevated concentrations of TCDD compared to those classified as non-exposed.

In examining the findings on cancer risk from the most informative epidemiological studies, a number of issues should be noted (IARC, 1997; Kogevinas, 2000). Low excess risks for all neoplasms combined were found in all industrial cohort studies with adequate exposure assessment. These excess risks were

Table II. Reproductive effects in experimental animals associated with dioxin exposure (modified from Birnbaum and Toovisto, 2000)

Effect	Species, comments
Infertility and fetal loss	Multiple species, high doses
Anovulation and suppression of the oestrous cycle	Rats, high doses
Ovarian dysfunction	Multiple species, high doses
Fetal loss (spontaneous abortions)	Rhesus monkeys
Endometriosis	Rhesus monkeys, chronic low concentration
Growth of surgically induced endometriotic cysts	Rats and mice (not at high concentrations due to ovarian atrophy)
Decreased spermatogenesis	Rat
Decreased circulating androgens	Sexually mature rat

Table III. Description of the population included in the most informative epidemiological studies examining effects of dioxin exposure

Country, references	No. of subjects	TCDD concentrations at time of blood extraction	Outcomes examined
United States plants (Fingerhut *et al*., 1991, Steenland *et al*., 1999; Egeland *et al*., 1994; Calvert *et al*., 1999)	5172 men in 12 herbicide production plants	Average TCDD concentrations in 1987: 233 pg/g lipid	Mortality for full cohort. Morbidity and biochemical parameters for small subsample
German accident cohort BASF (Zober *et al*., 1990; Ott and Zober, 1996)	247 (243 men, 4 women) involved directly in accident or clean-up	TCDD concentrations in 1988–1992; geometric mean = 15.4 ppt. High concentrations observed in workers with chloracne	Mortality, morbidity, biochemical parameters
Other German plants. Becher *et al*. (1996) includes Boehringer cohort (Manz *et al*., 1991; Nagel *et al*., 1994; Flesch-Janys *et al*., 1995)	2479 male workers employed in four German plants. Analyses of Boehringer cohort also include women	Boehringer cohort. TCDD concentrations 1985–1994: mean = 141.4 pg/g. Concentrations lower in a another plant. Background concentrations in remaining two plants	Mortality
Dutch plants (Bueno de Mesquita *et al*., 1993; Hooiveld *et al*., 1998)	2074 men employed in two plants	TCDD mean concentration in 1993: 53 pg/g in plant A. background concentrations in second plant	Mortality
IARC multi-country study (Saracci *et al*., 1991, Kogevinas *et al*., 1997; Vena *et al*., 1998).	21 863 male and female workers employed in 36 plants, 12 countries. Includes all above-mentioned cohorts apart from BASF (Zober *et al*., 1990)	TCDD range 3–389 pg/g (574 measurements in 10 cohorts, 7 countries)	Mortality, cancer incidence
Seveso industrial accident (Bertazzi *et al*., 1993, 1997; Landi *et al*., 1997; Mocarelli *et al*., 1996)	Population residing in Seveso area. Zone A (most contaminated) 750 subjects; zone B: 5000 subjects; zone R: 30000 subjects	Concentrations in 1996: zone A, 7 individuals, g = 53.2 ppt; zone B, 11 ppt; reference zone (non-ABR), 4.9 ppt	Mortality, cancer incidence, morbidity, biochemical parameters in adults and children
Military herbicide applicators—Ranch Hand (Michalek *et al*., 1990, 1998; Henriksen *et al*., 1996, 1997)	1261 men	Concentrations in 1984–1985: mean = 46 ppt; geometric mean = 15.7 ppt	Mortality, morbidity, biochemical parameters

Table IV. Mortality from all neoplasms in selected industrial cohorts with high exposure concentrations to polychlorinated dibenzo dioxins and furans

Reference	No. deaths	SMR (95% CI)
IARC International cohort		
Kogevinas *et al*. (1997)[a]	394	1.2 (1.1–1.3)
Industrial populations (high exposure sub-cohorts)		
Steenland *et al*. (1999)[b]	40	1.6 (1.2–1.8)
Becher *et al*. (1996)[c]	105	1.3 (1.0–1.5)
Hooiveld *et al*. (1997)[c]	51	1.5 (1.1–1.9)
Ott and Zober (1996)[d] (BASF accident)[e]	18	1.9 (1.1–3.0)

[a]Twenty years since first exposure.
[b]Standardized mortality ratio (SMR) for workers in highest septile of dioxin exposure. The SMR for the whole cohort was 1.13 (95% CI 1.02–1.25; 377 deaths).
[c]Cohorts I and II.[d]Cohort A.
[e]Workers with chloracne, 20 years after exposure during accident.
CI = confidence interval.

