# PROSTATE CANCER

# IARC MONOGRAPH'S

## IARC SUPPLEMENT 7

PAGE 79, 211, 225, 324, WITH WIKIPEDIA ATTACHED

## IARC 45

PAGE 92, 108, 219, 220

## IARC 98

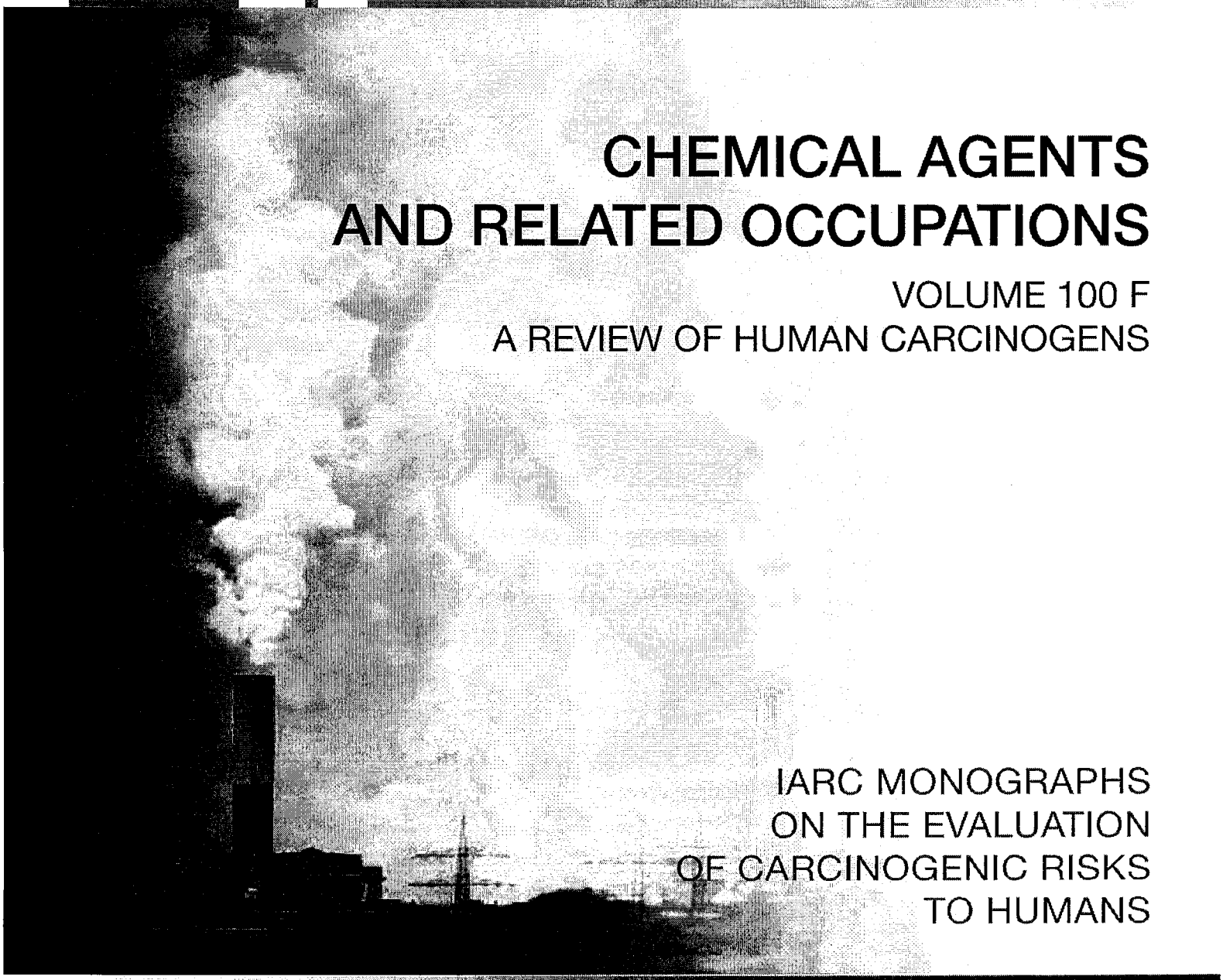
PAGE 399, 400, 556, 557 AND 558

IARC CHEMICAL LISTS OF SMOKE, SOOT AND EXHAUST

## IARC 100F

PAGES 258, 259, 260, 261, 262, 552 AND 559

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

**Table 1.5 Benzene in breath, blood and urine samples in the general population without occupational or known exposure to benzene[a]**

| Country | Analyte | Median/Mean | Reference |
|---|---|---|---|
| People's Republic of China | Urine | 120 ng/L | Kim *et al.* (2006a) |
| People's Republic of China | Urine | 69 ng/L | Waidyanatha *et al.* (2001) |
| People's Republic of China and Malaysia | Urine | 1.49 ng/L | Ong *et al.* (1995) |
| Estonia | Blood<br>Breath<br>Urine | 12 nmol/L<br>7 nmol/L<br>0.1 nmol/L | Kivistö *et al.* (1997) |
| Italy | Blood | 110 ng/L (NS)<br>219 ng/L (S) | Brugnone *et al.* (1998) |
| Italy | Urine | 1155 ng/L | Gobba *et al.* (1997) |
| Mexico | Blood | 0.63 µg/L (service attendants)<br>0.30 µg/L (street vendors)<br>0.17 µg/L (office workers) | Romieu *et al.* (1999) |
| Singapore | Blood<br>Urine | 1.27 nmol/L<br>1.29 nmol/L | Ong *et al.* (1996) |
| Thailand | Blood | 65.6 ppt | Navasumrit *et al.* (2005) |

[a] Including control workers
NS, non-smoker; S, smoker
From Johnson *et al.* (2007)

range from 0–42 ppm (1–136 mg/m$^3$) (Patel *et al.*, 2004).

Duarte-Davidson *et al.* (2001) assessed human exposure to benzene in the general population of the United Kingdom. It was estimated that infants (< 1 year old), the average child (11 years old), and non-occupationally exposed adults receive average daily doses of benzene in the range of 15–26 µg, 29–50 µg, and 75–522 µg, respectively. These values correspond to average airborne benzene concentrations in the range of 3.40–5.76 µg/m$^3$, 3.37–5.67 µg/m$^3$, and 3.7–41 µg/m$^3$ for these three groups, respectively.

Benzene concentrations in breath, blood and urine samples collected among the general populations (without occupational or known exposure to benzene) in Asia, Europe and North America are presented in Table 1.5 (Johnson *et al.*, 2007).

## 2. Cancer in Humans

In *IARC Monographs* Volume 29 (IARC, 1982) the Working Group concluded there was *sufficient evidence* in humans for the carcinogenicity of benzene, noting that a series of cohort and case–control studies showed statistically significant associations between occupational exposure to benzene and benzene-containing solvents and leukaemia (predominantly myelogenous leukaemia). In *IARC Monographs* Supplement 7 (IARC, 1987) benzene was classified as a Group-1 carcinogen, citing additional evidence of an increased incidence of acute nonlymphocytic leukaemia (ANLL) in workers exposed to benzene in three cohort studies, including an update of a cohort cited in Volume 29 (IARC, 1982). Since 1987, there have been numerous reports from cohort studies in populations exposed to benzene, including updates of earlier reports, and new case–control studies of leukaemia or its subtypes, non-Hodgkin lymphoma (NHL), multiple myeloma, and to a

lesser extent other tumours in adults. There have also been several case–control studies of childhood leukaemia with data on benzene, solvents, gasoline, and other related exposures. In addition, several meta-analyses have been published of one or more tumour sites.

[The Working Group decided to restrict its review to those case–control studies of paediatric cancers that included estimates of environmental benzene exposure, rather than surrogate exposures such as proximity to petrol stations or traffic. Also, the Working Group weighed more heavily the findings from studies with estimates of occupational exposure to benzene rather than broader measures (e.g. to solvents) in case–control studies. It was also decided not to rely in general on case–control studies where exposure assessment was limited to asking study subjects directly if they had been exposed to particular chemicals. Furthermore, the Working Group did not consider cohort studies of workers in synthetic rubber-manufacturing due to the difficulty of separating out effects from benzene *vs* those of other chemicals that may cause haematological malignancies. The Working Group decided not to take into consideration a series of meta-analyses of studies of petroleum workers (Wong & Raabe, 1995, 1997, 2000a, b). There were methodological concerns about the expansion from paper to paper of additional studies, cohorts, and countries, and the overall approach may dilute out the risks associated with relatively highly exposed subgroups of these populations that in general were not identified. In addition, an increased risk of ANLL – or the alternative classification, Acute Myelogenous Leukaemia (AML), which is more restrictive but still constitutes most of ANLL – was not detected in the initial meta-analysis by Wong & Raabe (1995), this body of work was not considered relevant for assessing what additional cancers may be associated with exposure to benzene beyond ANLL/AML. Abd finally, the Working Group noted that some meta-analyses of the same tumour came to opposite conclusions, which could be due to different inclusion/exclusion criteria, focusing on different subgroups of the study populations, or to different approaches to selecting risk estimates for inclusion (e.g. Lamm *et al.*, 2005; Steinmaus *et al.*, 2008), thus complicating the overall assessment of the literature. The Working Group therefore decided not to rely in general on results of meta-analyses in its evaluations.]

## 2.1 Leukemias and lymphomas

### *2.1.1 Acute non-lymphocytic leukaemia/ acute myelogenous leukaemia*

Since 1987, additional analyses of previously published cohort studies (e.g. results in Crump (1994) and Wong (1995), based on the cohort study described in Infante *et al.* (1977) and Rinsky *et al.* (1981, 1987), which reported an excess risk for combined (mostly acute) myelogenous and monocytic leukaemia) and new cohort studies with quantitative data on benzene exposure have shown evidence of a dose–response relationship between exposure to benzene and risk for ANLL/AML in various industries and in several countries (Hayes *et al.*, 1997; Rushton & Romaniuk, 1997; Divine *et al.*, 1999b; Guénel *et al.*, 2002; Collins *et al.*, 2003; Glass *et al.*, 2003; Bloemen *et al.*, 2004; Gun *et al.*, 2006; Kirkeleit *et al.*, 2008; see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.1.pdf). It was also noted that the NCI-CAPM cohort study found evidence of an increased risk for the combined category of ANLL and myelodysplastic syndromes (Hayes *et al.*, 1997). Case–control studies do not add substantively to these conclusions (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.2.pdf). In one case–control study an increased risk for childhood ANLL was found for maternal self-reported occupational exposure to benzene (Shu *et al.*, 1988; see Table 2.1 online). One case–control

study of childhood cancer in Denmark did not find an association of estimates of environmental benzene exposure from air pollution with an increased risk for ANLL (Raaschou-Nielsen *et al.*, 2001).

### 2.1.2 Acute lymphocytic leukaemia

Acute Lymphocytic Leukaemia (ALL) is now considered one subtype of NHL in the WHO-classification of lymphomas. In multiple cohorts there was a non-significantly increased risk for ALL, but the numbers of cases were small (Rushton, 1993; Wong *et al.*, 1993; Satin *et al.*, 1996; Divine *et al.*, 1999b; Lewis *et al.*, 2003; Kirkeleit *et al.*, 2008; Yin *et al.*, 1996; Guénel *et al.*, 2002; Gun *et al.*, 2006; see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.3.pdf). [The Working Group noted that the magnitude of the risk-estimate in the NCI-CAPM cohort (Yin *et al.*, 1996) was similar to the risk observed for ANLL in the same study, which was statistically significant. This approach has been suggested when attempting to interpret the association between occupational exposure to benzene and hematological subtypes that are less common than AML (Savitz & Andrews, 1997).]

