5 The risks of dioxin to human health

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Summary

Dioxins are toxic by-products which are generated in small amounts by natural burning processes and technical synthesis of some chlorinated organic compounds. The accident of Seveso, Italy in 1976 was viewed by public as a tragedy of apocalyptic proportions. Many birds, chickens and rabbits died, trees lost their leaves, and several thousands of people have been evacuated. Since then, dioxin has been viewed as the most toxic chemical known to man. Notwithstanding that only a few people died of acute dioxin poisoning, fear of dioxin has for the past 20 years been responsible for generating an enormous number of regulations.

The primary symptom of acute dioxin intoxication is chloracne. Hepatopathy, nervous disorders, gastrointestinal effects and skin lesions appear occasionally. Chronic effects include mutagenic, carcinogenic and teratogenic effects as well as adverse effects on immunity and reproduction. But epidemiological studies revealed that these consequent effects are optional and due to dioxin concentrations that are greater by a factor of 50 to 100 than those likely to occur in the general population following intake of dioxin by food (the primary source of exposure for humans). Since the introduction of regulations which limit dioxin production, its environmental burden and concentration in food has been decreasing, so fears of dioxin poisoning are now totally unjustified.

Table 8 **The different toxicity (LD_{50}) of PCDDs and PCDFs in relation to that of 2,3,7,8-TCDD and the appropriate toxic equivalents (TEQ)**

Compound	*LD50 (mg/kg)*	*TEQ*
2,3,7,8-tetrachloro-DD[1]	1	1
1,2,3,7,8-pentachloro-DD	2	0.5
1,2,3,7,8,9-hexachloro-DD	10	0.1
1,2,3,4,6,7,8-heptachloro-DD	100	0.01
1,2,4,7,8-pentachloro-DD	1125	0.00089
2,3,7-trichloro-DD	30000	0.00003
2,3,4,7,8-pentachloro-DF[2]	2	0.5
2,3,7,8-tetrachloro-DF	10	0.1
1,2,3,7,8,9-hexachloro-DF	10	0.1
1,2,3,7,8-pentachloro-DF	20	0.05
1,2,3,4,7,8,9-heptachloro-DF	100	0.01

1 DD = dibenzo-p-dioxin
2 DF = dibenzofuran

Introduction

The so-called dioxins are often referred to as the most toxic man-made chemicals. Specifically, there are two groups of chemical compounds which show a similar pattern of toxicity: 75 structure isomer or congener chlorodibenzo-p-dioxins and its best known member, the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and a further 135 congener chlorobenzofurans, from which the analogous substance 2,3,7,8-tetrachlorodibenzofuran (TCDF) is the most toxic. Regarding the polychlorinated dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) from a chemical point of view, the molecular stability and symmetry corresponds with the toxicity. Table 8 shows the rank of relative acute toxicity of some PCDDs and PCDFs.[1] The so-called toxic equivalents (TEQ) are values reduced to the toxicity of 2,3,7,8-TCDD expressed in terms of LD_{50} for a guinea pig.

Table 9 **Chemical accidents releasing dioxins and numbers of people involved**

Plant, Situated	*Country*	*Year*	*Exposed*	*Dead by dioxin*
Monsanto, Nitro, West Virginia	USA	1949	884	0
Boehringer, Ingelheim	Germany	1952/3	60	0
BASF, Ludwigshafen	Germany	1953	247	1
Boehringer, Hamburg	Germany	1954	31	0
Diamond Alcali Corp. N.J.	USA	1956	73	0
Hooker	USA	1956		0
Rhone-Poulenc, Grenoble	France	1956	17	0
Philips-Duphar, Amsterdam	Netherlands	1963	141	4*
Dow Chemicals, Midland	USA	1964	2192	0
Coalite & Chem.Prod., Bolsover	UK	1968	79	0
Stickstoffwerke Linz	Austria	1973	<100	0
Bayer Uerdingen	Germany	1974	<100	0
ICMESA, Seveso	Italy	1974	735 (Zone A)	0
		1976	4699 (zone B)	0

*In question.

