THYROID CANCER

IARC SUPPLEMENT 7

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WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISKS TO HUMANS

Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs* Volumes 1 to 42

SUPPLEMENT 7

LYON, FRANCE

1987

B. Evidence for carcinogenicity to animals (*sufficient*)

Amitrole was tested for carcinogenicity in mice by oral administration, skin application and transplacental exposure, in rats by oral and subcutaneous administration and in hamsters by oral administration. After oral administration, it produced thyroid tumours and benign and malignant liver tumours in mice of each sex, benign and malignant thyroid tumours in male and female rats and benign pituitary tumours in female rats[1].

C. Other relevant data

No data were available on the genetic and related effects of amitrole in humans.

Amitrole did not induce micronuclei in bone-marrow cells of mice or unscheduled DNA synthesis in hepatocytes of rats treated *in vivo*. It induced transformation of Syrian hamster embryo cells and increased the incidence of sister chromatid exchanges in Chinese hamster ovary cells; both positive and negative results were reported for mutation in cultured rodent cells. Amitrole did not induce sex-linked recessive lethal mutations or aneuploidy in *Drosophila*; it induced chromosomal aberrations in plants. Both positive and negative results were obtained in assays for gene conversion and mutation in fungi, but amitrole induced aneuploidy. It was not mutagenic to bacteria and did not induce DNA damage[2].

References

[1]*IARC Monographs, 41*, 293-317, 1986
[2]*IARC Monographs, Suppl. 6*, 64-67, 1987

ANAESTHETICS, VOLATILE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Data from postal surveys of cancer incidence among working populations showed a higher rate of cancer among female operating-room personnel than among controls[1-4], partly reflecting an excess of leukaemia and lymphoma[2]. In one of the studies[4], a higher rate of cancer was reported among dental assistants with relatively heavy exposure to anaesthetics, reflecting a higher prevalence of cervical and uterine cancer in women with heavier exposure to anaesthetics than in those with a lighter exposure (significant only for cancer of the cervix). All of these postal surveys had major shortcomings[5], with response rates varying from 40-82%. Five mortality studies were carried out on anaesthetists[6-10]. A deficiency of deaths from cancer was seen in four[6,8-10]; however, in one study[6], there was an excess of deaths from lymphoma and myeloma (17 observed, 8.9 expected, with a ratio of 1.9 [95% confidence interval, 1.2-2.6]) and, in another, a possible excess of cancer of the pancreas[7]. Cancer incidence was also studied in 28 235 registered nurses. Minor excesses of breast cancer, lymphoma and acute myelogenous leukaemia were balanced by deficits in cancers at other sites. No significant difference was found for active operation and

Several studies have shown elevated standardized mortality ratios for cancers at various sites among workers in the rubber industry (see p. 332), where there is potential exposure to 1,3-butadiene, among other chemicals[3].

B. Evidence for carcinogenicity to animals (*sufficient*)

1,3-Butadiene was tested for carcinogenicity in mice by inhalation. It was carcinogenic to animals of each sex, producing haemangiosarcomas of the heart, malignant lymphomas, alveolar/bronchiolar adenomas and carcinomas, papillomas and carcinomas of the stomach, hepatocellular adenomas and carcinomas, mammary-gland carcinomas and granulosa-cell tumours of the ovary[1]. Exposure of rats to 1,3-butadiene by inhalation resulted in increased incidences of tumours of the mammary gland, thyroid and pancreas[4].

C. Other relevant data

No data were available on the genetic and related effects of 1,3-butadiene in humans. It induced micronuclei and sister chromatid exchanges in bone-marrow cells of mice but not of rats treated *in vivo*. It was mutagenic to bacteria[5].

References

[1]*IARC Monographs, 39*, 155-179, 1986

[2]Matanoski, G.M. & Schwartz, L. (1987) Mortality of workers in styrene-butadiene polymer production. *J. occup. Med., 29*, 675-680

[3]*IARC Monographs, 28*, 183-230, 1982

[4]Owen, P.E., Glaister, J.R., Gaunt, I.F. & Pullinger, D.H. (1987) Inhalation toxicity studies with 1,3-butadiene. 3. Two year toxicity/carcinogenicity study in rats. *Am. ind. Hyg. Assoc. J., 48*, 407-413

[5]*IARC Monographs, Suppl. 6*, 126-128, 1987

1,4-BUTANEDIOL DIMETHANESULPHONATE (MYLERAN) (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Leukaemia patients who had been treated with Myleran developed many different cytological abnormalities, and some developed carcinomas[1-8]. A follow-up study of patients with bronchial carcinoma who were randomized to chemotherapy after pulmonary resection showed that of 69 who had been given Myleran and had survived five years, four developed acute nonlymphocytic leukaemia (three myelomonocytic leukaemias and one erythroleukaemia) and 15 others developed pancytopenia in the succeeding four years; among 148 other survivors at five years who had not been given Myleran, one case of pancytopenia appeared. Risk was not dose-related, although the cases were confined to those who had received no radiation and no other cytotoxic agent[9].

[22]Nettesheim, P., Creasia, D.A. & Mitchell, T.J. (1975) Carcinogenic and cocarcinogenic effects of inhaled synthetic smog and ferric oxide particles. *J. natl Cancer Inst., 55*, 159-169

[23]Feron, V.J., Emmelot, P. & Vossenaar, T. (1972) Lower respiratory tract tumours in Syrian golden hamsters after intratracheal instillations of diethylnitrosamine alone and with ferric oxide. *Eur. J. Cancer, 8*, 445-449

[24]*IARC Monographs, Suppl. 6*, 310-311, 1987

HEXACHLOROBENZENE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

No report of a direct association between hexachlorobenzene and human cancer is available. Hepatocellular carcinoma has been associated with porphyria[1-5]. However, although abnormal porphyrin metabolism persisted at least 20 years after an epidemic of porphyria cutanea tarda in Turkey, caused by consumption of grain treated with hexachlorobenzene[6], no excess cancer occurrence has been reported in this population 25 years after the accident[7].