In one case–control study in adults in Shanghai, a significant increased risk for ALL was found for the group with 15 or more years of self-reported occupational exposure to benzene (Adegoke *et al.*, 2003); another study in the USA had only three exposed cases (Blair *et al.*, 2001; Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.4.pdf). In a case–control study of childhood ALL no association was found with maternal self-reported occupational exposure to benzene, but a borderline significant association was noted with exposure to gasoline (Shu *et al.*, 1988; see Table 2.4 online). No association with self-reported maternal exposure to benzene was found in a large study of childhood ALL in the USA (Shu *et al.*, 1999; see Table 2.4 online). A case-control study of childhood cancer in Denmark did not find an association of estimated environmental exposure to benzene from air pollution with ALL (Raaschou-Nielsen *et al.*, 2001).

### 2.1.3 Chronic myelogenous leukaemia

Several studies in the petroleum industry and in other settings show non-significantly increased risks for CML, whereas other studies show no evidence of an association, including two that had quantitative estimates of exposure to benzene but no dose–response relationship (Rushton & Romaniuk, 1997; Guénel *et al.*, 2002; see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.5.pdf). Case–control studies have shown inconsistent results, with both increased risks (exposure for > 15 years was associated with an OR of 5.0 (1.8–13.9; Adegoke *et al.*, 2003) and no increase in risk (Björk *et al.*, 2001) reported (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.6.pdf).

### 2.1.4 Chronic lymphocytic leukaemia

Chronic Lymphocytic Leukaemia (CLL) – also referred to as small lymphocytic lymphoma (SLL) – is now considered as a subtype of NHL in the WHO-classification of lymphomas. CLL can be an indolent disease of the elderly, which raises questions about cohorts that are not followed up until the study population is relatively old and about studies that use mortality instead of incident data. In addition, the diagnosis of CLL was less frequently made in the past, until complete blood counts were routinely obtained in recent decades.

Several cohort studies in the petroleum industry showed mixed results, with some non-significantly increased risks reported and other studies showing no association (see Table 2.7 available at http://monographs.iarc.fr/ENG/

Monographs/vol100F/100F-19-Table2.7.pdf). In a nested case–control study in the Australian petroleum industry an increasing risk for CLL was detected with increasing exposure to benzene over a relatively small range of ppm–years, but the increase was not significant (Glass *et al.*, 2003). Similarly, in a nested case–control study within a cohort of French gas and electrical utility workers, a non-significant increase in risk with increasing years of benzene exposure was detected (Guénel *et al.*, 2002). Some evidence of risk with increasing benzene exposure was also found in a cohort study among petroleum workers in the United Kingdom, but the trends were not clear and interpretation is difficult as white- and blue-collar workers were mixed in the analysis and interactions may have been present (Rushton & Romaniuk, 1997). Updates of two cohort studies in the Southern US found an increased risk for CLL, which was significant in one cohort for workers hired before 1950, but not in the other (Huebner *et al.*, 2004).

A case–control study in Italy showed evidence of a dose–response relationship between the extent of benzene exposure with the number of years worked with benzene (Costantini *et al.*, 2008) and in a large multicentre international study in Europe a significant excess in risk for CLL was found with increasing exposure to benzene, but the dose–response was not significant (Cocco *et al.*, 2010; see Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.8.pdf). Blair *et al.* (2001) conducted a study in the Midwestern USA and found no association with benzene exposure although there were only three cases in the high-exposure category. In a study of women in Connecticut, a non-significantly increased risk for CLL was found with increasing exposure to benzene (Wang *et al.*, 2009; see Table 2.8 online).

### 2.1.5 Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of histological subtypes, and the definition of both NHL and its subtypes has evolved over the last several decades with the application and discontinuation of several classification schemes, which complicates the assessment of exposure to benzene and risk for NHL. For example, CLL – now classified by the WHO as a subtype of NHL – has generally not been combined with other types of NHL in reports from cohort studies of benzene-exposed workers or in earlier case–control studies of NHL. Further, given the indolent nature of some NHL subtypes, cohorts with only mortality data may underestimate associations with NHL. In most cohort studies an increased risk for NHL was not detected, one particular exception being the NCI-CAPM cohort study in China (Hayes *et al.*, 1997; Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.9.pdf). An excess of NHL was not detected in the Pilofilm cohort (Rinsky *et al.*, 2002) or in the Australian Health Watch study in an analysis of NHL combined with multiple myeloma (two-thirds of which were NHL cases) (Glass *et al.*, 2003).

Of 14 independent case–control studies that were considered informative, five showed evidence of increased risk with benzene exposure, two (Fabbro-Peray *et al.*, 2001; Dryver *et al.*, 2004) for NHL as a whole (Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.10.pdf). Data on histological subtypes of NHL have generally not been reported in publications of occupational cohort studies of benzene-exposed workers, but they have been mentioned in some case–control studies. For various benzene-exposure metrics, slightly increased, but non-significant risks for NHL were found in a case–control study among women in Connecticut, as well as higher risks – also non-significant – for follicular lymphoma

and diffuse large B-cell lymphoma (DLBCL), two common NHL subtypes (Wang *et al.*, 2009). Cocco *et al.* (2010) conducted an analysis of a large multicentre case–control study of NHL in Europe and found no significant increase in risk for B-cell NHL or DLBCL, but an elevated risk, albeit not statistically significant, for follicular lymphoma associated with exposure to benzene (see Table 2.10 online), and a significant association between combined exposure to benzene/toluene/xylene and follicular lymphoma. Other case–control studies showed increased, non-significant risks for one or both of these histological subtypes, and in one study in Italy a significant association was found between medium/high exposure to benzene and the risk for diffuse lymphoma (Miligi *et al.*, 2006; OR = 2.4, 95%CI: 1.3–1.5).

### 2.1.6 Multiple myeloma

Most cohort studies showed no association with multiple myeloma (MM) (Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.11.pdf). However, there was a statistically significant excess of MM reported for the Pliofilm cohort (SMR 4.1; 95%CI: 1.1–10.5, based upon four deaths) (Rinsky *et al.*, 1987), which did not persist in the most recent update (Rinsky *et al.*, 2002; see Table 2.11 online). In a cohort study among chemical workers at the Monsanto chemical company suggestive evidence was found of a dose–response relationship (Collins *et al.*, 2003), while in a cohort study of Norwegian workers in the upstream petroleum industry (i.e. the phases of oil extraction and initial transportion, which entail extensive exposure to crude oil) a significant increased risk for MM was found (Kirkeleit *et al.*, 2008).

Case–control studies of MM with estimates of exposure to benzene largely show no association (Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.12.pdf). An exception was an early study in which a significant association was found between risk for MM and the proportion of cases and controls with "solvent/benzene" exposure (La Vecchia *et al.*, 1989). In another study, borderline significant effects were detected (Costantini *et al.*, 2008). In a large multicentre case–control study of NHL in Europe there was no association of benzene exposure with MM (Cocco *et al.*, 2010).

A meta-analysis by Infante (2006) analysed data from seven well defined "benzene cohorts" outside of petroleum refining and found a statistically significant increase in risk for MM (RR 2.1; 95%CI: 1.3–3.5).

### 2.1.7 Hodgkin disease

There are sparse data on Hodgkin disease in studies of benzene-exposed cohorts, with most studies having very small numbers of cases and showing no association (see Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.13.pdf). Overall, there is no evidence of an increased risk. The relatively few case–control studies in adults also show no association (see Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.14.pdf). In a case–control study of childhood cancer in Denmark, an increased risk for Hodgkin disease was detected in association with estimated environmental exposures to benzene (Raaschou-Nielsen *et al.* (2001) (see Table 2.14 online).

## 2.2 Cancer of the lung

Cohort studies with information on potential or estimated benzene exposure and lung cancer are shown in Table 2.15 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.15.pdf). Although most studies show no association, in two cohorts with quantitative exposure-assessment evidence of a dose–response relationship was found (Hayes *et al.*, 1996; Collins

*et al.*, 2003) and in two others statistically significant increases in risk were observed (Lynge *et al.*, 1997; Sorahan *et al.*, 2005). A case–control study from Canada showed no association of exposure to benzene with lung cancer overall or with the major histological subtypes (Gérin *et al.*, 1998; see Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.16.pdf).

## 2.3 Cancer of the kidney

Cohort studies with results on kidney cancer are shown in Table 2.17 (available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.17.pdf). Results generally do not show any association. In a case–control study among males in Germany an association was found between exposure to benzene and an increased risk for kidney cancer (Pesch *et al.*, 2000), but in a study in Montreal, Canada, there was little evidence of an association (Gérin *et al.*, 1998) (see Table 2.18 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.18.pdf).

## 2.4 Other cancers

In the evaluation of the cohort studies that provided data on the cancer sites considered above, it was apparent that associations have occasionally been found with other cancer sites including malignant melanoma (Schnatter *et al.*, 1996; Consonni *et al.*, 1999; Lewis *et al.*, 2003), nose and stomach cancer (Fu *et al.*, 1996) and prostate cancer (Collingwood *et al.*, 1996), but overall there was no consistency across the cohorts.

# 3. Cancer in Experimental Animals

Studies on the carcinogenesis of benzene in rats and mice after exposure by inhalation, intragastric gavage, skin application, and by intraperitoneal or subcutaneous injection have been reviewed in *IARC Monographs* Volume 29 and in Supplement 7 (IARC, 1982, 1987). In Supplement 7 it was concluded that there is *sufficient evidence* in experimental animals for the carcinogenicity of benzene. Results of adequately conducted carcinogenicity studies reported before and after 1987 are summarized in Tables 3.1, 3.2, 3.3, 3.4.

Exposure to benzene by inhalation increased the incidence of Zymbal gland carcinomas, liver adenomas, and forestomach and oral cavity carcinomas in female rats (Maltoni *et al.*, 1982a, c, 1983, 1985, 1989). It also increased the incidence of lymphohaematopoietic (lymphoma, myelogenous) neoplasms in male and female mice (Snyder *et al.*, 1980; Cronkite *et al.*, 1984, 1989; Farris *et al.*, 1993), and Zymbal gland carcinomas, squamous cell carcinomas of the preputial gland, and lung adenomas in male mice (Snyder *et al.*, 1988; Farris *et al.*, 1993).

Oral administration of benzene increased the incidence of Zymbal gland carcinomas and oral-cavity papillomas and carcinomas in rats of both sexes, of carcinomas of the tongue, papillomas and carcinomas of the skin and of the lip and papillomas of the palate in male rats, of forestomach acanthomas in both sexes of the rat, and of forestomach carcinomas in female rats (Maltoni & Scarnato, 1979; Maltoni *et al.*,1982b, 1983, 1988, 1989; NTP, 1986; Maronpot, 1987; Huff *et al.*, 1989; Mehlman, 2002). Given by the oral route, benzene also increased the incidence of Zymbal gland carcinomas, forestomach papillomas, lymphomas, and lung adenomas and carcinomas in mice of both sexes, of liver carcinomas, adrenal gland pheochromocytomas, harderian gland adenomas and preputial gland squamous cell carcinomas in male mice,

rubber-manufacturing industry. [The Working Group noted that in none of the studies adjustments were made for tobacco or alcohol use.]