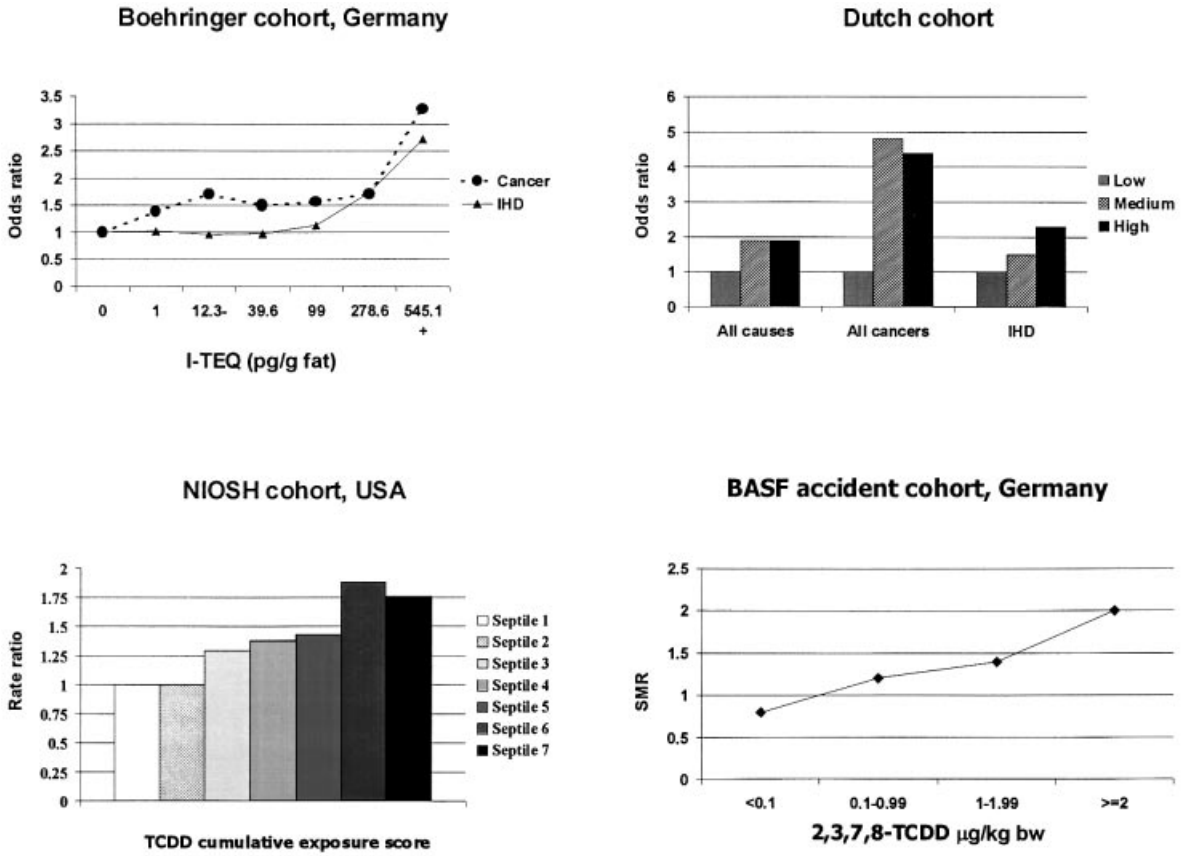

Figure 2. Cancer mortality by dioxin exposure in the industrial cohorts in Germany (Boehringer cohort: Flesch-Janys *et al*., 1995; BASF accident cohort: Ott and Zober, 1996), The Netherlands (Hooivelt *et al*., 1998) and the USA (NIOSH cohort, Steenland *et al*., 1999). IHD = ischaemic heart disease; SMR = standardized mortality ratio; TCDD = tetrachlorodibenzo-*p*-dioxin; NIOSH = National Institute for Occupational Safety and Health.