B. Evidence for carcinogenicity to animals (*sufficient*)

Hexachlorobenzene was tested by oral administration in one experiment in mice and in one in hamsters. In mice, it produced liver-cell tumours in animals of each sex; in hamsters of each sex, it produced hepatomas, liver haemangioendotheliomas and thyroid adenomas. An experiment involving intraperitoneal administration in mice was considered to be inadequate[6]. In a study in rats fed hexachlorobenzene in the diet, hepatomas, hepatocellular carcinomas, bile-duct adenomas and renal-cell adenomas were observed[8]. In a two-generation feeding study in rats with lower dose levels, increased incidences of parathyroid adenomas and adrenal phaeochromocytomas were observed in animals of each sex and liver neoplastic nodules in females of the F_1 generation[9]. After 90 weeks' feeding of hexachlorobenzene to rats, 100% of surviving females and only 16% of males had developed liver tumours[10].

C. Other relevant data

No data were available on the genetic and related effects of hexachlorobenzene in humans. It did not induce dominant lethal mutations in rats treated *in vivo*. It did not induce chromosomal aberrations in cultured Chinese hamster cells or mutation in bacteria[11].

References

[1]Kordač, V. (1972) Frequency of occurrence of hepatocellular carcinoma in patients with porphyria cutanea tarda in long-term follow-up. *Neoplasma, 19*, 135-139

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF CARCINOGENIC RISKS TO HUMANS

Occupational Exposures in Petroleum Refining; Crude Oil and Major Petroleum Fuels

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1989

3.3 Epidemiological studies and case reports of carcinogenicity to humans

(*a*) *Cohort study*

A large retrospective cohort mortality study of US petroleum producing and pipeline workers was reported by Divine and Barron (1987). To be included in the study, men had to have been employed for at least six months at a producing or pipeline location and to have worked at some time during the period 1946–80. Vital status was ascertained for 97.8% of the cohort, which comprised 11 098 white men; death certificates were obtained for all but 3.4% of the deceased. Complete occupational histories were available from company records. Standardized mortality ratios (SMRs) were calculated in comparison with rates for US white males, and mortality was studied by length of employment, latency, whether producing or pipeline workers, and selected job categories. The SMR for all causes of death was significantly low (1886 observed; SMR, 0.63; 95% confidence interval [CI], 0.61–0.66), as was that for all cancers (393 observed; SMR, 0.68; 95% CI, 0.61–0.75). There was a significant excess of thyroid cancer among men employed as pumper-gaugers in petroleum production, but this was based on four cases only. A significant deficit of lung cancer (109 observed; SMR, 0.61; 95% CI, 0.50–0.73) was found among producing and pipeline workers, and no death from testicular cancer was observed although 3.2 were expected.

(*b*) *Case-control studies*

(i) *Lung cancer*

In an attempt to explain an excess of lung cancer cases observed in a cluster of parishes in Louisiana, USA, Gottlieb *et al.* (1979) conducted a case-control study, the design of which is described in the monograph on occupational exposures in petroleum refining (p. 102). An elevated risk for lung cancer was observed among black men aged over 53 years who had been employed in petroleum exploration and production (odds ratio, 1.6; 95% CI, 1.0–2.6). By logistic analysis, the ratio associated with crude oil exploration and drilling was three fold among persons over the age of 62 in parishes with petroleum or paper industries. [The Working Group noted that, since information used in this study was extracted directly from death certificates and since no account was taken of cigarette smoking, caution should be applied in interpreting the results.]

Gottlieb (1980) reanalysed the risk of lung cancer in relation to work in the petroleum mining and refining industry in the men included in the previous study. A group of 200 men with lung cancer and 170 control men who had worked in petroleum mining (125 cases, 112 controls) and refining (75 cases, 58 controls) were identified. The odds ratio for lung cancer associated with employment in the petroleum industry (mining and refining combined) was estimated at 1.2 (95% CI, 1.1–1.4). For welders, operators, boiler makers and painters, and oil-field workers taken as a group (mining and refining combined), the odds ratio was 2.3 (95% CI, 1.4–3.9). [The Working Group noted that information on exposure was extracted directly from death certificates; that no information on cigarette smoking was available; that cases were older than controls, which, in itself, may explain the difference observed; and that mining and refining occupations were combined.]

compounds, including hydrocarbons and hydrogen sulfide. Skin contact with crude oils, which contain polycyclic aromatic compounds, may also occur during these operations. Accidental releases of crude oil into the aquatic environment are also potential sources of human exposure.

4.2 Experimental data[1]

Samples of crude oil from single sources and composite blends were tested for carcinogenicity by skin application in ten experiments in mice. Four samples of crude oil from single sources produced benign and malignant or unspecified skin tumours in two experiments. In one experiment, a composite sample produced a low incidence of skin carcinomas; in a similar experiment using the same treatment regimen but a blend of slightly different composition, no skin tumour was observed. The conduct and/or reporting of the results of six other experiments in mice were inadequate for evaluation.

Skin application to mice of fractions of two crude oil samples distilled under laboratory conditions and corresponding to various refinery streams produced skin tumours.

One sample of crude oil produced skin papillomas in rabbits in one experiment. Two other experiments were inadequate for evaluation.