## 2.8 Cancer of the prostate

The previous *IARC Monograph* (IARC, 1982) concluded that the evidence of excess risk for prostate cancer was *limited* and that the evidence for a causal association with occupational exposures was inadequate.

### *2.8.1 Cohort studies*

Kogevinas *et al.* (1998) reported excess risks for prostate cancer in five studies (Norseth *et al.*, 1983; Delzell & Monson 1984a, in the industrial-products department; Bernardinelli *et al.*, 1987; Solionova & Smulevich, 1993; Weiland *et al.*, 1996). Other studies did not report any excess (Delzell & Monson, 1984b, 1985b; in the aerospace-products and re-claim departments; Gustavsson *et al.*, 1986; Sorahan *et al.*, 1989; Szeszenia-Dabrowska *et al.*, 1991).

Since then, only one case–cohort study that investigated the association between prostate cancer and work in the rubber-manufacturing industry has been published (Zeegers *et al.*, 2004). In this study a non-statistically significant increased risk for prostate cancer was found.

### *2.8.2 Synthesis*

The Working Group concluded that there is weak evidence of excess risk for prostate cancer among workers in the rubber-manufacturing industry.

## 2.9 Other cancers

The previous *IARC Monograph* (IARC, 1982) determined that for cancers of the brain, thyroid and pancreas, the evidence was *inadequate* for an excess in occurrence of these cancers and for a causal association with occupational exposures.

### *2.9.1 Cohort studies*

Kogevinas *et al.* (1998) reported that findings for other cancer sites were not consistent between studies, or were derived from too few studies. Since this review, studies on workers in the rubber-manufacturing industry with excess cancers of the brain, pancreas, gallbladder, cervix and liver have been reported (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-31-Table2.6.pdf).

### *2.9.2 Synthesis*

The Working Group concluded that there is little evidence of excess risks for cancers at sites other than those mentioned above, being associated with work in the rubber-manufacturing industry. [Excess risks found in single studies may be related to specific exposure circumstances occurring in particular rubber-manufacturing plants. One problem in evaluating findings for other cancer sites is that reporting may have been incomplete in cohort and case–control studies, with possibly preferential reporting of positive findings.]

# 3. Cancer in Experimental Animals

No data were available to the Working Group.

# 4. Other Relevant Data

The rubber-manufacturing industry has used and still uses a wide variety of substances that belong to many different chemical categories, e.g. carbon black, aromatic amines, PAH, *N*-nitrosamines, mineral oils, other volatile organic compounds from curing fumes, trace amounts of monomers from synthetic rubber like 1,3-butadiene, acetonitrile, styrene, vinyl chloride, ethylene oxide, etc. (See Section 1). For this reason, it has been difficult to relate the observed

cancer hazards in the rubber-manufacturing industry to exposure to specific chemicals.

Table 4.1 presents a list of bio-monitoring studies and cytogenetic assays among workers in the rubber-manufacturing industry in various countries and at different times. These studies have focused on analysis of chromosomal aberrations, sister-chromatid exchange, micronucleus formation, premature chromosome condensation, DNA breakage, DNA-adduct formation, mutagenicity in urine, and mutation in the *HPRT* gene. For each of these endpoints, in most studies a positive response has been observed in exposed workers compared with non-exposed controls. It is noted that the studies listed in Table 4.1 span a period of approximately 25 years.

The multiple genetic and cytogenetic effects observed among workers employed in the rubber-manufacturing industry provide strong evidence to support genotoxicity as one mechanism for the observed increase in cancer risk. However, due to the complexity and changing nature of the exposure mixture and the potential interactions between exposures in this industry, other mechanisms are also likely to play a role.

While it is clear that exposures to some agents in the rubber-manufacturing industry have been reduced over time, the outcome of recent cytogenetic studies continues to raise concerns about cancer risks.

## 5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures in the rubber-manufacturing industry. Occupational exposures in the rubber-manufacturing industry cause leukaemia, lymphoma, and cancers of the urinary bladder, lung, and stomach.

lso, a positive association has been observed between occupational exposures in the rubber-manufacturing industry and cancers of the prostate, oesophagus, and larynx.

No data in experimental animals with relevance to the rubber-manufacturing industry were available to the Working Group.

The multiple genetic and cytogenetic effects observed among workers employed in the rubber-manufacturing industry provide strong evidence to support genotoxicity as one mechanism for the observed increase in cancer risks. However, due to the complexity and changing nature of the exposure mixture and the potential interactions between exposures in the rubber-manufacturing industry, other mechanisms are also likely to play a role. While it is clear that exposure to some agents in the rubber-manufacturing industry has been reduced over time, the results of recent cytogenetic studies continue to raise concerns about cancer risks.

Occupational exposures in the rubber-manufacturing industry are *carcinogenic to humans (Group 1).*

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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

# ACRYLONITRILE (Group 2A)

## A. Evidence for carcinogenicity to humans (*limited*)

In the USA, 1345 male workers potentially exposed to acrylonitrile in a textile fibre plant and observed for 20 or more years had a greater than expected incidence of lung cancer (8 observed, 4.4 expected). The risk was greater among workers with more than five years' exposure (6 observed, 2.3 expected) or with jobs where exposure was likely to have been heavier (6 observed, 2.7 expected) than among workers with shorter duration of exposure (2 observed, 1.4 expected) or low levels of exposure (2 observed, 1.4 expected)[1,2]. Further follow-up of this cohort until 1981 revealed a continued excess of lung cancer (10 observed, 7.2 expected), although during the actual follow-up period (1976-1981) there was no excess (2 observed, 2.8 expected). The updating also showed, however, a significant excess of cancer of the prostate (6 observed, 1.8 expected)[3]. In a similar study at another US textile fibre plant, an excess of prostatic cancer (5 cases observed, 1.9 expected) was observed, but there was no excess of lung cancer[4]. In the UK, a study of 1111 male workers exposed to acrylonitrile during polymerization between 1950 and 1968 and followed for ten years or more revealed five stomach cancers (1.9 expected), two colon cancers (1.1 expected), two brain cancers (0.7 expected) and nine cancers of the respiratory tract (7.6 expected)[5]. Among 327 rubber workers exposed to acrylonitrile in the USA, excesses were noted for cancers of the lung (9 observed, 5.9 expected), bladder (2 observed, 0.5 expected) and of the lymphatic and haematopoietic system (4 observed, 1.8 expected). The risk for lung cancer was greatest among workers with five to 14 years' exposure and $\geq$15 years of latency (4 observed, 0.8 expected)[6]. Another study of rubber workers in the USA, however, showed no association between exposure to acrylonitrile and lung cancer[7]. In the Federal Republic of Germany, one study of 1469 workers exposed to acrylonitrile in 12 different plants showed excesses of bronchial cancer (11 observed, 5.7 expected) and of tumours of the lymphatic system (4 observed, 1.7 expected)[8].

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

Acrylonitrile was tested for carcinogenicity in rats by oral administration and by inhalation. Following its oral administration, it induced neoplasms of the brain, squamous-cell papillomas of the stomach and Zymbal-gland carcinomas; tumours of the tongue, small intestine and mammary gland were also reported[1,9,10]. Following its inhalation, neoplasms of the central nervous system, mammary gland, Zymbal gland and forestomach were observed[1,11].

## C. Other relevant data

Acrylonitrile did not enhance the frequency of chromosomal aberrations in lymphocytes of exposed workers in one study[12].

In animals treated *in vivo*, acrylonitrile did not induce dominant lethal mutations, chromosomal aberrations (in bone-marrow cells or spermatogonia) or micronuclei in mice, or chromosomal aberrations in rat bone-marrow cells. It bound covalently to rat liver DNA

# Acrylonitrile

From Wikipedia, the free encyclopedia

**Acrylonitrile** is an organic compound with the formula $CH_2CHCN$. It is a colorless volatile liquid, although commercial samples can be yellow due to impurities. In terms of its molecular structure, it consists of a vinyl group linked to a nitrile. It is an important monomer for the manufacture of useful plastics such as polyacrylonitrile. It is reactive and toxic at low doses.[3]

## Contents



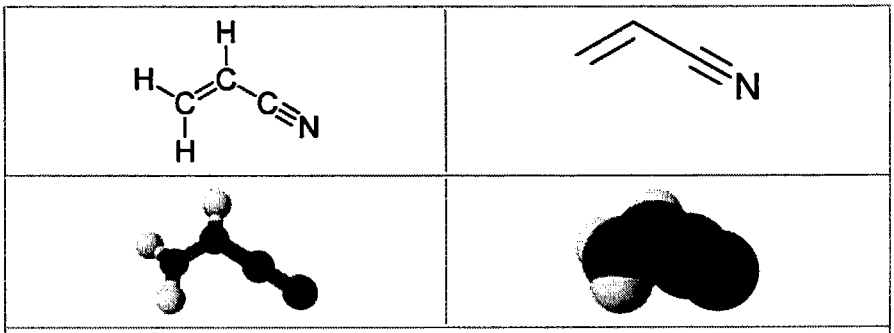
## Production

Acrylonitrile is produced by catalytic ammoxidation of propylene, also known as the SOHIO process. In 2002, world production capacity was estimated at 5 million tonnes per year.[3][4] Acetonitrile and hydrogen cyanide are significant byproducts that are recovered for sale.[3] In fact, the 2008–2009 acetonitrile shortage was caused by a decrease in demand for acrylonitrile.[5]

$$2CH_3\text{-}CH{=}CH_2 + 2NH_3 + 3O_2 \rightarrow 2CH_2{=}CH\text{-}C{\equiv}N + 6H_2O$$

In the SOHIO process, propylene, ammonia, and air (oxidizer) are passed through a fluidized bed reactor containing the catalyst at 400–510 °C and 50–200 kPag. The reactants pass through the reactor only once, before being quenched in aqueous sulfuric acid. Excess propylene, carbon monoxide, carbon dioxide, and dinitrogen that do not dissolve are vented directly to the atmosphere, or are incinerated. The aqueous solution consists of acrylonitrile, acetonitrile, hydrocyanic acid, and ammonium sulfate (from excess ammonia). A recovery column removes bulk water, and acrylonitrile and acetonitrile are separated by distillation. Historically, one of the first successful catalysts was bismuth phosphomolybdate