Table V. Standardized mortality ratios for selected tumours in the 21 863 workers of the IARC international cohort study exposed to phenoxy herbicides or chlorophenols, by exposure to TCDD or higher chlorinated dioxins, 1939–1992

Cause of death (ICD-9 codes)	Workers exposed to TCDD or higher chlorinated dioxins			Workers not exposed to TCDD or higher chlorinated dioxins			All workers exposed to any phenoxy herbicide or chlorophenol[a]		
	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI
All causes	2728	1.00	0.97–1.04	1367	0.91	0.86–0.96	4159	0.97	0.94–1.00
All malignant neoplasms	710	1.12	1.04–1.21	398	0.96	0.87–1.06	1127	1.06	1.00–1.13
Breast, female (174)	9	2.16	0.99–4.10	3	0.53	0.11–1.56	12	1.23	0.63–2.14
Breast, male (175)	2	2.56	0.31–9.26	0	0	0.00–7.69	2	1.55	0.19–5.60
Endometrium and uterus (179, 181–182)	3	3.41	0.70–9.96	1	1.16	0.03–6.48	4	2.30	0.63–5.89
Ovary (183)	0	0	0.00–2.62	1	0.45	0.01–2.51	1	0.28	0.01–1.53
Prostate (185)	43	1.11	0.81–1.50	25	1.10	0.71–1.62	68	1.10	0.85–1.39
Testis (186)	4	1.31	0.36–3.35	3	1.33	0.28–3.90	7	1.30	0.52–2.68
Thyroid (193)	2	1.36	0.16–4.91	2	2.17	0.26–7.85	4	1.65	0.45–4.23
Other endocrine organs (194)	2	2.25	0.27–8.12	3	6.38	1.32–18.65	5	3.60	1.17–8.39

[a]Exposure to TCDD or higher chlorinated dioxins could not be evaluated for 479 workers 64 deaths, including one death from soft tissue sarcoma, and one from non-Hodgkin lymphoma in one plant producing phenoxy herbicides, who are included in this column together with those shown in the two middle columns.

TCDD = tetrachlorodibenzo-*p*-dioxin; ICD-9 = *International Classification of Diseases*, 9th revision; SMR = standardized mortality ratio; CI = confidence interval.

highly statistically significant and an effect of chance can be excluded. The risk tended to be higher for those workers with the highest exposures. Risks for some specific cancers have been increased in some of these studies (lymphomas, multiple myeloma, soft-tissue sarcoma, lung cancer, liver cancer, breast cancer, testicular cancer, endometrium) but, overall, results are not consistent between studies and there no specific cancer appears to predominate. There are very few precedents of carcinogens affecting the risk for all cancers without any clear excess for any specific cancer (IARC, 1997). Finally it should be noted that the strongest evidence comes from studies on subjects with 2–3 orders of magnitude higher exposure than the general population. To extrapolate to the general population, it is necessary to use models and assume similar effects at high and low doses.

At present, the real dilemmas are not whether dioxins are or not carcinogens, but rather on the quantification of the risk associated with the low-level exposure of the general population. Furthermore it is not clear from the epidemiological evidence whether specific cancers, including reproductive system cancers, are more (or less) strongly associated with dioxin exposure than other sites.

Non-cancer effects in humans

Human exposure to 2,3,7,8-TCDD has been associated with various non-cancer effects (Table VI). Most of the hypotheses examined are 'biologically plausible' in the sense that there exists some evidence from animal or laboratory experiments supporting such an effect. Most available epidemiological studies, however, have focused on cancer mortality and were not designed to evaluate morbidity, e.g. neuropsychological effects, nor transient effects such as changes in reproductive hormones. Epidemiological evidence exists only for a few of these effects, and, in contrast to laboratory evidence, results from epidemiological studies are inconsistent for most effects other than cancer. The evidence in humans is currently conclusive only for dermatological effects and temporary increases in liver enzymes, while there is increasing evidence for an association with cardiovascular diseases. A summary of the evidence on selected effects is presented.