4.3 Human data

In a retrospective cohort mortality study of a large group of male employees in petroleum producing and pipeline operations, mortality from all types of cancer was low, except from thyroid cancer. There was a significant deficit of lung cancer and no death from testicular cancer.

In a population-based case-control study, an elevated risk for lung cancer was observed among older men who had been employed in petroleum exploration and production. Reanalysis of the risk for lung cancer among men who had worked in the petroleum mining and refining industry showed an elevated risk for lung cancer among welders, operators, boiler makers, painters and oil-field workers taken as a group; no data were available on smoking habits.

In one of two case-control studies, an excess risk for testicular cancer was observed among petroleum and natural gas extraction workers. No such excess was found in the other study.

In a case-control study of cancer at many sites, an association was observed between exposure to crude oil and rectal and squamous-cell lung cancer. However, the association was based on small numbers and may have been confounded by life style factors.

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[1]Subsequent to the meeting, the Secretariat became aware of a study in which skin tumours were reported in mice after application to the skin of East Wilmington crude oil (Clark *et al.*, 1988).

WORLD HEALTH ORGANIZATION
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IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

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Painting, Firefighting, and Shiftwork

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testicular cancer. Eleven testicular cancers were observed versus 7.1 expected (SIR, 1.55; 95% CI: 0.8–2.8). For the years 1990–1996, the SIR for testicular cancer was 3.0 (95% CI: 1.3–5.9).

Ma *et al.* (2005) examined age- and gender-adjusted mortality rates of 36 813 professional firefighters employed during 1972–1999 in Florida, USA, and compared those with that of the Florida general population. The study population consisted of 34 796 male and 2017 female professional firefighters. The racial/ethnic composition was caucasian (90.1%), hispanic (7%), and black (6.5%). Employment as a firefighter was ascertained from employment records in the Florida State Fire Marshall Office. Surrogate information on occupational exposures in firefighting was collected by examining the year of certification and duration of employment as a firefighter. No information was collected on smoking histories. A total of 1411 male and 38 female deaths with known causes were identified in this cohort. In male firefighters, a deficit of overall mortality from cancer was observed (SMR, 0.85). Excess risks were observed for male breast cancer (SMR, 7.41; 95% CI: 1.99–18.96), and thyroid cancer (SMR, 4.82; 95% CI: 1.30–12.34), each based on four cases. Mortality from bladder cancer was increased and approached statistical significance (SMR, 1.79; 95% CI: 0.98–3.00). Female firefighters had similar overall cancer mortality patterns to Florida women (SMR, 1.03), but the numbers were small for specific cancer sites.

In a further analysis of the same cohort, Ma *et al.* (2006) determined the relative cancer risk for firefighters in the State of Florida compared with the Florida general population. Employment as a firefighter was ascertained from employment records in the Florida State Fire Marshall Office. Cancer incidence was determined through linkage to the Florida Cancer Data System, a statewide cancer registry estimated to capture 98% of cancers in Florida residents. No pathological verification of cancer diagnoses was undertaken. A total of 970 male and 52 female cases of cancer were identified; 6.7% of the cohort were lost to follow-up. Male firefighters had significantly increased incidence rates of cancers of the bladder (SIR, 1.29; 95% CI: 1.01–1.62), testis (SIR, 1.60; 95% CI: 1.20–2.09), and of the thyroid (SIR, 1.77; 95% CI: 1.08–2.73). Female firefighters had significantly increased incidence rates of overall cancer (SIR, 1.63; 95% CI: 1.22–2.14), cervical (SIR, 5.24; 95% CI: 2.93–8.65) and thyroid cancers (SIR, 3.97; 95% CI: 1.45–8.65), and Hodgkin disease (SIR, 6.25; 95% CI: 1.26–18.26).

2.2 Case–control studies

Case–control studies have been used to examine the risk of firefighting and its association with various types of cancers. In all but one of these studies, ten or fewer firefighters were included in the case and/or control group. Several studies combined broad occupational categories with heterogeneous exposures such as firefighter and fireman, with the latter not necessarily working as a firefighter. These types of studies may result in exposure misclassification. Even within specific occupational groups such as firefighters, all would not have the same intensity or type of exposures. The

Table 2.6 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Bates (2007) California, USA 1988–2003	Oesophagus Colorectum Lung Melanoma Prostate Testis Bladder Brain Thyroid Leukaemias Non-Hodgkin lymphoma Multiple myeloma	3659 cases (all men) from the California Cancer Registry, aged 21–80 years; 94% histologically confirmed	All other males in registry that were not firefighters (n=800448) from California Cancer Registry except those diagnosed with cancers of the lung, bronchus, prostate, colorectum, and skin melanomas.	California Cancer Registry records	Oesophagus Stomach Colorectum Caecum Pancreas Lung & bronchus Melanoma Prostate Testis Bladder Kidney & renal pelvis cancer Brain Thyroid cancer Leukaemias Non-Hodgkin lymphoma Multiple myeloma	62 51 282 52 63 495 323 1144 70 174 101 71 32 100 159 37	1.48 (1.14–1.91) 0.80 (0.61–1.07) 0.90 (0.79–1.03) 1.09 (0.82–1.44) 0.90 (0.70–1.17) 0.98 (0.88–1.09) 1.50 (1.33–1.70) 1.22 (1.12–1.33) 1.54 (1.18–2.02) 0.85 (0.72–1.00) 1.07 (0.87–1.31) 1.35 (1.06–1.72) 1.17 (0.82–1.67) 1.22 (0.99–1.49) 1.07 (0.90–1.26) 1.03 (0.75–1.43)	SES quintile	Use of other cancer controls may have biased study toward null