The mounting public fears of dioxin and the Seveso accident

Dioxins were synthesized for the first time in the 19th century; they have been produced as by-products in all chlorination processes of aromatic compounds for some decades. But the first observations of dioxin toxicity did not appear until the late 1940s, following accidents at Monsanto, BASF, and other herbicide manufactures (see Table 9).

Although many people were exposed to relatively high concentrations of TCDD, chloracne was the only symptom presented in most cases[2] whereas other toxic effects were much more seldom. During

the next three decades, only one assured death was confirmed (and four other deaths possibly associated). Nevertheless by the late 1970s dioxins were perceived to be extremely toxic, especially by environmental activists. From that time, the denouncement of dioxin began with an unscientific and moralizing attitude. For example, it was described as an 'insidious' substance.[3]

The 1976 Seveso plant accident was the landmark in the judgement of dioxins for several reasons. In particular, the people directly affected were scared and that fear was transmitted by the media to the rest of the world, as the dramatic event unfolded. At 12 noon on Saturday 10 July 1976, an explosion occurred during the production of 2,4,5-trichlorophenol in ICMESA's factory near Seveso, about 25 km north of Milan. A cloud of toxic material, estimated to contain between 159 grams and 2 kg of TCDD, escaped into the environment and debris fell on an area of about 2.8 km^2. People soon detected dermal lesions and when they saw that many animals (birds, chickens, and rabbits) died, and trees lost their leaves, they were frightened. The authorities divided the contaminated area into three zones (A, B, and R) and within 20 days of the explosion had evacuated 211 families (a total of 735 people) from zone A. 4,699 people lived in zone B, and 31,800 lived in zone R. All the residents were given extensive medical examinations from 1976 to 1985, but chloracne in a small segment of the population was the only abnormal finding detected.[4]

The accident at Seveso was not just an unfortunate explosion in a chemical plant, but it was confirmation of the fears that had been peddled by environmental groups about organochlorine compounds. Seveso became a *menentekel* ("the writing on the wall") for green activists – and was used to justify bans on production of chlorine and all organic compounds containing chlorine.

If Seveso represents the birth of the dioxin scare then Times Beach, a small town near St. Louis, Missouri (USA), represents the climax. Early in 1983, dioxin was detected in oil sprayed on local roads in traces of 50–100 ng/kg. In response, authorities evacuated all of the town's 2,240 residents, in spite of the fact that only a few casualties were caused by this allegedly potent toxin.

Table 10 **Rank of acute toxicity as minimum fatal doses of some substances**

Substance	*Toxicity (mg/kg)*	*Mol Wt.*
Botulism toxin A	0.00003	900,000
Tetanus toxin	0.0001	150,000
Ricin	0.02	63,000
Diphtheria toxin	0.3	72000
Crototoxin	0.2	21,000
TCDD	1	320
Tetrodotoxin	10	319
Aflatoxin B1	10	312
Curarine I	500	597
Strychnine N-oxide	500	350
Nicotine	1000	162
Isoflurophate (DFP)	3000	184
Sodium cyanide	10,000	49
Sodium phenobarbital	100,000	232

Table 11 **Acute toxicity in terms of LD_{50} of TCDD in different species**

Species	*LD50 (mg/kg)*
guinea pig	0.6–2.5
mink	4
rat	22–320
chicken	50
rhesus monkey	50–70
dog	100–<3,000
mouse	114–280
rabbit	115–275
hamsters	1150–5,000
humans	>1000–>5000

Subsequently, the hazard posed by dioxin was re-evaluated, and it is this revised analysis that most people in the research community consider to be state-of-the-art science. Yet even today, many environmentalists believe that revised views about dioxin are a sham.[5]

The Seveso accident and the public attention it attracted was the impetus for some scientists to examine the acute toxicity of TCDD and other PCDDs and PCDFs. But in order to attract research funding, the impacts of dioxin were over-stated and TCDD became known as the "most toxic chemical known to man." It is true that a few dioxins (i.e. TCDD and TCDF) are very toxic, but only to the most susceptible animals. For example, Table 10 lists some toxins and demonstrates the eminent position of TCDD according to the minimum dose necessary to induce death.[6]

But dioxin's rank in Table 10 must be compared with that of Table 11, which shows the LD_{50} of TCDD to different species.[7] Perhaps unsurprisingly, the toxicity of TCDD shows a difference of three orders of magnitude between the most susceptible guinea pigs and the more resistant hamsters or humans. TCDD is a substance whose toxicity is comparable to that of nicotine, for example, but probably not any more toxic, and therefore it is far from being the apocalyptic "super-toxin" described by green pressure groups. Their dramatic exaggerations, without differentiation and reservation, have been well received by the public and so the hazard posed by dioxin is generally perceived to be greater justified by the evidence.