Thyroid function effects

Thyroid function has been associated with dioxin exposure in some cohorts of production workers and in Ranch Hand, but results were seldom statistically significant, nor consistent between studies (Sweeney and Mocarelli, 2000). In a 2,4,5-trichlorophenol (TCP) production factory there were no significant differences in thyroxine radioimmunoassay and thyroxine-binding globulin (TBG) between exposed and unexposed workers (Suskind and Hertzberg, 1984). In the BASF accident cohort, thyroid-stimulating hormone (TSH), thyroxine and TBG were within normal concentrations, while TGB and thyroxine concentrations were positively correlated with TCDD concentrations (Ott *et al*., 1994). In the National Institute for Occupational Safety and Health (NIOSH) cohort, differences between exposed and non-exposed were not statistically significant, although free thyroxin index and thyroxine were elevated in TCP production workers (Calvert *et al*., 1999). In the Operation Ranch Hand cohort, a slight increase in TSH concentrations was associated with TCDD although results were not statistically significant (Grubbs *et al*., 1995).

Reproductive system effects

Decreased testosterone and increased gonadotrophin concentrations were found in workers of the NIOSH cohort (Egeland *et al*., 1994) producing TCP with high TCDD concentrations. No association was found in Operation Ranch Hand (Henriksen *et al*., 1996). Exposure concentrations however in this latter cohort were considerably lower than those in the NIOSH production cohort.

Table VI. Summary of the strength of epidemiological evidence on effects other than cancer and tetrachlorodibenzo-*p*-dioxin exposure

Effect	Epidemiological evidence
Dermatological effects (chloracne)	Proven association
Gastrointestinal effects and liver enzymes	Temporary increases in liver enzymes, proven
Cardiovascular diseases and changes in lipid concentrations	Positive association in most 'high dose' studies but results not entirely consistent. Dose-response in some studies
Diabetes	Overall, results not consistent. lncreased risks in Seveso and Ranch Hand (morbidity)
Reproductive hormones/ reproductive outcome	Inconsistent results regarding reproductive hormones. Change in sex ratio in high exposed couples in Seveso. No data yet on possible effects in women, e.g. endometriosis, fertility
Thyroid function	Some (small) differences reported in thyroxine, thyroid-stimulating hormone, thyroxine-binding globulin, and T3 % uptake concentrations. Results not entirely consistent
Neurological/psychological effects	Inconsistent findings. Some effects reported in Ranch Hand and Seveso (polyneuropathies, abnormal co-ordination). No association with depression
Respiratory system	Inconsistent evidence. Irritative effects and reduced FEV_1 and FVC in some studies
Urinary system	No major renal or bladder dysfunctions observed
Immunological effects	Inconsistent findings

FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

A modification of sex ratio at birth with an excess of females over males (Table VII) was described in the period 1977–1984 in the most TCDD-contaminated area in Seveso (Mocarelli *et al*., 1996). This was particularly evident for couples with very high exposure of both parents to TCDD. These findings we recently confirmed through an expanded analysis of 239 men and 296 women in Seveso (Mocarelli *et al*., 2000). An increased probability of female births ($P = 0.008$) was particularly associated with TCDD concentrations in the serum samples of the fathers. This effect was observed at concentrations <20 ng per kg body weight. The most extreme modification of the sex ratio was observed among fathers exposed when they were younger than 19 years old (sex ratio = 0.38, 95% CI 0.30–0.47). A biological explanation of this phenomenon has not yet been provided. Comparable analyses in other dioxin-, PCB- or PCDF-exposed populations have not replicated these findings (Michalek *et al*., 1998; Rogan *et al*., 1999). These populations, however, have had considerably lower exposure to TCDD than that in Seveso.

There have so far been no epidemiological studies, evaluating the association between TCDD exposure and endometriosis or other reproductive outcomes such as time to pregnancy. It has been pointed out (Bois and Eskenazi, 1994) that the dioxin exposure among women in Seveso is comparable to the dose producing experimental endometriosis in rhesus monkeys (Rier *et al*., 1993). A retrospective study is currently underway examining these effects among women in Seveso.