SES, socioeconomic status

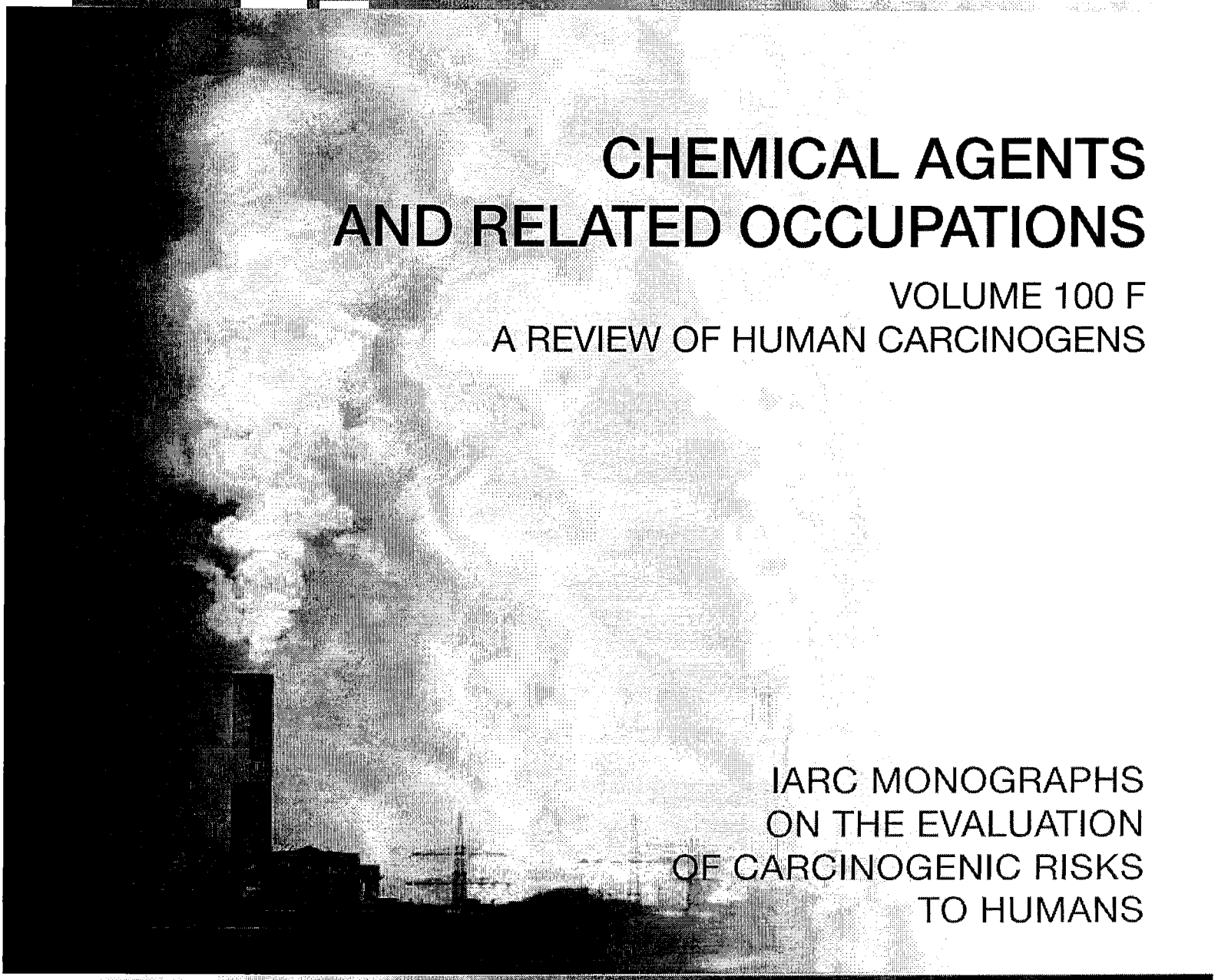
population [SMR, 1.16; 95% CI: 1.02–1.32; 219 observed cases]. For the small group of ex-shiftworkers, 29 deaths were observed versus 25.9 expected [SMR, 1.12; 95% CI: 0.75–1.61], and in the group of day workers, 201 deaths versus 197.1 were observed during follow-up [SMR, 1.02; 95% CI: 0.88–1.17]. For death from cancers of the lung, stomach, bladder, and leukaemia, observed versus expected numbers were, respectively, 94/84.4, 36/25.2, 7/6.6, and 2/3.7 among shiftworkers. Similar patterns were seen in day workers and in ex-shiftworkers. [This study was based on a survivor population with 10 years or more experience of shiftwork which may have underestimated a true increased risk if less than 10 years of shiftwork increased the mortality.]

A census-based ecological cohort study from Sweden included all members of the Swedish population (≥ 20 hours/week) in both 1960 and 1970 (Schwartzbaum *et al.*, 2007). The censuses included individual information about social status and industry but not about work schedules. Therefore, a job–exposure matrix was established for assessment of shiftwork. It relied on a sample of the Swedish population ($n = 46\ 438$) collected during 1977–1981, which included information on usual occupation and work schedules. Shiftwork was defined as a schedule with three or more possible shifts per day or work hours during the night for at least one day during the week preceding the interview. About 3% of the men and less than 0.3% of the women participating in the censuses were classified as having done shiftwork, defined by working in industries in 1960 and 1970 where at least 40% of the participants from the survey had reported such a work schedule. Follow-up for cancer in the Swedish Cancer registry was from 1971–1989, and SIRs were calculated on the basis of person–years of follow-up and national rates of specific cancers taken from the Swedish Cancer registry. The SIRs for cancer among men were all close to unity during the 19 years of follow-up, except for kidney (1.14; 95% CI: 1.00–1.31), skin (1.20; 95% CI: 1.02–1.41), and other and unspecified cancers (1.27; 95% CI: 1.07–1.50). For the subgroup of men participating in the 1970 census only, the SIR for thyroid cancer was elevated (1.35; 95% CI: 1.02–1.79). Results changed minimally when the shiftwork status was based only on the 1970 census or other attempts to change the exposure definition. [The major limitation of this study was an unavoidable potential for misclassification of exposure resulting in null results, and to some extent, uncontrolled confounding. Cohort members were followed-up to 1989, although follow-up through 2006 had been possible].