To impartially evaluate the risks of dioxin, we need information on its generation and occurrence, on its path and mechanisms in the organism and finally, epidemiological data.

Generation and occurrence

Dioxins originate in all processes of combustion of organic material together with anorganic or organic substances which contain chlorine, at a temperature less than 1000° C, especially when catalysed by copper. For this reason, they are not just man-made but they

are also naturally generated by burning wood. For example it has been estimated that, on average as much as 60 kilograms of PCDDs are produced annually just from wild forest fires in Canada alone.[8] This is about 10 times more than the amount formed in the exceptional Seveso plant accident. Naturally generated TCDD/TCDFs are responsible for the fact that there were measurable background concentrations of dioxin before humans began to produce chlorine and chlorinated organic compounds.[9]

Man-made dioxins are often produced inadvertently during manufacturing processes, and become components of waste emissions from industrial plants, especially those which manufactured organochlorines. Important sources include the production of antiseptic hexachlorophene, the preservative pentachlorophenol, the fungicide hexachlorobenzene and the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), where TCDD is produced as a contaminant.[10] Furthermore, dioxins are created by waste incinerators, power plants and recycling processes for heavy metal, in particular by cable-burning factories, because of the combustion of PVC insulation together with copper.

One special case was the copper smelting factory in Marsberg, Southern Westphalia, Germany, where from 1938 to 1945 the poor copper ore was smelted together with coal and salt. The red clinker "Kieselrot" was a by-product, and about 800,000 tons of it were utilized until as recently as 1978, as a surfacing material for thousands of leisure centres, playgrounds and sport fields in Germany without perception of any consequent effects by users during these decades. Its high PCDD/xPCDF-contamination up to 200,000 µg/kg was not detected until 1991, but after this, public fears of dioxin led to the closure and decontamination of many such places at immense cost.[11]

Apart from these point sources of dioxin, there are many diffuse emissions, especially by cars which use leaded fuel, and through domestic heating. Dioxin emissions in the atmosphere have a half-life of about 3 to 5 days, but those deposited in the earth degrade slowly and their half-life is about 10 to 20 years. PCDD/PCDFs are

Table 12 **Contamination of the environment by dioxins, given in toxic equivalents (TEQ).**

Material	*TEQ (ng/kg)*
soil of farmland	2–8
soil farmland after sludge deposition	7–14
soil of woodland	20–30
soil of motorway roadside	< 2800
soil in Seveso, Italy	
zone R (mean; maximum)	7; <79
zone B (mean; maximum)	25; <360
zone A (mean; maximum)	1900; <45,000
soil in Times Beach, Mo, USA (mean; maximum)	50–100; <404,000
red clinker, Marsberg, Germany ("Kieselrot")	<200,000
soil in Rheinfelden, Germany (Dynamit Nobel)	<3,800,000
human milk from The Netherlands and Germany	5–100
'normal' non-contaminated cow milk	<3
meat (beef, mutton, pork)	<1
sea fish	about 20–40
fresh water fish	<5,000

extremely insoluble in water (the solubility of TCDD is 2×10^{-7} g/l) and they continue in the surface without being dispersed by rainfall. For the same reason, they are also not re-absorbed by roots. Vegetables contain undetectable traces if any, and dioxins do not play any significant role in most foods of plant origin. Two exceptions are kale and zucchini; dioxin accumulates in them to a certain degree.[12] Generally, the contamination of vegetables results from dioxin emissions, and foliaceous vegetables are more contaminated by dust than root vegetables. Table 12 shows the burden of some materials.