**Acrylonitrile**



| Names | |
|---|---|
| Preferred IUPAC name<br>Prop-2-enenitrile | |
| Other names<br>Acrylonitrile<br>2-Propenenitrile<br>Cyanoethene,<br>Vinylcyanide (VCN)<br>Cyanoethylene[1]<br>Propenenitrile[1] | |
| **Identifiers** | |
| CAS Number | 107-13-1 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=107-13-1) ✓ |
| ChEBI | CHEBI:28217 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=28217) ✓ |
| ChEMBL | ChEMBL445612 (https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/ChEMBL445612) ✓ |
| ChemSpider | 7567 (http://www.chemspider.com/Chemical-Structure.7567.html) ✓ |
| ECHA InfoCard | 100.003.152 (https://echa.europa.eu/substance-information/-/substanceinfo/100.003.152) |
| EC Number | 608-003-00-4 |
| Jmol 3D model | Interactive image (http://chemapps.stolaf.edu/jmol/jmol.php?model=N%23CC%3DC)<br>Interactive image (http://chemapps.stolaf.edu/jmol/jmol.php?model=C%3DCC%23N) |
| KEGG | C01998 (http://www.kegg.jp/entry/C01998) ✓ |
| PubChem | 7855 (https://pubchem.ncbi.nlm.nih.gov/compound/7855) |
| RTECS number | AT5250000 |
| UNII | MP1U0D42PE (http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=MP1U0D42PE) ✓ |
| UN number | 1093 |
| InChI | |
| SMILES | |
| **Properties** | |
| Chemical formula | $C_3H_3N$ |
| Molar mass | 53.06 g·mol$^{-1}$ |
| Appearance | Colourless liquid |

Acrylonitrile induces apoptosis in human umbilical cord mesenchymal stem cells [12]

## Environmental effects

Acrylonitrile is harmful to aquatic life.[9]

## References


1. "NIOSH Pocket Guide to Chemical Hazards #0014". National Institute for Occupational Safety and Health (NIOSH).
2. "Acrylonitrile". *Immediately Dangerous to Life and Health.* National Institute for Occupational Safety and Health (NIOSH).
3. James F. Brazdil (2005), "Acrylonitrile", *Ullmann's Encyclopedia of Industrial Chemistry*, Weinheim: Wiley-VCH, doi:10.1002/14356007.a01_177.pub3
4. "The Sohio Acrylonitrile Process". American Chemical Society National Historic Chemical Landmarks. Retrieved 2013-05-13.
5. A. Tullo. "A Solvent Dries Up". *Chemical & Engineering News.* **86**: 27. doi:10.1021/cen-v086n047.p027.
6. See:
    - C. Moureu (1893) "Contribution à l'étude de l'acide acrylique et de ses dérivés" (http://babel.hathitrust.org/cgi/pt?id=uc1.31822017842394;view=1up;seq=149) (Contribution to the study of acrylic acid and of its derivatives), *Annales de chimie et de physique*, 7th series, **2** : 145-212 ; see especially pp. 187-189 ("Nitrile acrylique ou cyanure de vinyle (Propène-nitrile)").
    - Moureu (1893) "Nitrile acrylique, cyanure de vinyle (propène-nitrile)," (http://gallica.bnf.fr/ark:/12148/bpt6k282008w/f436.image.r=BulletindelaSocieteChimiquedeParis.langFR) *Bulletin de la Société chimique de France*, 3rd series, **9** : 424-427.
7. "Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide" (http://monographs.iarc.fr/ENG/Monographs/vol71/index.php). IARC Monographs, Volume 71 (1999)
8. Acrylonitrile Fact Sheet (CAS No. 107-13-1) (http://www.epa.gov/chemfact/acry-fs.txt). epa.gov
9. "CDC - ACRYLONITRILE - International Chemical Safety Cards - NIOSH". *www.cdc.gov.* Retrieved 2015-07-31.
10. "Acrylonitrile: Carcinogenic Potency Database" (http://potency.berkeley.edu/chempages/ACRYLONITRILE.html). *berkeley.edu.*
11. Acrylonitrile Fact Sheet: Support Document (CAS No. 107-13-1) (http://www.epa.gov/chemfact/acry-sd.txt). epa.gov
12. Sun X (Jan 2014). "Cytotoxic effects of acrylonitrile on human umbilical cord mesenchymal stem cells in vitro.". *J Mol Med Rep.* **9** (1): 97–102. doi:10.3892/mmr.2013.1802. PMID 24248151.


## External links

- National Pollutant Inventory – Acrylonitrile (http://www.npi.gov.au/database/substance-info/profiles/7.html)
- Comparing Possible Cancer Hazards from Human Exposures to Rodent Carcinogens (http://potency.berkeley.edu/MOE.html)
- Acrylonitrile – Integrated Risk Information System (http://www.epa.gov/iris/subst/0206.htm), U.S. Environmental Protection Agency
- CDC – NIOSH Pocket Guide to Chemical Hazards – Acrylonitrile (http://www.cdc.gov/niosh/npg/npgd0014.html)
- OSHA Table Z-1 for Air Contaminants (https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9992)



Categories: Alkenes | Fumigants | Hazardous air pollutants | IARC Group 2B carcinogens | Monomers | Nitriles | Commodity chemicals

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supported on silica as a heterogeneous catalyst. Further improvements have since been made.[3]

### Historical

Acrylonitrile was first synthesized by the French chemist Charles Moureu (1863–1929) in 1893.[6]

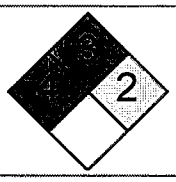
## Uses

Acrylonitrile is used principally as a monomer to prepare polyacrylonitrile, a homopolymer, or several important copolymers, such as styrene-acrylonitrile (SAN), acrylonitrile butadiene styrene (ABS), acrylonitrile styrene acrylate (ASA), and other synthetic rubbers such as acrylonitrile butadiene (NBR). Dimerization of acrylonitrile affords adiponitrile, used in the synthesis of certain polyamides. Small amounts are also used as a fumigant. Acrylonitrile and derivatives, such as 2-chloro-acrylonitrile, are dienophiles in Diels-Alder reactions. Acrylonitrile is also a precursor in the industrial manufacture of acrylamide and acrylic acid.[3]

## Health effects

Acrylonitrile is highly flammable and toxic at low doses. It undergoes explosive polymerization. The burning material releases fumes of hydrogen cyanide and oxides of nitrogen. It is classified as a Class 2B carcinogen (possibly carcinogenic) by the International Agency for Research on Cancer (IARC),[7] and workers exposed to high levels of airborne acrylonitrile are diagnosed more frequently with lung cancer than the rest of the population.[8] It evaporates quickly at room temperature (20 °C) to reach dangerous concentrations; skin irritation, respiratory irritation, and eye irritation are the immediate effects of this exposure.[9]

Acrylonitrile increases cancer in high dose tests in male and female rats and mice.[10]

| | |
|---|---|
| Density | 0.81 g/cm$^3$ |
| Melting point | −84 °C (−119 °F; 189 K) |
| Boiling point | 77 °C (171 °F; 350 K) |
| Solubility in water | 70 g/L |
| Vapor pressure | 83 mmHg[1] |
| **Hazards** | |
| Main hazards | flammable,<br>reactive,<br>toxic,<br>potential occupational carcinogen[1] |
| Safety data sheet | ICSC 0092 (http://www.inchem.org/documents/icsc/icsc/eics0092.htm) |
| NFPA 704 |  |
| Flash point | −1 °C; 30 °F; 272 K |
| Autoignition temperature | 471 °C (880 °F; 744 K) |
| Explosive limits | 3–17% |
| Lethal dose or concentration (*LD*, *LC*): | |
| $LC_{50}$ (median concentration) | 500 ppm (rat, 4 hr)<br>313 ppm (mouse, 4 hr)<br>425 ppm (rat, 4 hr)[2] |
| $LC_{Lo}$ (lowest published) | 260 ppm (rabbit, 4 hr)<br>575 ppm (guinea pig, 4 hr)<br>636 ppm (rat, 4 hr)<br>452 ppm (human, 1 hr)[2] |
| US health exposure limits (NIOSH): | |
| PEL (Permissible) | TWA 2 ppm C 10 ppm [15-minute] [skin][1] |
| REL (Recommended) | Ca TWA 1 ppm C 10 ppm [15-minute] [skin][1] |
| IDLH (Immediate danger) | 85 ppm[1] |
| **Related compounds** | |
| Related compounds | acrylic acid,<br>acrolein |
| Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa). | |
| ✓ verify (what is ✓✗ ?)<br>Infobox references | |

Pathways of exposure for humans include emissions, auto exhaust, and cigarette smoke that can expose the human subject directly if they inhale or smoke. Routes of exposure include inhalation, oral, and to a certain extent dermal uptake (tested with volunteer humans and in rat studies).[11] Repeated exposure causes skin sensitization and may cause central nervous system and liver damage.[9]

There are two main excretion processes of acrylonitrile. The primary method is excretion in urine when acrylonitrile is metabolized by being directly conjugated to glutathione. The other method is when acrylonitrile is metabolized with 2-cyanoethylene oxide to produce cyanide end products that ultimately forms thiocyanate, which is excreted via urine, or carbon dioxide and eliminated through the lungs.[11] Metabolites can be detected in the blood and urine.[7]

urinary bladder and the adrenal glands; however, because of the lack of matched controls, it could not be concluded whether tumour induction was due to a combined effect of the three chemicals or of any one of them[4].

### C. Other relevant data

Neither chromosomal aberrations (in two patients) nor sister chromatid exchanges (in three patients) were induced following administration of 5-fluorouracil[5].

5-Fluorouracil induced micronuclei but not specific locus mutations in mice treated *in vivo*. It induced aneuploidy, chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster cells. It did not induce sex-linked recessive lethal mutations in *Drosophila*, but caused genetic crossing-over in fungi. Studies on mutation in bacteria were inconclusive[5].

### References

[1]*IARC Monographs, 26*, 217-235, 1981

[2]Boice, J.D., Greene, M.H., Keehn, R.J., Higgins, G.A. & Fraumeni, J.F., Jr (1980) Late effects of low-dose adjuvant chemotherapy in colorectal cancer. *J. natl Cancer Inst., 64*, 501-511

[3]Ferguson, T. (1980) Prevention and delay of spontaneous mammary and pituitary tumors by long- and short-term ingestion of 5-fluorouracil in Wistar-Furth rats. *Oncology, 37*, 353-356

[4]Habs, M., Schmähl, D. & Lin, P.Z. (1981) Carcinogenic activity in rats of combined treatment with cyclophosphamide, methotrexate and 5-fluorouracil. *Int. J. Cancer, 28*, 91-96

[5]*IARC Monographs, Suppl. 6*, 316-318, 1987

## FORMALDEHYDE (Group 2A)

### A. Evidence for carcinogenicity to humans (*limited*)

A number of epidemiological studies using different designs have been completed on persons in a variety of occupations with potential exposure to formaldehyde[1-24]. Cancers that occurred in excess in more than one study are: Hodgkin's disease, leukaemia, and cancers of the buccal cavity and pharynx (particularly nasopharynx), lung, nose, prostate, bladder, brain, colon, skin and kidney[1]. The studies reported are not entirely independent; the plant studied by Liebling *et al.*[2] and Marsh[1,3] is also included in the study by Blair *et al.*[4]; the case-control study of Fayerweather *et al.*[5] includes some subjects who were later studied by Blair *et al.*[4]. Detailed estimates of formaldehyde exposure levels were made in the studies of British chemical workers[6], US formaldehyde producers and users[4], Finnish wood workers[7] and US chemical workers[5], and for the case-control studies of Vaughan *et al.*[8,9] and Hayes *et al.*[10].

In the study of US producers and users of formaldehyde, 11% of the subjects were not exposed, 12% had an estimated time-weighted average (TWA) exposure of <0.1 ppm (<0.12 mg/m$^3$), 34% a TWA of 0.1-<0.5 ppm (0.12-<0.6 mg/m$^3$), 40% a TWA of 0.5-<2 ppm

to be 1.5- to 1.8-fold greater than that in the general population. Associations between foundry work and lung cancer have similarly been observed in studies of mortality statistics[1].