2.3 Aircraft crew

Cancer risk of airline personnel has been studied since the 1990s in about ten countries. The main reason to study these cohorts has been exposure to cosmic radiation, and sometimes passive smoking or electromagnetic fields. Shiftwork as causal factor has not been explicitly mentioned, but in the latest studies, there has be discussion on the potential role of frequent disruptions of circadian rhythm. An alteration in melatonin metabolism decreasing the oncostatic function of this hormone has been hypothesized to be a potential biological mechanism. [It has been questioned whether flight attendants should be considered as shiftworkers.]

IARC MONOGRAPHS



CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

The epidemiological evidence for an association with specific subtypes of haematolymphatic malignancies is weaker, mainly since numbers are lower, giving imprecise risk estimates. However, when malignant lymphomas and leukaemias are distinguished, the evidence is strongest for leukaemia.

3. Cancer in Experimental Animals

3.1 1,3-Butadiene

Studies on the carcinogenesis of 1,3-butadiene in rats and mice have been reviewed in previous IARC *Monographs* (IARC, 1999, 2008) and by Grosse *et al.* (2007). The results of adequately conducted carcinogenicity studies are summarized in Table 3.1. There were no additional studies reported in the published literature since *IARC Monograph* Volume 97 (IARC, 2008).

1,3-Butadiene was tested for carcinogenicity by inhalation exposure in one study in rats and four studies in mice.

Inhalation of 1,3-butadiene induced tumours in rats at exposure concentrations ranging from 1000 to 8000 ppm [2200–17650 mg/m^3], and in multiple organs in mice at exposure concentrations ranging from 6.25 to 1250 ppm [13.8–2760 mg/m^3]. In rats, 1,3-butadiene caused a significantly increased incidence of carcinomas of the Zymbal gland, sarcomas of the uterus, adenomas and carcinomas (combined) of the mammary gland, and follicular cell adenomas of the thyroid gland in females. In males, it caused malignant gliomas and adenomas of the pancreas and testes in males (Owen *et al.*, 1987; Owen & Glaister, 1990; Melnick *et al.*, 1993; Melnick & Huff, 1993). In mice of both sexes, 1,3-butadiene caused a significantly increased incidence of Harderian gland adenomas and carcinomas, heart haemangiosarcomas, lymphoid tissue neoplasms (lymphoma, histiocytic sarcoma), lung adenomas and carcinomas, hepatocellular adenomas and carcinomas, and fore-stomach papillomas and carcinomas. It caused mammary gland cancers, benign tumours and carcinomas of the ovary, and skin sarcomas in females. It also caused preputial gland carcinomas and kidney tubule adenomas in males (NTP, 1984, 1993; Huff *et al.*, 1985; Miller *et al.*, 1989; Melnick *et al.*, 1990a, b, 1993; Melnick & Huff, 1993; Hong *et al.*, 2000; Melnick & Sills, 2001; Kim *et al.*, 2005). No increased incidence of tumours was observed in one study in mice exposed once to 1,3-butadiene at concentrations up to 10 000 ppm [22000 mg/m^3] (Bucher *et al.*, 1993).

3.2 Diepoxybutane

Diepoxybutane, a metabolite of 1,3-butadiene, was tested for carcinogenicity by inhalation in one study in rats and one study in mice, by four skin-application studies in mice, by one subcutaneous injection study in rats and two such studies in mice, and by one gavage and one intraperitoneal injection study in mice (Tables 3.1, 3.2, 3.3, 3.4).

Diepoxybutane increased the incidence of adenomas of the Harderian gland in female mice, and of squamous cell carcinoma of the nose in female rats after inhalation exposure (Henderson *et al.*, 1999, 2000). Subcutaneous injection resulted in an increased incidence of fibrosarcomas in female rats and female mice. The gavage study in mice did not produce any tumours (Van Duuren *et al.*, 1966). Intra-peritoneal injection led to an increased incidence of lung tumours in strain A/J mice (Shimkin *et al.*, 1966). Two skin-application studies in mice resulted in an increased incidence of dermoid carcinomas (Van Duuren *et al.*, 1963, 1965).

cancers including major cancers are, overall, inconsistent between studies. It should be borne in mind that the general population is exposed to levels that are much lower than those experienced by the industrial populations.

The Working Group did not review the epidemiological evidence of other PCDDs, PCDFs or PCBs with a dioxin-like activity.

3. Cancer in Experimental Animals

3.1 *2,3,7,8-Tetrachlorodibenzo-para-dioxin*

Carcinogenicity studies with several strains of rats, mice and Syrian hamsters treated with 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) via the oral route (gavage or diet), by intra-peritoneal injection, or by skin application have been reviewed in *IARC Monograph* Volume 69 (IARC, 1997). At the time, the review of the available data led to the conclusion that there is *sufficient evidence* in experimental animals for the carcinogenicity of TCDD. The present *Monograph* also evaluates relevant carcinogenicity studies in TCDD-treated experimental animals that were published since 1997. The results of adequately conducted carcinogenicity studies are summarized below and in Table 3.1 and Table 3.2.