Diabetes

TCDD-exposed subjects had higher mean glucose concentrations compared to those unexposed in the NIOSH study (Calvert *et al*., 1999), in the Operation Ranch Hand study (Henriksen *et al*., 1997), and in the BASF accident cohort at the time of the study, but not compared with concentrations estimated at the time of last exposure (Ott *et al*., 1994). No association was found in workers from Nitro, West Virginia (Suskind and Hertzberg 1984). In Operation Ranch Hand (Henriksen *et al*., 1997) the prevalence of diabetes, and the use of oral medication to control diabetes, increased with increasing exposure to TCDD, whereas the time to diabetes onset decreased with dioxin exposure. Among US TCP production workers (part of the NIOSH cohort), the prevalence of diabetes was not associated with TCDD serum concentrations. However, subjects with very high TCDD concentrations (>1500 pg/g) tended to have high prevalence of diabetes (Calvert *et al*., 1999). In the NIOSH cohort (Steenland *et al*., 1999), mortality from diabetes (any mention on the death certificate) showed a negative exposure-response trend. Increased mortality from diabetes was seen among females in zones A and B in Seveso, while no excess was observed among men (Pesatori *et al*., 1998).

Effects in children

In animal experiments, TCDD has been shown to affect the reproductive and immunological systems and also to affect neurodevelopment. The findings of epidemiological studies in industrial populations, the population of Seveso and the Ranch Hand cohort examining reproductive outcomes such as spontaneous abortions, birth weight or birth defects are inconsistent. Most studies did not identify statistically significant differences between exposed and unexposed subjects (Townsend *et al*., 1982; Suskind and Hertzberg, 1984; Mastroiacovo *et al*., 1988; Rylander *et al*., 1995; Wolfe *et al*., 1995; Feeley and Brouwer, 2000). Two European studies have associated exposure to dioxins during the prenatal period and during lactation with thyroid function in children and observed various alterations in thyroid hormones (Pluim *et al*., 1993; Koopman-Esseboom *et al*., 1994). Exposure to high concentrations of dioxins has been associated with developmental dental defects. Hypomineralized enamel defects have been shown in normal breastfed children to be associated with exposure to background concentrations of dioxins (Alaluusua *et al*., 1999).

Neurodevelopmental effects in children have been mostly examined in relation to exposure to mixtures of organochlorinated compounds, predominantly PCB. Two birth cohorts in The Netherlands also examined dioxin exposure. In the

Table VII. Sex distribution of children born in zone A (highest exposure), Seveso, between April 1997 and December 1984 by TCDD concentrations (ppt) of the parents in 1976 (from Mocarelli *et al*., 1996)

Family	TCDD in 1976			
	Father	Mother	Male	Female
1	2340	960	0	1
2	1490	485	0	2
3	1420	463	0	1
4	509	257	0	1
5	444	126	0	2
6	436	434	0	1
7	208	245	0	1
8	176	238	0	1
9	104	1650	0	2
10	65.4	26.6	1	0
11	55.1	27.6	1	0
12	29.6	36.5	1	0
13	29.3	ND	1	1

TCDD = tetrachlorodibenzo-*p*-dioxin; ND = no data.

Rotterdam-Groningen cohort, there were no significant effects of the total postnatal PCB-dioxin TEQ exposure at 3 months of age. At 7 months, greater PCB and dioxin exposure through breastfeeding had a significantly adverse effect on the psychomotor outcome among breastfeeders (Koopman-Esseboom *et al*., 1999). At 18 months and at 24 months, an effect of lactational exposure to these compounds could not be detected (Huisman *et al*., 1995; Koopman-Esseboom *et al*., 1999; Patandin *et al*., 1999). In the Amsterdam cohort, neither neonatal nor enhanced maturation effects were clearly observed after infant exposure to dioxins and dibenzofurans (Ilsen *et al*., 1996; Pluim *et al*., 1996), although there was a trend for the most highly exposed group to score lower in neuromotor functioning tests (Hempel test). Infant studies have shown that PCB exposure, particularly prenatal exposure, might be related to adverse effects on the neurodevelopment and behaviour of children. There are still only limited data on dioxin exposure.

Conclusion

Results from cohort studies indicate an excess risk for mortality from cancer and ischaemic heart disease, particularly among the most exposed workers. Results are still inconsistent concerning other health outcomes. Experimental data indicate that endocrine and reproductive effects should be among the most sensitive in both animals and humans. Epidemiological studies have evaluated only a few of these effects.

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