In two studies in which site-specific cancer deaths among iron and steel foundry workers were compared with corresponding rates for the general population, significantly increased risks for cancer of the digestive system were observed; in one, the elevated risk was for cancers in the 'digestive system', in the other, it was for 'stomach cancer'[1].

Results of studies of a single cohort of steel foundry workers in the USA showed a significantly elevated risk of cancer of the genito-urinary system when compared with the entire steel worker population under study, the risk being significantly elevated also for some specific sites (prostate and kidney)[1].

Elevated lung cancer risks have also been reported in a grey-iron foundry[2], in steel foundries[3], in iron and steel foundries[2] and among persons living near steel foundries[4]. No consistent excess of lung cancer, however, was reported among foundrymen employed in a nickel-chromium alloy foundry[5]. Other cancer excesses reported have included leukaemia, stomach cancer and urogenital cancer[2]. Despite the absence of information to specify definitely the carcinogenic substances in the work environment (e.g., polynuclear aromatic hydrocarbons, silica [see p. 341], metal fumes, formaldehyde [see p. 211]), the consistency of the excess in studies from around the world shows that certain exposures in iron and steel founding can cause lung cancer in humans. Most studies lacked information on smoking, but, when it was available, it did not appear that tobacco use could explain the lung cancer excess.

### B. Other relevant data

Antigenicity against benzo[*a*]pyrene diol epoxide-DNA adducts has been demonstrated in peripheral lymphocytes of foundry workers[5].

## References

[1] *IARC Monographs, 34*, 133-190, 1984

[2] IARC Monographs, *42*, 39-143, 1987

[3] Fletcher, A.C. & Ades, A. (1984) Lung cancer mortality in a cohort of English foundry workers. *Scand. J. Work Environ. Health, 10*, 7-16

[4] Lloyd, O.L., Smith, G., Lloyd, M.M., Holland, Y. & Gailey, F. (1985) Raised mortality from lung cancer and high sex ratios of births associated with industrial pollution. *Br. J. ind. Med., 42*, 475-480

[5] Cornell, R.G. & Landris, J.R. (1984) *Mortality patterns among nickel/chromium alloy foundry workers.* In: Sunderman, F.W., Jr, ed., *Nickel in the Human Environment* (*IARC Scientific Publications No. 53*), Lyon, International Agency for Research on Cancer, pp. 87-93

[6] *IARC Monographs, Suppl. 6*, 344, 1987

patients, two adenocarcinomas of the liver were found, with no indication of a direct association with exposure to PCBs[9]. Ultrasonic and tumour marker examination of two series of 79 and 125 patients with 'Yusho' disease in 1983 and 1984, respectively, did not reveal any case of hepatic-cell carcinoma[10]. Two studies of the PCB content of fat tissues and cancer occurrence were available. An association was suggested between PCB concentrations in subcutaneous abdominal adipose tissue and the occurrence of cancers of the stomach, colon, pancreas, ovaries and prostate[11]. No indication emerged of a relationship between PCB content in extractable breast fat tissue and the occurrence of breast cancer[12].

The available studies suggest an association between cancer and exposure to PCBs. The increased risk from hepatobiliary cancer emerged consistently in different studies. Since, however, the numbers were small, dose-response relationships could not be evaluated, and the role of compounds other than PCBs could not be excluded, the evidence was considered to be limited.

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

Certain PCBs (particularly with greater than 50% chlorination) produced benign and malignant liver neoplasms in mice and rats after their oral administration[1,13,14]. Oral administration of Aroclor 1254 to rats yielded hepatocellular adenomas and carcinomas as well as intestinal metaplasia and a low, statistically nonsignificant incidence of stomach adenocarcinomas[15]. PCBs were inadequately tested in mice for induction of skin tumours[16,17]. In several studies, oral or intraperitoneal administration of PCBs enhanced the incidences of preneoplastic lesions[18–20] and of neoplasms[21,22] of the liver induced in rats by *N*-nitrosodiethylamine or 2-acetylaminofluorene. In one study, intragastric administration of PCBs to mice increased the incidence of lung tumours induced by intraperitoneal administration of *N*-nitrosodimethylamine[23].

**C. Other relevant data**

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

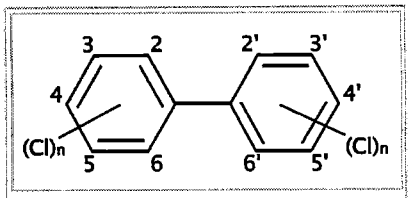
Dominant lethal effects were not induced in rats administered PCBs orally, but were produced in rats nursed by females that had received PCBs orally. PCBs did not induce chromosomal aberrations in bone-marrow cells or spermatagonia of rats treated *in vivo*; micronuclei were not induced in bone-marrow cells of mice in one study, while equivocal results were obtained in a second study in which the PCBs were administered in corn oil. They did not transform Syrian hamster embryo cells *in vitro*. PCBs induced DNA strand breaks and unscheduled DNA synthesis in rat hepatocytes *in vitro*. Neither chromosomal breakage nor aneuploidy was induced in *Drosophila*. PCB mixtures did not induce SOS repair and were not mutagenic to bacteria[24].

2,2′,5,5′-Tetrachlorobiphenyl induced DNA strand breaks in mouse cells *in vitro*. 2,4,5,2′,4′,5′-Hexachlorobiphenyl but not 3,4,5,3′,4′,5′-hexachlorobiphenyl inhibited intercellular communication in Chinese hamster V79 cells. Purified 2,4,2′,4′-, 2,5,2′,5′- and

# Polychlorinated biphenyl

From Wikipedia, the free encyclopedia

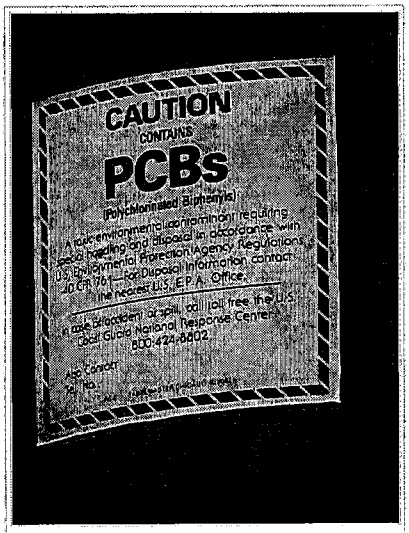
A **polychlorinated biphenyl (PCB)** is an organic chlorine compound with the formula $C_{12}H_{10-x}Cl_x$. Polychlorinated biphenyls were once widely deployed as dielectric and coolant fluids in electrical apparatus, carbonless copy paper and in heat transfer fluids.[1] Because of their longevity, PCBs are still widely in use, even though their manufacture has declined drastically since the 1960s, when a host of problems were identified.[2] Because of PCBs' environmental toxicity and classification as a persistent organic pollutant, PCB production was banned by the United States Congress in 1979 and by the Stockholm Convention on Persistent Organic Pollutants in 2001.[3] The International Research Agency on Cancer (IRAC), rendered PCBs as definite carcinogens in humans. According to the U.S. Environmental Protection Agency (EPA), PCBs cause cancer in animals and are probable human carcinogens.[4] Many rivers and buildings including schools, parks, and other sites are contaminated with PCBs, and there have been contaminations of food supplies with the toxins.




Chemical structure of PCBs. The possible positions of chlorine atoms on the benzene rings are denoted by numbers assigned to the carbon atoms.

Some PCBs share a structural similarity and toxic mode of action with dioxin.[5] Other toxic effects such as endocrine disruption (notably blocking of thyroid system functioning) and neurotoxicity are known.[6] The maximum allowable contaminant level in drinking water in the United States is set at zero, but because of water treatment technologies, a level of 0.5 parts per billion is the de facto level.[7]

The bromine analogues of PCBs are polybrominated biphenyls (PBBs), which have analogous applications and environmental concerns.




PCB warning label on a power transformer known to contain PCBs.

## Contents



## Physical and chemical properties

### Physical properties

The compounds are pale-yellow viscous liquids. They are hydrophobic, with low water solubilities — 0.0027-0.42 ng/L for Aroclors,[8], but they have high solubilities in most organic solvents, oils, and fats. They have low vapor pressures at room temperature.

They have dielectric constants of 2.5~2.7,[9] very high thermal conductivity,[8], and high flash points (from 170 to 380 °C).[8]

The density varies from 1.182 to 1.566 kg/L.[8] Other physical and chemical properties vary widely across the class. As the degree of chlorination increases, melting point and lipophilicity increase, and vapour pressure and water solubility decrease.[8]

PCBs do not easily break down or degrade, which made them attractive for industries. PCB mixtures are resistant to acids, bases, oxidation, hydrolysis, and temperature change.[10]

They can generate extremely toxic dibenzodioxins and dibenzofurans through partial oxidation. Intentional degradation as a treatment of unwanted PCBs generally requires high heat or catalysis (see Methods of destruction below).

PCBs readily penetrate skin, PVC (polyvinyl chloride), and latex (natural rubber).[11] PCB-resistant materials include Viton, polyethylene, polyvinyl acetate (PVA), polytetrafluoroethylene (PTFE), butyl rubber, nitrile rubber, and Neoprene.[11]

### Structure and toxicity

PCBs are derived from biphenyl, which has the formula $C_{12}H_{10}$, sometimes written $(C_6H_5)_2$. In PCBs most of the H's are replaced by chloride. It is a mixture of compounds, given the single identifying CAS number 1336-36-3 (https://tools.wmflabs.org/magnustools/cas.php?language=en&cas=1336-36-3&title=) ). There are 209 configurations with 1 to 10 chlorine atoms, of which about 130 are found in commercial PCBs.[8][2]

Toxic effects vary depending on the specific PCB. In terms of their structure and toxicity, PCBs fall into 2 distinct categories, referred to as coplanar or non-*ortho*-substituted arene substitution patterns and noncoplanar or *ortho*-substituted congeners.