TCDD was tested for carcinogenicity by oral administration (gavage or dose feed) in four studies in mice and six studies in rats, by skin (topical) application in two studies in mice, by intraperitoneal injection in one study in mice, one study in rats and one study in hamsters and by subcutaneous injection in one study in hamsters. TCDD produced tumours in both sexes of mice and rats, and in multiple organs and tissues.

Oral administration of TCDD caused increased incidences of thyroid follicular adenomas and hepatocellular adenomas and carcinomas in male and female mice, of alveolar/bronchiolar adenomas and carcinomas in male mice, and of histiocytic lymphomas and subcutaneous fibrosarcomas in female mice. In rats, it caused increased incidences of hepatocellular adenomas in males and females, cholangiocarcinomas and hepatocellular carcinomas in females, lung cystic keratinizing epitheliomas and squamous-cell carcinomas in females, adrenal gland (cortex) adenomas and squamous-cell carcinomas of the hard palate/nasal turbinates in males and females, tongue squamous-cell carcinomas and thyroid follicular adenomas and carcinomas combined in males, subcutaneous fibromas in males and subcutaneous fibrosarcomas in females, and pituitary adenomas, uterine and oral mucosa (gingival) squamous-cell carcinomas and pancreatic adenomas and carcinomas combined in females (Van Miller *et al.*, 1977; Kociba *et al.*, 1978; Tóth *et al.*, 1979, NTP, 1982a, 2006a; Della Porta *et al.*, 1987; Goodman & Sauer, 1992; Hays *et al.*, 1997, Yoshizawa *et al.*, 2005). Skin application or gavage caused benign and malignant tumours of the skin in female mice including transgenic mice (NTP, 1982b; Wyde *et al.*, 2004). Hamsters that received TCDD by intraperitoneal or subcutaneous injection developed squamous-cell carcinomas of the facial skin (Rao *et al.*, 1988). Intraperitoneal injection caused increased incidence of hepatocellular adenomas and carcinomas in female mice and of lymphomas in male and female mice (Della Porta *et al.*, 1987).

Several studies in mice showed that administration of TCDD with known carcinogens enhanced the incidence of skin papillomas, lung adenomas, liver adenomas and hepatoblastomas. In female rats, TCDD co-administered with various nitrosamines enhanced the incidence of focal hepatic lesions. In one study, TCDD enhanced the incidence of lung carcinomas in ovariectomized female rats following administration of *N*-nitrosodiethylamine (NDEA) (IARC, 1997). In two more recent studies in female rats, TCDD given orally or subcutaneously enhanced

2,3,7,8-Tetrachlorodibenzodioxin

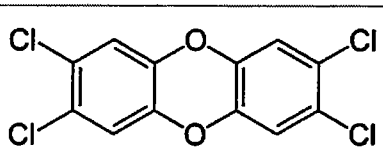
From Wikipedia, the free encyclopedia

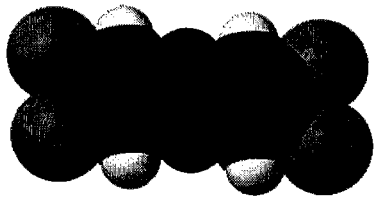
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (**TCDD**) is a polychlorinated dibenzo-*p*-dioxin (sometimes shortened, though inaccurately, to simply "dioxin") with the chemical formula $C_{12}H_4Cl_4O_2$. TCDD is a colorless solid with no distinguishable odor at room temperature. It is usually formed as a side product in organic synthesis and burning of organic materials.

TCDD is the most potent compound (congener) of its series (polychlorinated dibenzodioxins, known as PCDDs or simply dioxins) and became known as a contaminant in Agent Orange, an herbicide used in the Vietnam War.[4] TCDD was released into the environment in the Seveso disaster.[5] It is a persistent environmental contaminant usually present in a complex mixture of dioxin-like compounds, and is a carcinogen.[6]

Contents

2,3,7,8-Tetrachlorodibenzodioxin





Names	
IUPAC name	2,3,7,8-tetrachlorodibenzo[*b*,*e*][1,4]-dioxin [1]
Other names	Tetradioxin; Tetrachlorodibenzodioxin; Tetrachlorodibenzo-*p*-dioxin
Identifiers	
CAS Number	1746-01-6 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=1746-01-6) ✓
Abbreviations	TCDD; TCDBD
ChEBI	CHEBI:28119 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=28119) ✓
ChEMBL	ChEMBL30327 (https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/ChEMBL30327) ✓
ChemSpider	14865 (http://www.chemspider.com/Chemical-Structure.14865.html) ✓
Jmol 3D model	Interactive image (http://chemapps.stolaf.edu/jmol/jmol.php?model=Clc2cc1Oc3c%28Oc1cc2Cl%29cc%28Cl%29c%28Cl%29c3)
KEGG	C07557 (http://www.kegg.jp/entry/C07557) ✓
PubChem	15625 (https://pubchem.ncbi.nlm.nih.gov/compound/15625)
UNII	DO80M48B6O (http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=DO80M48B6O) ✗
InChI	
SMILES	
Properties	
Chemical formula	$C_{12}H_4Cl_4O_2$
Molar mass	321.97 g/mol
Appearance	colorless to white crystalline solid[2]
Density	1.8 g cm^{-3}
Melting point	305 °C (581 °F; 578 K)
Solubility in water	0.2 µg/L at 25 °C[3]
log P	6.8
Vapor pressure	1.5×10^{-9} mmHg

Health effects

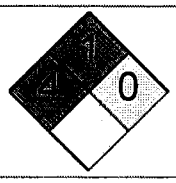
The Expert Group of the World Health Organization considered developmental toxicity as the most pertinent risk of dioxins to human beings.[7] Because people are usually exposed simultaneously to a number of dioxin-like chemicals, a more detailed account is given at dioxins and dioxin-like compounds.