Intake and elimination of dioxins in the organism

In humans, respiratory and transcutaneous intake of PCDDs and PCDFs represent only about two percent of total intake. Two-thirds

Table 13 **Average daily intake of dioxins (pg per person) via food consumption in the early nineties in the Federal Republic of Germany[13]**

Food	*Consumption (g fat)*	*Intake TCDD (pg)*	*Total TEQ (pg)*	*Share*
Milk, milk products	27.6	4.6	41.7	32.00%
Meat, eggs + products	37.1	7	39	29.90%
Fish, fish products	1	5.1	33.9	26.00%
Vegetable	28	2.2	6.3	4.80%
Miscellaneous	6.9	1.1	9.4	7.30%
Total	100.6	20	130.3	100%

of dioxin contamination occurs from foods of animal origin, the rest results from dust on foods of plant origin. For instance, an average daily intake of dioxins via food consumption is given in Table 13.

The intake of TCDD/PCDFs leads to deposition in the adipose tissue of human beings. About 10 per cent of the concentration is found in the liver, and one percent in blood serum. There is a strong inverse correlation between the acute toxicity of TCDD and the relative portion of fatty tissue of the whole body mass. The fat has, so to speak, a detoxication power – by depositing dioxins and keeping them away from susceptible tissues, especially from the liver. However, dioxins can be mobilized from the fatty tissue by starvation or during lactation. Therefore, mother's milk contains relatively high concentrations of dioxins. Generally, dioxins are slowly eliminated from the body (with a biological half-life of 7.1 years, of 6 to 10 years, respectively, depending on the particular tissue in which they are stored). In the past, the rate of intake of dioxins was higher than the rate of elimination. The concentration of dioxins thus increased in proportion to age from <10 ng/kg fat at birth to about 70 ng/kg at the age of seventy.[14]

But as a result of decreasing environmental contamination, the accumulation rate is decreasing. For instance, in Germany the TEQ concentrations in human milk were decreasing from mean values

between 30–35 ng/kg fat in the mid-1980s to values of about 20 ng/kg fat in the early 1990s.[15]

Mode of action

There is a consensus that the first and essential step, before any effects are observed from TCDD in organisms, is the binding to and activation of the aromatic hydrocarbon receptor (AHR). It is activated by ligand binding and by dimerization with the AHR nuclear translocator (arnt). This complex interacts in the cell nucleus with the DNA and initiates a cascade of events by induction of genes encoding enzymes that catalyze the metabolism of foreign compounds.[16] In this way, they regulate the expression of enzymes, such as specific forms of cytochrome P450 that metabolizes lipid-soluble, foreign compounds and the enzymes provide a means for the rapid elimination of such xenobiotics.

The AHR is a member of the basic helix-loop-helix superfamily of DNA-binding proteins, and an essential protein – as an AHR-deficient mouse line has shown.[17] Almost half of these mice died shortly after birth, although the survivors reached maturity and were fertile. However, the survivors showed decreased accumulation of lymphocytes in the spleen and lymph nodes, although not in the thymus; their livers were reduced in size by 50 per cent and exhibited bile duct fibrosis. These effects illustrate that the AHR plays an important physiological role and its loss deprives the organism of its normal defence against some as yet unidentified endogenous toxic substances.

Therefore, the AHR is a general defence system. It not only binds to more or less toxic aromatic endogenous compounds, but also to exogenous substances. Apart from dioxin, there is – especially in foods of plant origin – also a broad spectrum of naturally-occurring aromatic compounds, and even anticarcinogenic flavonoids, polyphenols and indoles[18] which bind to and activate the AHR. This fact underlines the suggestion that many, if not all, of the toxic effects of dioxin which are mediated by the AHR may also be created by

other substances in the same way. For that reason dioxin does not possess toxic effects in all cases. If this is so, low concentrations of dioxin well below the dissociation constant of dioxin from the AHR are unlikely to lead to toxicity. Current knowledge suggests that there is every reason to believe that the biological response to dioxin begins slowly at a concentration of about 1–10 ng/kg. But it shoots up after passing a critical concentration about of 100 ng/kg reaching its maximum about at 10 mg/kg.[19] In this case, selective alterations of P450 expression may result from an imbalance between activation of toxic and/or carcinogenic compounds, and its detoxication in tissue.