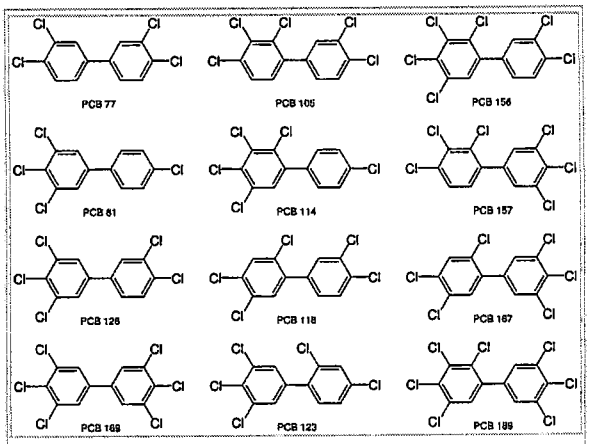
**Coplanar or non-*ortho***

The coplanar group members have a fairly rigid structure, with their two phenyl rings in the same plane. It renders their structure similar to polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans, and allows them to act like PCDDs, as an agonist of the aryl hydrocarbon receptor (AhR) in organisms. They are considered as contributors to overall dioxin toxicity, and the term dioxins and dioxin-like compounds is often used interchangeably when the environmental and toxic impact of these compounds is considered.[12][13]

**Noncoplanar**

Noncoplanar PCBs, with chlorine atoms at the *ortho* positions cause neurotoxic and immunotoxic effects, but at levels much higher than normally associated with dioxins. They do not activate the AhR, and are not considered part of the dioxin group, and as of 1998 had been of less concern to regulatory bodies.[14]

Di-ortho-substituted, non-coplanar PCBs interfere with intracellular signal transduction dependent on calcium which may lead to neurotoxicity.[15] In 2000 it was shown that ortho-PCBs can disrupt thyroid hormone transport by binding to transthyretin.[16]



Structures of the twelve dioxin-like PCBs

## Alternative names

Commercial PCB mixtures were marketed under the following names:[17][18]

**Brazil**

- Ascarel

**Former Czechoslovakia**

- Delor

**France**

- Phenoclor
- Pyralène (both used by Prodolec)

**Germany**

- Clophen (used by Bayer)

**Italy**

- Apirolio
- Fenclor

**Japan**

- Kanechlor (used by Kanegafuchi)
- Santotherm (used by Mitsubishi)
- Pyroclor

**Former USSR**

- Sovol
- Sovtol

**United Kingdom**

- Aroclor xxxx (used by Monsanto Company)
- Askarel

**United States**

- Aroclor xxxx (used by Monsanto Company)
- Asbestol
- Askarel
- Bakola131
- Chlorextol - Allis-Chalmers trade name
- Hydol
- Inerteen (used by Westinghouse)
- Noflamol
- Pyranol/Pyrenol, Chlorinol (widely used in GE's oil-filled "chlorinol"-branded metal can capacitors, detected by a pungent characteristic odor released by them (especially when they fail) in appliances/consumer & commercial electronic units & motors that utilized them from the early 1960s-late 1970s such as many A/C units, Seeburg Jukeboxes & Zenith TVs) (used by General Electric)
- Saf-T-Kuhl
- Therminol FR Series (Monsanto ceased production in 1971 [19]).

### Aroclor mixtures

The only North American producer, Monsanto Company, marketed PCBs under the trade name **Aroclor** from 1930 to 1977. These were sold under trade names followed by a 4-digit number. In general, the first two digits refer to the number of carbon atoms in the biphenyl skeleton (for PCBs this is 12); the second two numbers indicate the percentage of chlorine by mass in the mixture. Thus, Aroclor 1260 has 12 carbon atoms and contains 60% chlorine by mass. An exception is Aroclor 1016, which also has 12 carbon atoms, but has 42% chlorine by mass. Aroclor 1016 was prepared by the fractional distillation of Aroclor 1242, which excluded the higher boiling (i.e., more highly chlorinated) congeners.

Different Aroclors were used at different times and for different applications. In electrical equipment manufacturing in the USA, Aroclor 1260 and Aroclor 1254 were the main mixtures used before 1950; Aroclor 1242 was the main mixture used in the 1950s and 1960s until it was phased out in 1971 and replaced by Aroclor 1016.[8]

## Production

One estimate (2006) suggested that 1 million tons of PCBs had been produced. 40% of this material was thought to remain in use.[1] Another estimate put the total global production of PCBs on the order of 1.5 million tons. The United States was the single largest producer with over 600,000 tons produced between 1930 and 1977. The European region follows with nearly 450,000 tons through 1984. It is unlikely that a full inventory of global PCB production will ever be accurately tallied, as there were factories in Poland, East Germany, and Austria that produced unknown amounts of PCBs.[20]

## Applications

PCB's utility was based largely on their chemical stability, including low flammability, and high dielectric constant. In an electric arc, PCBs generate incombustible gases. Use of PCBs is commonly divided into closed and open applications.[1] Examples of closed applications include coolants and insulating fluids (transformer oil) for transformers and capacitors, such as those used in old fluorescent light ballasts,[21] hydraulic fluids, lubricating and cutting oils, etc. In contrast, the major open application of PCBs was in carbonless copy ("NCR") paper, which even nowadays results in paper contamination.[22] Other open applications were as plasticizers in paints and cements, stabilizing additives in flexible PVC coatings of electrical cables and electronic components, pesticide extenders, reactive flame retardants and sealants for caulking, adhesives, wood floor finishes, such as *Fabulon* and other products of Halowax in the U.S.,[23] de-dusting agents, waterproofing compounds, casting agents.[8] Because of its use as a plasticizer in paints and especially "coal tars" that were used widely to coat water tanks, bridges and other infrastructure pieces.

## Environmental transport and transformations

PCBs have entered the environment through both use and disposal. The environmental fate of PCBs is complex and global in scale.[8]

**Water**

Because of their low vapour pressure, PCBs accumulate primarily in the hydrosphere, despite their hydrophobicity, in the organic fraction of soil, and in organisms.

The hydrosphere is the main reservoir. The immense volume of water in the oceans is still capable of dissolving a significant quantity of PCBs.

**Air**

A small volume of PCBs has been detected throughout the earth's atmosphere. The atmosphere serves as the primary route for global transport of PCBs, particularly for those congeners with one to four chlorine atoms. In the atmosphere, PCBs may be degraded by hydroxyl radicals, or directly by photolysis of carbon-chlorine bonds (even if this is a less important process).

Atmospheric concentrations of PCBs tend to be lowest in rural areas, where they are typically in the picogram per cubic meter range, higher in suburban and urban areas, and highest in city centres, where they can reach 1 ng/m³ or more. In Milwaukee, an atmospheric concentration of 1.9 ng/m³ has been measured, and this source alone was estimated to account for 120 kg/year of PCBs entering Lake Michigan.[24] In 2008, concentrations as high as 35 ng/m³, 10 times higher than the EPA guideline limit of 3.4 ng/m³, have been documented inside some houses in the U.S.[23]

Volatilization of PCBs in soil was thought to be the primary source of PCBs in the atmosphere, but research suggests ventilation of PCB-contaminated indoor air from buildings is the primary source of PCB contamination in the atmosphere.[25]

#### Biosphere

In biosphere, PCBs can be degraded by either bacteria or eukaryotes, but the speed of the reaction depends on both the number and the disposition of chlorine atoms in the molecule: less substituted, meta- or para-substituted PCBs undergo biodegradation faster than more substituted congeners.

In bacteria, PCBs may be dechlorinated through reductive dechlorination, or oxidized by dioxygenase enzyme.

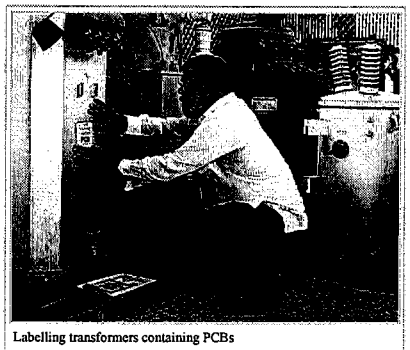
In eukaryotes, PCBs may be oxidized by the cytochrome P450 enzyme.

Like many lipiphilic toxins, PCBs biomagnify up the food chain. For instance, ducks can accumulate PCBs from eating fish and other aquatic life from contaminated rivers, and these can cause harm to human health or even death when eaten.[26]

PCBs can be transported by birds from aquatic sources onto land via feces and carcasses.[27]

## Health effects

The toxicity of PCBs varies considerably among congeners. The coplanar PCBs, known as nonortho PCBs because they are not substituted at the ring positions ortho to (next to) the other ring, (i.e. PCBs 77, 126, 169, etc.), tend to have dioxin-like properties, and generally are among the most toxic congeners. Because PCBs are almost invariably found in complex mixtures, the concept of toxic equivalency factors (TEFs) has been developed to facilitate risk assessment and regulation, where more toxic PCB congeners are assigned higher TEF values on a scale from 0 to 1. One of the most toxic compounds known, 2,3,7,8-tetrachlorodibenzo[p]dioxin, a PCDD, is assigned a TEF of 1.[28]


Labelling transformers containing PCBs

### Exposure and excretion

In general individuals are exposed to PCBs overwhelmingly through food, much less so by breathing contaminated air, and least by skin contact. Once exposed, some PCBs may change to other chemicals inside the body. These chemicals or unchanged PCBs can be excreted in feces or may remain in a person's body for years, with half lives estimated at 10–15 years.[29] PCBs collect in body fat and milk fat.[30] PCBs biomagnify up the food web and are present in fish and waterfowl of contaminated aquifers.[31] Infants are exposed to PCBs through breast milk or by intrauterine exposure through transplacental transfer of PCBs [30] and are at the top of the food chain.[32]:249ff

### Signs and symptoms

#### Humans

The most commonly observed health effects in people exposed to extremely high levels of PCBs are skin conditions, such as chloracne and rashes, but these were known to be symptoms of acute systemic poisoning dating back to 1922. Studies in workers exposed to PCBs have shown changes in blood and urine that may indicate liver damage. In Japan in 1968, 280 kg of PCB-contaminated rice bran oil was used as chicken feed, resulting in a mass poisoning, known as Yushō disease, in over 1800 people.[33] Common symptoms included dermal and ocular lesions, irregular menstrual cycles and lowered immune responses.[34][35][36] Other symptoms included fatigue, headaches, coughs, and unusual skin sores.[37] Additionally, in children, there were reports of poor cognitive development.[34]

Women exposed to PCBs before or during pregnancy can give birth to children with lowered cognitive ability, immune compromise, and motor control problems.[38][39][40]

There is evidence that crash dieters that have been exposed to PCBs have an elevated risk of health complications. Stored PCBs in the adipose tissue becomes mobilized into the blood when individuals begin to crash diet.[41] PCBs have shown toxic and mutagenic effects by interfering with hormones in the body. PCBs, depending on the specific congener, have been shown to both inhibit and imitate estradiol, the main sex hormone in females. Imitation of the estrogen compound can feed estrogen-dependent breast cancer cells, and possibly cause other cancers, such as uterine or cervical. Inhibition of estradiol can lead to serious developmental problems for both males and females, including sexual, skeletal, and mental development issues.[42] In a cross-sectional study, PCBs were found to be negatively associated with testosterone levels in adolescent boys.[43]

High PCB levels in adults have been shown to result in reduced levels of the thyroid hormone triiodothyronine, which affects almost every physiological process in the body, including growth and development, metabolism, body temperature, and heart rate. It also resulted in reduced immunity and increased thyroid disorders.[29][44]

#### Animals

Animals that eat PCB-contaminated food even for short periods of time suffer liver damage and may die. In 1968 in Japan, 400,000 birds died after eating poultry feed that was contaminated with PCBs.[45] Animals that ingest smaller amounts of PCBs in food over several weeks or months develop various health effects, including anemia; acne-like skin conditions (chloracne); liver, stomach, and thyroid gland injuries (including hepatocarcinoma),, and thymocyte apoptosis.[29] Other effects of PCBs in animals include changes in the immune system, behavioral alterations, and impaired reproduction.[29] PCBs that have dioxin-like activity are known to cause a variety of teratogenic effects in animals. Exposure to PCBs causes hearing loss and symptoms similar to hypothyroidism in rats.[46]