Cancer

TCDD was classified in 1997 by the International Agency for Research on Cancer as a carcinogen for humans (group 1).[6] In the occupational cohort studies available for the

classification, the risk, even at very high exposures, was weak and borderline detectable.[8][9] Therefore, human data were not deemed sufficient, and the classification was, in essence, based on animal experiments and mechanistic considerations.[6] This has been criticized as a deviation from IARC classification rules.[10] It is much debated whether TCDD is carcinogenic only at high doses which also cause toxic damage of tissues.[11][12][13] Moreover, a recent review concludes that, after 1997, further studies do not support an association between TCDD exposure and cancer risk.[14] New studies include the update of Vietnam veteran studies from Ranch Hand operation, which concluded that after 30 years the results do not provide evidence of disease.[15]

There is also direct epidemiological evidence that TCDD is not carcinogenic at low doses, and in some studies cancer risk has even decreased.[16] This is called a J-shape dose-response, low doses decrease the risk, and only higher doses increase the risk.[17]

Hazards	
Main hazards	carcinogen, teratogen[2]
EU classification (DSD)	 T+
R-phrases	R26/27/28 R45
S-phrases	S36/37 S62
NFPA 704	
Flash point	164.2 °C (327.6 °F; 437.3 K)
US health exposure limits (NIOSH):	
PEL (Permissible)	none[2]
REL (Recommended)	Ca[2]
IDLH (Immediate danger)	N.D.[2]
Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa).	
✗ verify (what is ✓✗ ?)	
Infobox references	

Mechanism of action

TCDD and dioxin-like compounds act via a specific receptor present in all cells: the aryl hydrocarbon (AH) receptor.[18][19][20] This receptor is a transcription factor which is involved in expression of genes; in fact it has been shown that high doses of TCDD either increase or decrease the expression of several hundred genes in rats.[21] Genes of enzymes activating the breakdown of foreign and often toxic compounds are classic examples of such genes. TCDD increases the enzymes breaking down, e.g., carcinogenic polycyclic hydrocarbons such as benzo(a)pyrene.[22]

These polycyclic hydrocarbons also activate the AH receptor, but less than TCDD and only temporarily.[22] Even many natural compounds present in vegetables cause some activation of the AH receptor.[23] This phenomenon can be viewed as adaptive and beneficial, because it protects the organism from toxic and carcinogenic substances. Excessive and persistent stimulation of AH receptor, however, leads to a multitude of adverse effects.[22]

The physiological function of the AH receptor has been the subject of continuous research. One obvious function is to increase the activity of enzymes breaking down foreign chemicals or normal chemicals of the body as needed. There may be other functions, however, related to growth of various organs or other regulatory functions. The AH receptor is phylogenetically highly conserved transcription factor with a history of at least 500 million years, and found in all vertebrates, and its ancient analogs are important regulatory proteins even in more primitive species.[20] In fact, knock-out animals with no AH receptor are prone to illness and developmental problems.[20] Taken together, this implies the necessity of a basal degree of AH receptor activation to achieve normal physiological function.

While the mutagenic and genotoxic effects of TCDD are sometimes disputed[11] and sometimes confirmed[24] it does foster the development of cancer. Its main action in causing cancer is cancer promotion; it promotes the carcinogenicity initiated by other compounds. Very high doses may, in addition, cause cancer indirectly; one of the proposed mechanisms is oxidative stress and the subsequent oxygen damage to DNA.[12] There are other explanations such as endocrine disruption or altered signal transduction.[11][25] The endocrine disrupting activities seem to be dependent on life stage, being anti-estrogenic when estrogen is present (or in high concentration) in the body, and estrogenic in the absence of estrogen.[26]

Teratogenic effects

In Vietnam and the USA teratogenic or birth defects were observed in children of persons that were exposed to Agent Orange or 2,4,5-T that contained TCDD as an impurity out of the production process. However the scientific data supporting a causal link between Agent Orange/dioxin exposure and birth defects is controversial and weak, in part due to poor methodology. In 2006 Anh Duc Ngo and

colleagues, of the University of Texas Health Science Center in Austin, published a meta-analysis that exposed a large amount of heterogeneity/(different findings) between studies, a finding consistent with a lack of consensus on the issue.[27] Despite this, statistical analysis of the studies they examined resulted in data that the increase in birth defects/relative risk(RR) from exposure to agent orange/dioxin "appears" to be on the order of 3 in Vietnamese funded studies but 1.29 in the rest of the world. With a casual relationship near the threshold of statistical significance in still-births, cleft palate, and neural tube defects, with spina bifida being the most statistically significant defect.[28] The large discrepancy in RR between Vietnamese studies and those in the rest of the world have been suggested to be due to bias in the Vietnamese studies.[27]

Sources

TCDD has never been produced commercially except as a pure chemical for scientific research. It is, however, formed as a synthesis side product when producing certain chlorophenols or chlorophenoxy acid herbicides.[8] It may also be formed along with other polychlorinated dibenzodioxins and dibenzofuranes in any burning, especially if certain metal catalysts such as copper are present (see dioxins and dioxin-like compounds).[29]

The greatest production occurs from waste incineration, metal production, and fossil-fuel and wood combustion.[30] Total US emissions of PCCD/Fs were reduced from ca. 14 kg TEq in 1987 to 1.4 kg TEq in 2000.[31]