However, it is unclear whether there are also other dioxin receptors beside AHR. There are some examples for such inconsistent effects caused by TCDD. Some hormone-like effects support this view.

Clinical manifestations of PCDD/PCDFs

Chloracne is the main symptom of an intoxication by dioxins. However, it is an unspecific toxic effect, caused not only by dioxins but also by all chlorinated aromatic compounds, (including DDT, PCB, and PCP). Indeed, chloracne has been known since 1899 as Perna disease because workers were contaminated with *per*chloro*na*phthaline. Furthermore, chloracne is correlated with vitamin A deficiency, which may be depleted by dioxin. But it is unclear whether chloracne is actually due to vitamin A deficiency. Finally, there are no clinical and histological differences between chloracne and *acne vulgaris* (common acne).

In Seveso, 447 persons fell ill with chloracne, but most of them recovered from it after some weeks. Eleven years later, only three persons continued to suffer from strong chloracne type 4. The serum TCDD levels of five persons from Seveso Zone A suffering from chloracne varied from 826 to 27,821 ng/kg but most of them had serum levels higher than 15,000 ng/kg. However, others without chloracne showed TCDD levels from 1772 to 10,439 ng/kg,

whereas the levels of general uncontaminated population were less than 20 ng/kg.[20] The complex causes of chloracne suggest that it is not possible to determine an exact threshold dose of TCDD.

About ten percent of those who suffered from chloracne were inflicted with various other skin problems following contamination by TCDD, including: itching, skin fragility, oiliness or thickening of skin, lack of perspiration, porphyria cutanea tarda, body hirsuteness, thinning of scalp hair and growth of longer, darker hair in the eyebrows.

Furthermore, a wide variety of other conditions were associated with exposure to dioxin: hepatic effects were described with hepatomegaly, elevated levels of liver enzymes and lipid metabolism disorder, manifesting in increased serum triglycerides, and hypo- as well as hypercholesterinemia. Even a high exposure to TCDD leads only to transient injuries,[21] but these are boosted by alcohol consumption. In no case was the wasting syndrome (showing hepatic oedema, starvation and cachexia) shown to occur in rats intoxicated with TCDD, observed in humans.

Gastrointestinal effects after dioxin contamination primarily involve nausea and a decreased anal sphincter tone. Other gastrointestinal diseases claimed to result from TCDD contact, for example gastritis or gastrointestinal ulcer disease, showed no statistically significant association with any measure of TCDD exposure.[22]

Central and peripheral nervous disorders were reported, such as an elevated suicide rate of men suffering from severe chloracne, loss of hearing, sense of smell or taste, neurasthenia characterized by tendency to anger or irritability, sleep disorders, and emotional instability.[23]

Chronic toxicity

Chronic toxicity of TCDD/TCDFs was purported to be due to mutagenic, carcinogenic, teratogenic effects as well as adverse effects on immunity and reproduction. The suspicion came from observations

in animals which were fed with relatively high doses of dioxin. The question whether humans exposed to lower concentrations are at risk can be answered only by exhaustive bio-statistical studies on the most highly exposed populations.

The toxic effects of high doses of dioxin on reproductive capacity of animals given high doses of dioxin include an elevated rate of abortion, miscarriage, stillbirth, deformity and malformation. But fertility disorders were not observed when rhesus monkeys were fed even with doses up to 25 ng TCDD/kg administered over a period of two years. The observations from the Seveso region are statistically consistent with the animal experiments (Bertazzi et al., 1993). Only the frequency of haemangiomas was somewhat higher than expected, but their spontaneous frequency is high in any case.[24]

The significance of another animal experiment in which rhesus monkeys developed endometriosis, is as yet unclear. In a group of monkeys fed daily doses of 25 ng dioxin/kg for four years, 71 per cent had moderate to severe disease after fifteen years, compared to 42 per cent of monkeys fed a lower dose of 5 ng/kg and compared to a control group which were not fed dioxin and without endometriosis.[25] Overall, embryotoxic effects of dioxin do not seem to occur in humans below a (high) daily dose of >1–10 ng TEQ/kg.