### Cancer

In 2013, the International Agency for Research on Cancer (IARC) classified dioxin-like PCBs as human carcinogens.[47] According to the U.S. EPA, PCBs have been shown to cause cancer in animals and evidence supports a cancer-causing effect in humans.[4] Per EPA, studies have found increases in malignant melanoma and rare liver cancers in PCB workers.[4]

In 2013, the International Association for Research on Cancer (IARC) determined that the evidence for PCBs causing non-Hodgkin Lymphoma is "limited" and "not consistent".[47] In contrast an association between elevated blood levels of PCBs and non-Hodgkin lymphoma had been previously accepted.[48]

PCBs may play a role in the development of cancers of the immune system because some tests of laboratory animals subjected to very high doses of PCBs have shown effects on the animals' immune system, and some studies of human populations have reported an association between environmental levels of PCBs and immune response.[4]

## History

In 1865 the first "PCB-like" chemical was discovered, and was found to be a byproduct of coal tar. Years later in 1881, German chemists synthesized the first PCB in a laboratory. Between then and 1914, large amounts of PCBs were released into the environment, to the extent that there are still measurable amounts of PCBs in feathers of birds currently held in museums.[49]

In 1935, Monsanto Chemical Company (now Solutia Inc) took over commercial production of PCBs from Swann Chemical Company which had begun in 1929. PCBs, originally termed "chlorinated diphenyls", were commercially produced as mixtures of isomers at different degrees of chlorination. The electric industry used PCBs as a non-flammable replacement for mineral oil to cool and insulate industrial transformers and capacitors. PCBs were also commonly used as heat stabilizer in cables and electronic components to enhance the heat and fire resistance of PVC.[50]

In the 1930s, the toxicity associated with PCBs and other chlorinated hydrocarbons, including polychlorinated naphthalenes, was recognized because of a variety of industrial incidents.[51] Between 1936 and 1937, there were several medical cases and papers released on the possible link between PCBs and its detrimental health effects. In 1936 a U.S. Public Health Service official described the wife and child of a worker from the Monsanto Industrial Chemical Company who exhibited blackheads and pustules on their skin. The official attributed these symptoms to contact with the worker's clothing after he returned from work. In 1937, a conference about the hazards was organized at Harvard School of Public Health, and a number of publications referring to the toxicity of various chlorinated hydrocarbons were published before 1940.[52] In 1947 Robert Brown reminded chemists that Arochlors were "objectionably toxic. Thus the maximum permissible concentration for an 8-hr. day is 1 mg/m$^3$ of air. They also produce a serious and disfiguring dermatitis".[53]

In 1954 Japan, Kanegafuchi Chemical Co. Ltd. (Kaneka Corporation) first produced PCBs, and continued until 1972.[8]

Through the 1960s Monsanto Chemical Company knew increasingly more about PCB's harmful effects on humans and the environment, per internal leaked documents released in 2002, yet PCB manufacture and use continued with few restraints until the 1970s.[54]

In 1966, PCBs were determined by Swedish chemist Dr. Soren Jensen to be an environmental contaminant.[55] Jensen, according to a 1994 article in Sierra, named chemicals PCBs, which previously, had simply been called "phenols" or referred to by various trade names, such as Aroclor, Kanechlor, Pyrenol, Chlorinol and others.

In 1972, PCB production plants existed in Austria, the then Federal Republic of Germany, France, Great Britain, Italy, Japan, Spain, USSR, and USA.[8]

In the early 1970s, Ward B. Stone of the New York State Department of Environmental Conservation (NYSDEC) first published his findings that PCBs were leaking from transformers and had contaminated the soil at the bottom of utility poles.

There have been allegations that Industrial Bio-Test Laboratories engaged in data falsification in testing relating to PCBs.[56][57][58][59]

In 2003, Monsanto and Solutia Inc., a Monsanto corporate spin-off, reached a $700 million settlement with the residents of West Anniston, Alabama who had been affected by the manufacturing and dumping of PCBs.[60][61] In a trial lasting six weeks, the jury found that "Monsanto had engaged in outrageous behavior, and held the corporations and its corporate successors liable on all six counts it considered - including negligence, nuisance, wantonness and suppression of the truth."[62]

Existing products containing PCBs which are "totally enclosed uses" such as insulating fluids in transformers and capacitors, vacuum pump fluids, and hydraulic fluid, are allowed to remain in use.[63]

Old power transformers are a major legacy source of PCBs. Even units not originally filled with PCB may be contaminated, since PCB and oil mix freely and any given transformer may have been refilled from hoses or tanks also used with PCBs.

The public, legal, and scientific concerns about PCBs arose from research indicating they are likely carcinogens having the potential to adversely impact the environment and, therefore, undesirable as commercial products. Despite active research spanning five decades, extensive regulatory actions, and an effective ban on their production since the 1970s, PCBs still persist in the environment and remain a focus of attention.[8]

## Pollution due to PCBs

### Belgium

In 1999, the Dioxin Affair occurred when 50 kg of PCB transformer oils were added to a stock of recycled fat used for the production of 500 tonnes of animal feed, eventually affecting around 2,500 farms in several countries.[64][65] The name *Dioxin Affair* was coined from early misdiagnosis of dioxins as the primary contaminants, when in fact they turned out to be a relatively small part of the contamination caused by thermal reactions of PCBs. The PCB congener pattern suggested the contamination was from a mixture of Aroclor 1260 & 1254. Over 9 million chickens, and 60,000 pigs were destroyed because of the contamination. The extent of human health effects has been debated, in part because of the use of differing risk assessment methods. One group predicted increased cancer rates, and increased rates of neurological problems in those exposed as neonates. A second study suggested carcinogenic effects were unlikely and that the primary risk would be associated with developmental effects due to exposure in pregnancy and neonates.[65] Two businessmen who knowingly sold the contaminated feed ingredient received two-year suspended sentences for their role in the crisis.[66]

### Italy

The Italian company Caffaro, located in Brescia, specialized in producing PCBs from 1938 to 1984, following the acquisition of the exclusive rights to use the patent in Italy from Monsanto. The pollution resulting from this factory and the case of Anniston, in the USA, are the largest known cases in the world of PCB contamination in water and soil, in terms of the amount of toxic substance dispersed, size of the area contaminated, number of people involved and duration of production.

The values reported by the local health authority (ASL) of Brescia since 1999 are 5,000 times above the limits set by Ministerial Decree 471/1999 (levels for residential areas, 0.001 mg/kg). As a result of this and other investigations, in June 2001, a complaint of an environmental disaster was presented to the Public Prosecutor's Office of Brescia. Research on the adult population of Brescia showed that residents of some urban areas, former workers of the plant, and consumers of contaminated food, have PCB levels in their bodies that are in many cases 10-20 times higher than reference values in comparable general populations.[67] PCBs entered the human food supply by animals grazing on contaminated pastures near the factory, especially in local veal mostly eaten by farmers' families.[68] The exposed population showed an elevated risk of Non-Hodgkin lymphoma, but not for other specific cancers.[69]

### Japan

In 1968, a mixture of dioxins and PCBs got into rice bran oil produced in northern Kyushu. Contaminated cooking oil sickened more than 1860 people. The symptoms were called Yushō disease.[33]

In Okinawa, high levels of PCB contamination in soil on Kadena Air Base were reported in 1987 at thousands of parts per million, some of the highest levels found in any pollution site in the world.[70]

### Republic of Ireland

In December 2008, a number of Irish news sources reported testing had revealed "extremely high" levels of dioxins, by toxic equivalent, in pork products, ranging from 80 to 200 times the EU's upper safe limit of 1.5 pg WHO-$TEQ_{DFP}$/μg i.e. 0.12 to 0.3 parts per billion.[71][72]

Brendan Smith, the Minister for Agriculture, Fisheries and Food, stated the pork contamination was caused by PCB-contaminated feed that was used on 9 of Ireland's 400 pig farms, and only one feed supplier was involved.[71][73] Smith added that 38 beef farms also used the same contaminated feed, but those farms were quickly isolated and no contaminated beef entered the food chain.[74] While the contamination was limited to just 9 pig farms, the Irish government requested the immediate withdrawal and disposal of all pork-containing products produced in Ireland and purchased since 1 September 2008. This request for withdrawal of pork products was confirmed in a press release by the Food Safety Authority of Ireland on December 6.[75]

It is thought that the incident resulted from the contamination of fuel oil used in a drying burner at a single feed processor, with PCBs. The resulting combustion produced a highly toxic mixture of PCBs, dioxins and furans, which was included in the feed produced and subsequently fed to a large number of pigs.[76]

### Kenya

In Kenya, a number of cases have been reported in the 2010s of thieves selling transformer oil, stolen from electric transformers, to the operators of roadside food stalls for use in deep frying. When used for frying, it is reported that transformer oil lasts much longer than regular cooking oil. The downside of this misuse of the transformer oil is the threat to the health of the consumers, due to the presence of PCBs.[77]

### Slovakia

The chemical plant **Chemko** in Strážske (east Slovakia) was an important producer of polychlorinated biphenyls for the former communist block (Comecon) until 1984. Chemko contaminated a large part of east Slovakia, especially the sediments of the Laborec river and reservoir Zemplínska šírava.[78][79]

### Slovenia

Between 1962 and 1983, the Iskra Kondenzatorji company in Semič (White Carniola, Southeast Slovenia) manufactured capacitors using PCBs. Due to the wastewater and improperly disposed waste products, the area (including the Krupa and Lahinja rivers) became highly contaminated with PCBs. The pollution was discovered in 1983, when the Krupa river was meant to become a water supply source. The area was sanitized then, but the soil and water are still highly polluted. Traces of PCBs were found in food (eggs, cow milk, walnuts) and Krupa is still the most PCB-polluted river in the world.

### United Kingdom

Monsanto manufactured PCBs at its chemical plant in Newport, South Wales, until the mid- to late-1970s. During this period, waste matter, including PCBs, from the Newport site was dumped at a disused quarry near Groes-faen, west of Cardiff, from where it continues to be released in waste water discharges.[80]

### Spain

Several cetacean species have very high mean blubber PCB concentrations likely to cause population declines and suppress population recovery. Striped dolphins, bottlenose dolphins and killer whales were found to

have mean levels that markedly exceeded all known marine mammal PCB toxicity thresholds. The western Mediterranean Sea and the south-west Iberian Peninsula were identified as "hotspots".[81]

### United States

#### Alabama

PCBs (manufactured through most of the 20th century) originating from Monsanto Chemical Company in Anniston, Alabama were dumped into Snow Creek, which then spread to Choccolocco Creek, then Logan Martin Lake.[82] In the early 2000s, class action lawsuits were settled by local land owners, including those on Logan Martin Lake, and Lay Reservoir (downstream on the Coosa River), for the PCB pollution. Donald Stewart, former Senator from Alabama, first learned of the concerns of hundreds of west Anniston residents after representing a church which had been approached about selling its property by Monsanto. Stewart went on the be the pioneer and lead attorney in the first and majority of cases against Monsanto and focused on residents in the immediate area known to be most polluted. Other attorneys later joined in to file suits for those outside the main immediate area around the plant; one of these was the late Johnnie Cochran.

In 2007, the highest pollution levels remained concentrated in Snow and Choccolocco Creeks.[83] Concentrations in fish have declined and continue to decline over time; sediment disturbance, however, can resuspend the PCBs from the sediment back into the water column and food web.