Other animals

By far most information on toxicity of dioxin-like chemicals is based on animal studies utilizing TCDD.[4][20][32][33] Almost all organs are affected by high doses of TCDD. In short-term toxicity studies in animals the typical effects are anorexia and wasting, and even after a huge dose animals die only 1 to 6 weeks after the TCDD administration.[33] Seemingly similar species have varying sensitivities to acute effects: lethal dose for a guinea pig is about 1 µg/kg, but to a hamster it is more than 1,000 µg/kg. A similar difference can be seen even between two different rat strains.[33] Various hyperplastic (overgrowth) or atrophic (wasting away) responses are seen in different organs, thymus atrophy is very typical in several animal species. TCDD also affects the balance of several hormones. In some species, but not in all, severe liver toxicity is seen.[20][33] Taking into account the low doses of dioxins in the present human population, only two types of toxic effects have been considered to cause a relevant risk to humans: developmental effects and cancer.[20]

Developmental effects

Developmental effects occur at very low doses in animals. They include frank teratogenicity such as cleft palate and hydronephrosis.[34] Development of some organs may be even more sensitive: very low doses perturb the development of sexual organs in rodents,[34][35][36] and the development of teeth in rats.[37] The latter is important in that tooth deformities were also seen after the Seveso accident[38] and possibly after a long breast-feeding of babies in the 1970s and 1980s when the dioxin concentrations in Europe were about ten times higher than at present.[39]

Cancer

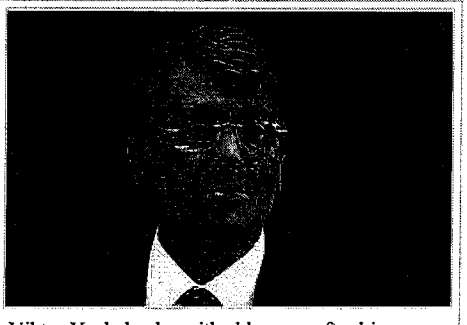
Cancers can be induced in animals at many sites. At sufficiently high doses TCDD has caused cancer in all animals tested. The most sensitive is liver cancer in female rats, and this has long been a basis for risk assessment.[40] Dose-response of TCDD in causing cancer does not seem to be linear,[13] and there is a threshold below which it seems to cause no cancer. TCDD is not mutagenic or genotoxic, in other words, it is not able to initiate cancer, and the cancer risk is based on promotion[11] of cancer initiated by other compounds or on indirect effects such as disturbing defense mechanisms of the body e.g. by preventing apoptosis or programmed death of altered cells.[9][19] Carcinogenicity is associated with tissue damage, and it is often viewed now as secondary to tissue damage.[11]

TCDD may in some conditions potentiate the carcinogenic effects of other compounds. An example is benzo(a)pyrene that is metabolized in two steps, oxidation and conjugation. Oxidation produces epoxide carcinogens that are rapidly detoxified by conjugation, but some molecules may escape to the nucleus of the cell and bind to DNA causing a mutation, resulting in cancer initiation. When TCDD increases the activity of oxidative enzymes more than conjugation enzymes, the epoxide intermediates may increase, increasing the possibility of cancer initiation. Thus a beneficial activation of detoxifying enzymes may lead to deleterious side effects.[41]

Cases of exposure

There have been a number of incidents where people have been exposed to high doses of TCDD or with a combination of TCDD and other

dioxin-like chemicals, including:


Viktor Yushchenko with chloracne after his TCDD poisoning incident

- In 1976, thousands of inhabitants of Seveso, Italy were exposed to TCDD after an accidental release of several kilograms of TCDD from a pressure tank. A number of animals died, and high concentrations of TCDD, up to 56,000 pg/g of fat, were noted especially in children playing outside and eating local food. The acute effects were limited to about 200 cases of chloracne.[42] Long-term effects seem to include a slight excess of multiple myeloma and myeloid leukaemia,[26] as well as some developmental effects such as disturbed development of teeth[38] and excess of girls born to fathers who were exposed as children.[43] Several other long-term effects have been suspected, but the evidence is not very strong.[5]
- In Vienna, two women were poisoned at their workplace in 1997, and the measured concentrations in one of them were the highest ever measured in a human being, 144,000 pg/g of fat. This is about one hundred thousandfold compared with TCDD concentrations in most people today, and about ten thousandfold compared with the sum of all dioxin-like compounds in young people today. She survived but suffered from difficult chloracne for several years. The poisoning likely happened in October 1997, but was not discovered until April 1998. At the institute where the women worked as secretaries, high concentrations of TCDD were found in one of the labs, suggesting that the compound had been produced there. The police investigation failed to find clear evidence and no one was ever prosecuted. Aside from malaise and amenorrhea there were surprisingly few other symptoms or abnormal laboratory findings.[44]
- In 2004, then-presidential candidate Viktor Yushchenko of Ukraine was poisoned with a large dose of TCDD. His blood TCDD concentration was measured 108,000 pg/g of fat,[45] which is the second highest ever measured. This concentration implies a dose exceeding 2 mg, or 25 μg/kg of body weight. Also he suffered from chloracne for many years, but again after initial malaise, other symptoms or abnormal laboratory findings were few.[45]
- An area of polluted land in Italy, known as the Triangle of death, is contaminated with TCDD due to years of illegal waste disposal by organized crime.[46][47][48]

See also

- Toxic Equivalency

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- U.S. National Library of Medicine: Hazardous Substances Databank – 2,3,7,8-Tetrachlorodibenzodioxin (http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@na+@rel+2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN)
- Dioxin synopsis (http://www.thl.fi/dioxin)
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