Preliminary observations show an alteration of the human sex ratio in the offspring of people exposed to high concentration of TCDD in zone A in Seveso. No males and only females were born during the first biological half-life of TCDD from 1976 to 1984 to families in which both father and mother had serum TCDD levels above of 100 ng/kg (measured in 1976). Altogether, there was an excess of 48 females versus 26 males. But this ratio declined to 64 females versus 60 males in the years from 1985 to 1994.[26]

However, the undoubted effects of dioxin on the organism seem to be balanced on a long-term basis by the human body's regulatory systems, as another example shows. The effect of dioxin on the function of the thyroid gland was known from animal studies, the thyroid hormone concentrations of newborn babies were investigated. After delivery, thyroxine (T4) and T4/thyroid binding

globulin (TBG) ratio were elevated to statistically significant levels in the high-exposure group of infants fed with mother's milk containing 38 (29–63) ng TEQ/kg compared with those who were given milk which contained only 19 (9–28) ng TEQ/kg. But eleven weeks after birth, compensation had occurred in the T4 and T4/TBG ratio.[27]

Finally, there may exist acute toxic effects of TCDD/TCDFs on the cellular immune system[28] as confirmed by AHR-deficient mice.[29] Long-term effects, for example skin prone to inflammation and infection, are claimed but not confirmed. Of course, similar processes are seen in *acne vulgaris* and the consequence of such a discovery would be the necessary acceptance of an immunodeficiency in all humans suffering from any form of acne. In any case, single observations of depressed reactions of T lymphocytes from humans contaminated by TCDD could not be evaluated with statistical significance.[30]

The conclusion from it is that there is a certain possibility of impairment of immune and reproductive system and the liver by very high concentrations of dioxin, but that such concentrations are seldom reached even in exposed and highly contaminated humans.

Carcinogenicity

In the late 1970s an important animal experiment was conducted showing that TCDD[31] possessed carcinogenic properties. The study's result induced terrible fears but these were largely due to ignorance and possibly even conscious scaremongering. However, there were scientific as well as popular misunderstandings around the study.

The scientific problem results from difficulties associated with transposing the results of animal experiments to humans.[32] In the experiments which found TCDD to be carcinogenic in animals, the doses of TCDD used were extraordinarily high. What was not taken into account was that at such large doses, many naturally occurring chemicals induce increased mitogenesis. Because of the correlation between mitogenesis and carcinogenesis, each mitogenic substance inevitably possesses a certain carcinogenic property.[33]

The popular misunderstandings concern the belief that cancer is a rare and irreversible one-step event caused by synthetic chemical carcinogens and that there is no safe dose or practical threshold below which no adverse effects occur. None of these perceptions are correct, although they seem to be responsible for regulations in many countries.

In reality, cancer is always a complex multi-step process triggered by mutagens, prevented or stopped by DNA repair enzymes as well as anticancer substances, and promoted by others including by misled hormonal and immunological control mechanisms of the organism. Therefore cancer induction on the cell level happens frequently, particularly since about half of all known natural as well as synthetic chemicals are probably 'carcinogenic'.[34]

However, in contrast to the hundreds of chemicals that have been observed to possess carcinogenic activity in laboratory animals, less than three dozen are known actually to induce cancer in humans. The reason that all other chemicals are under suspicion is that the traditional toxicological risk assessment assumes that there is a linear relationship between dose and effect. However, the existence of a threshold for carcinogenesis seems rather a good explanation for why macroscopic cancers fortunately develop rarely. If a threshold does exist, this means that many fears of carcinogens are unfounded.

Unlike most of the chemical carcinogens which have been identified in laboratory animals, TCDD does not appear to be directly genotoxic or to be converted to a genotoxic metabolite. In the cascade of events leading to cancer, TCDD is rather a promoter – as are many other compounds – inducing different enzymes and factors of cell growth. But it is by no means an initiating substance or a complete carcinogen which shows both an initiating and promoting function. The hormone-like properties of TCDD are especially due to opposite effects. On the one hand, TCDD enhances the growth of some forms of cancer, but on the other hand, it also inhibits the growth of hormone dependent tumours.[35] A further hormone effect is the dependence of tumour growth upon sex. Male

animals generally are more resistant to cancer induction by TCDD than females. Altogether, TCDD is neither a typical anticancer substance nor a typical carcinogen, but a co-carcinogen acting through epigenetic mechanisms.

Dioxin has frequently been the subject of scaremongering by campaigners and others, who claim that it induces cancer; equally the producers of dioxin have sought to counter such fears. As a result, numerous disputes concerning the 'true' impact of dioxin have erupted. In response, epidemiological studies were undertaken in order to answer the question about the carcinogenicity of TCDD. However, perhaps inevitably, these often came under fire from one side or the other. They were charged with alleged falsification of data, for example the early Monsanto studies[36], or with subjectively tendentious and unproven conclusions, for example the paper on the Boehringer Hamburg accident.[37]

Notwithstanding all of this, the epidemiologic studies show reliable results.[38] They found that mortality from several cancers previously associated with TCDD, i.e. cancers of stomach and liver, nasal cancers and Hodgkin's disease as well as non-Hodgkin lymphoma, was not significantly elevated in their cohorts in comparison with the general population. The mean serum TCDD levels, as adjusted for lipids, varied in the Fingerhut study in different sub-cohorts between 233 and 418 ng/kg, although all the workers had received their last occupational exposures 15 to 37 years earlier. Of course, the induced dioxin dose was higher by a factor of about 5 to 35. A mean level of 7 ng/kg was found in the control group of the unexposed population. Zober et al. described median values in blood of 8.4 ng/kg for the group without chloracne and 24.5 ng/kg for the group with chloracne.[39] The highest value observed by Zober et al. was 553 ng/kg,[40] which implies, extrapolating to the time of exposure 35 years before, a blood level of TCDD of more than 20,000 ng/kg, which is extremely high. Similar values were determined in Seveso as mentioned above.[41] Table 14 shows the results of the four studies.

One further result of the Fingerhut study in 1991 was a statistically significant increase in mortality for soft-tissue sarcoma (SMR

Table 14 **Mortality follow-up studies of persons exposed to TCDD by several studies**

Specification	*Bertazzi et al.*		*Collins et al.*	*Fingerhut et al.*	*Zober et al.*
Exposed persons	724	4,824	754	5172	247
Person-years of observation	2,313[1,3]	15,603[2,3]	23,198	116,748	8,398
	2,255[1,4]	15,781[2,4]			
Years of observation	9	9	38	15-37	34
All deaths	–	–	363	1052	78
Deaths by all cancers	7[1,3]	36[2,3]	102 (= 28%)	265 (= 25%)	23 (= 29%)
	7[1,4]	76[2,4]			
Standardized mortality ratios (SMR)	100[1,3] [50–210][5]	80[2,3] [60–110]	120 [90–140]	115 [102–130]	117 [80–166]
	70[1,4] [30–150]	110[2,4] [90–140]			
Deaths by respiratory cancers	0[1,3](expected 0.2)	2[2,3]	38	89[6]	4
	0[1,4](expected 1.8)	24[2,4]		40[7]	
SMR	–	-80[2,3] [20–340]	110 [80-150]	111[6] [89–137]	201 [69–460]
	–	-110[2,4] [80–170]		139[7] [99–189]	

1 Zone A 2 Zone B 3 Female 4 Male 5 CI = Confidence Interval 6 All Exposed 7 Exposed > 1 Year.

922; CI 190-2,695) as well as a weak increase in mortality from cancers of the trachea, bronchus, and lung (SMR 139, CI 99–189).[42] In 1993, Collins et al. confirmed these findings but they showed that all soft-tissue sarcomas occurred among workers with 4-amino-biphenyl exposure, whereas no soft-tissue sarcomas were found among workers with TCDD exposure alone.[43]

Finally, the excess mortality due to all malignancies, determined in the studies between the SMR values (baseline 100) and that of 120, 115, and 117 respectively,[44] result from overestimation of the SMR.

Two points are worth considering. First, the causes of death are well diagnosed in the verum groups, whereas the death certificates of the general population give a less precise diagnosis and are not exact. Summary causes of death are overvalued in death certificates and, conversely, rare and exact diagnoses are undervalued.[45] For that reason, the figures of well diagnosed deaths for example of soft-tissue sarcoma, are underestimated in the general population and overestimated in the group of exposed workers. Second, the possible contribution of life style factors as well as occupational exposure to other chemicals cannot be excluded. Excess mortality by soft-tissue sarcomas in the Fingerhut study was such a case, illustrated by Collins et al.[46]

In the end, the TCDD load resulting from occupational exposure (two orders of magnitude higher than ambient concentrations) may result in a small increased cancer risk – of about the same order of magnitude as some lifestyle factors, such as alcohol consumption and smoking. However, the studies are not conclusive. On the one hand, it is obvious that high dioxin levels are linked to cancer in animals. On the other hand, it is unclear whether carcinogenicity of dioxin varies according to concentration in a similarly extreme manner as it does in acute toxicity. But a general consensus exists that there is no evidence that near-background exposure levels are likely to cause cancer.

Health risk assessments

The search for adverse health effects from dioxin has found no unequivocal epidemiological evidence sufficient to link dioxin to human cancers, suppression of immune function, or reproductive effects, even for workers exposed to somewhat higher concentrations of dioxin. Chloracne is the only generally recognised result of dioxin exposure in humans. Therefore, any purported risk to the general population of near-background exposure levels should be refuted. This risk assessment is supported by the known mode of action of dioxin, and the fact that dioxin below its dissociation constant from the AHR is unlikely to lead to toxicity.

Nevertheless, some national agencies, for instance the US Environmental Protection Agency (EPA) or the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV) in Germany perpetuate a false risk assessment by blurring the boundary between science and policy.[47]

This obvious disparity between the concerns of scientists and that of the public and politicians is due to the different points of view. Most people find involuntary hazards – those beyond their control, such as the health risk from dioxin exposure – far more abhorrent than voluntary hazards, such as the cancer risk from smoking cigarettes. Moreover, people tend to find processes controlled by others – such as a factory pollution – more 'risky' than actions under their own control, such as driving a car. Therefore relatively low threshold values were assessed by these government agencies. But these thresholds and the regulations they justify cannot remove the uncertainties if the existing risks are not identified clearly.

Notes

1 Müller RK, 1993.
2 Kimmig & Schulz, 1957
3 Bosshardt, 1973
4 Anonymus, 1988
5 Wartenberg (1992).
6 Forth et al. (1987).
7 Müller HE (1991).
8 Abelson (1994).
9 Czuczwa et. al. (1985), Hashimoto et al. (1990).
10 Kimmig and Schulz (1957); May (1973).
11 Heudorf (1993).
12 Hülster (1994).
13 Beck (1994).
14 Beck (1994).
15 Beck (1994).
16 Birnbaum (1994); Hoffmann et al. (1991); Johnson (1991).
17 Fernandez-Salguero et al. (1995).
18 Prochaska et al. (1992).; Zhang et al. (1992, 1994).
19 Roberts (1991).
20 Anonymus (1988).
21 Mocarelli et al. (1986).
22 Calvert et al. (1992).
23 Barbieri et al. (1988); Oliver (1975).
24 Neubert (1985).
25 Rier et al. (1993).
26 Mocarelli et al. (1996).
27 Pluim et al. (1992).
28 Vos and Moore (1973).
29 Fernandez-Salguero (1995).
30 Hoffmann et al. (1986).
31 Kociba et al. (1978, 1979).
32 Rall (1988).
33 Ames and Gold (1990); Cohen & Ellwein (1990).
34 Huff et al. (1988).
35 Bertazzi et al. (1993).
36 Zack and Gaffey (1983); Roberts (1991).
37 Manz et al. (1991); Carlo & Sund (1991); Triebig (1991).
38 Bertazzi et al. (1993); Collins et al. (1993); Fingerhut et al. (1991); and Zober et al. (1990).
39 Zober et al. (1990).
40 Observed by Zober et al. (1990).
41 Anonymous (1988).
42 Fingerhut et al. (1991).
43 Collins et al. (1993).
44 Collins et al. (1993); Fingerhut et al. (1991); Zober et al. (1990).
45 Höpker & Burkhardt (1984).
46 Collins et al. (1993).
47 (Bradfield et al. 1994; Stone 1995).

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