#### Great Lakes

In 1976 environmentalists found PCBs in the sludge at Waukegan Harbor, the southwest end of Lake Michigan. They were able to trace the source of the PCBs back to the Outboard Marine Corporation that was producing boat motors next to the harbor. By 1982, the Outboard Marine Corporation was court-ordered to release quantitative data referring to their PCB waste released. The data stated that from 1954 they released 100,000 tons of PCB into the environment, and that the sludge contained PCBs in concentrations as high as 50%.[84][85]

Late during the construction of new on- and off-ramps in the M-13 interchange on the Zilwaukee bridge approach, workers uncovered an uncharted landfill containing PCB-contaminated waste, necessitating an environmental cleanup. In August 22, 1989, The Detroit Free Press noted that the clean up costs would cost over $100,000 and delay the opening of the ramps to the M-13 interchange in Zilwaukee, which were scheduled for opening that year.[86]

Much of the Great Lakes area were still heavily polluted with PCBs in 1988, despite extensive remediation work.[87] Locally caught fresh water fish and shellfish are contaminated with PCBs, and their consumption is restricted.[88]

#### Indiana

From the late 1950s through 1977, Westinghouse Electric used PCBs in the manufacture of capacitors in its Bloomington, Indiana plant. Reject capacitors were hauled and dumped in area salvage yards and landfills, including Bennett's Dump, Neal's Landfill and Lemon Lane Landfill.[89] Workers also dumped PCB oil down factory drains, which contaminated the city sewage treatment plant.[90] The City of Bloomington gave away the sludge to area farmers and gardeners, creating anywhere from 200 to 2000 sites, which remain unaddressed. Over 2 million pounds of PCBs were estimated to have been dumped in Monroe and Owen counties. Although federal and state authorities have been working on the sites' environmental remediation, many areas remain contaminated. Concerns have been raised regarding the removal of PCBs from the karst limestone topography, and regarding the possible disposal options. To date, the Westinghouse Bloomington PCB Superfund site case does not have a Remedial Investigation/Feasibility Study (RI/FS) and Record of Decision (ROD), although Westinghouse signed a US Department of Justice Consent Decree in 1985.[89] The 1985 consent decree required Westinghouse to construct an incinerator that would incinerate PCB-contaminated materials. Because of public opposition to the incinerator, however, the State of Indiana passed a number of laws that delayed and blocked its construction. The parties to the consent decree began to explore alternative remedies in 1994 for six of the main PCB contaminated sites in the consent decree. Hundreds of sites remain unaddressed as of 2014. Monroe County will never be PCB-free, as noted in a 2014 Indiana University program about the local contamination.[89]

On 15 February 2008, Monroe County approved a plan to clean up the three remaining contaminated sites in the City of Bloomington, at a cost of $9.6 million to CBS Corp., the successor of Westinghouse. In 1999, Viacom bought CBS, so they are current responsible party for the PCB sites.[91]

#### Massachusetts

Pittsfield, in western Massachusetts, was home to the General Electric (GE) transformer and capacitor divisions, and electrical generating equipment built and repaired in Pittsfield powered the electrical utility grid throughout the nation. PCB-contaminated oil routinely migrated from GE's 254-acre (1.03 $km^2$) industrial plant located in the very center of the city to the surrounding groundwater, nearby Silver Lake, and to the Housatonic River, which flows through Massachusetts, Connecticut, and down to Long Island Sound.[92] PCB-containing solid material was widely used as fill, including oxbows of the Housatonic River.[92] Fish and waterfowl who live in and around the river contain significant levels of PCBs and are not safe to eat.[93]

New Bedford Harbor, which is a listed Superfund site,[94] contains some of the highest sediment concentrations in the marine environment.[95]

#### New York

Pollution of the Hudson River is largely due to dumping of PCBs by General Electric from 1947 to 1977.[96] GE dumped an estimated 1.3 million pounds of PCBs into the Hudson River during these years.[97] This pollution caused a range of harmful effects to wildlife and people who eat fish from the river or drink the water.[98]

Love Canal is a neighborhood in Niagara Falls, New York that was heavily contaminated with toxic waste including PCBs.[99]

Eighteen Mile Creek in Lockport, New York is an EPA Superfund site for PCBs contamination.[100]

#### North Carolina

One of the largest deliberate PCB spills in American history occurred in the summer of 1978 when 31,000 gallons of PCB-contaminated oil were illegally sprayed in 3-foot (0.91 m) swaths along the roadsides of some 240 miles (390 km) of North Carolina highway shoulders in 14 counties and at the Fort Bragg Army Base. The crime, known as "the midnight dumpings", occurred over nearly 2 weeks, as drivers of a black-painted tanker truck drove down one side of rural Piedmont highways spraying PCB-laden waste and then up the other side the following night.

Under Governor James B. Hunt, Jr., state officials then erected large, yellow warning signs along the contaminated highways that read: "CAUTION: PCB Chemical Spills Along Highway Shoulders." The illegal dumping is believed to have been motivated by the passing of the Toxic Substances Control Act (TSCA), which became effective on August 2, 1978 and increased the expense of chemical waste disposal.

Within a couple of weeks of the crime, Robert Burns and his sons, Timothy and Randall, were arrested for dumping the PCBs along the roadsides. Burns was a business partner of Robert "Buck" Ward, Jr., of the Ward PCB Transformer Company, in Raleigh. Burns and sons pleaded guilty to state and Federal criminal charages; Burns received a three to five-year prison sentence. Ward was acquitted of state charges in the dumping, but was sentenced to 18 months prison time for violation of TSCA.

Cleanup and disposal of the roadside PCBs generated controversy, as the Governor's plan to pick up the roadside PCBs and to bury them in a landfill in rural Warren County were strongly opposed in 1982 by local residents.[101]

In October 2013, at the request of the South Carolina Department of Health and Environmental Control (SCDHEC), the City of Charlotte, North Carolina decided to stop applying sewage sludge to land while authorities investigated the source of PCB contamination.[102] In February 2014, the City of Charlotte admitted PCBs have entered their sewage treatment centers as well.[103]

After the 2013 SCDHEC had issued emergency regulations[104] the City of Charlotte discovered high levels of PCBs entering its sewage waste water treatment plants, where sewage is converted to sewage sludge.[103] The city at first denied it had a problem, then admitted an "event" occurred in February 2014, and in April that the problem had occurred much earlier.[102][105] The city stated that its very first test with a newly changed test method revealed very high PCB levels in its sewage sludge farm field fertilizer. Because of the widespread use of the contaminated sludge, SCDHEC subsequently issued PCB fish advisories for nearly all streams and rivers bordering farm fields that had been applied with city waste.[106]

#### Ohio

The Clyde cancer cluster (also known as the Sandusky County cancer cluster) is a childhood cancer cluster that has affected many families in Clyde, Ohio and surrounding areas. PCBs were found in soil in a public park within the area of the cancer cluster.

In Akron, Ohio, soil was contaminated and noxious PCB-laden fumes had been put into the air by an electrical transformer deconstruction operation from the 1930s to the 1960s.[107]

#### South Carolina

From 1955 until 1977, the Sangamo Weston plant in Pickens, SC, used PCBs to manufacture capacitors, and dumped 400,000 pounds of PCB contaminated wastewater into the Twelve Mile Creek. In 1990, the EPA declared the 228 acres (0.92 $km^2$) site of the capacitor plant, its landfills and the polluted watershed, which stretches nearly 1,000 acres (4.0 $km^2$) downstream to Lake Hartwell as a Superfund site. Two dams on the Twelve Mile Creek are to be removed and on Feb. 22, 2011 the first of two dams began to be dismantled. Some contaminated sediment is being removed from the site and hauled away, while other sediment is pumped into a series of settling ponds.[108][109]

In 2009, the state environmental regulators SCDHEC noted fish species in Lake Wateree contained exceptionally high levels of PCB contamination and posted adviseries that fish from the lake were unsafe to eat.

In 2013, the state environmental regulators issued a rare emergency order, banning all sewage sludge from being land applied or deposited on landfills, as it contained very high levels of PCBs. The problem had not been discovered until thousands of acres of farm land in the state had been contaminated by the hazardous sludge. A criminal investigation to determine the perpetrator of this crime was launched.[110]

#### Washington

As of 2015, several bodies of water in the state of Washington were contaminated with PCBs, including the Columbia River, the Duwamish River, Green Lake, Lake Washington, the Okanogan River, Puget Sound, the Spokane River, the Walla Walla River, the Wenatchee River, and the Yakima River.[111] A study by Washington State published in 2011 found that the two largest sources of PCB flow into the Spokane River were City of Spokane stormwater (44%), municipal and industrial discharges (20%).[112] PCBs entered the environment through paint, hydraulic fluids, sealants, inks and have been found in river sediment and wild life. Spokane utilities will spend $300 million to prevent PCBs from entering the river in anticipation of a 2017 federal deadline to do so.[113] In August 2015 Spokane joined other U.S cities like San Diego and San Jose, California, and Westport, Massachusetts. in seeking damages from Monsanto.[114]

#### Wisconsin

From 1954 until 1971, the Fox River in Appleton, Wisconsin had PCBs deposited into it from Appleton Paper/NCR, P.H. Gladfelter, Georgia Pacific and other notable local paper manufacturing facilities. The Wisconsin DNR estimates that after wastewater treatment the PCB discharges to the Fox River due to production losses ranged from 81,000 kg to 138,000 kg. (178,572 lbs. to 304,235 lbs). The production of Carbon Copy Paper and its byproducts led to the discharge into the river. Fox River clean up is ongoing.[115]

## Regulation

In 1972 the Japanese government banned the production, use, and import of PCBs.[8]

In 1973, the use of PCBs in "open" or "dissipative" sources, such as plasticisers in paints and cements, casting agents, fire retardant fabric treatments and heat stabilizing additives for PVC electrical insulation, adhesives, paints and waterproofing, railroad ties was banned in Sweden.

In 1979, concern over the toxicity and persistence (chemical stability) of PCBs in the environment led the United States Congress to ban their domestic production.[116]

In 1981, the UK banned closed uses of PCBs in new equipment, and nearly all UK PCB synthesis ceased; closed uses in existing equipment containing in excess of 5 litres of PCBs were not stopped until December 2000.[117]

## Methods of destruction

### Physical

PCBs are technically attractive because of their inertness, which includes their resistance to combustion. Nonetheless, they can be effectively destroyed by Incineration at 1000 °C. When combusted at lower temperatures, they convert in part to more hazardous materials, including dibenzofurans and dibenzodioxins. When conducted properly, the combustion products are water, carbon dioxide, and hydrogen chloride. In some cases, the PCBs are combusted as a solution in kerosene. PCBs have also been destroyed by pyrolysis in the presence of alkali metal carbonates.[1]

Thermal desorption is highly effective at removing PCBs from soil.[118]

### Chemical

PCBs are fairly chemically unreactive, this property being attractive for its application as an inert material. They resist oxidation.[119] Many chemical compounds are available to destroy or reduce the PCBs. Commonly, PCBs are degraded by basis mixtures of glycols, which displace some or all chloride. Also effective are reductants such as sodium or sodium naphthenide.[1] Vitamin B12 has also shown promise.[120]

### Microbial

Some micro-organisms degrade PCBs by reducing the C-Cl bonds. Microbial dechlorination tends to be rather slow-acting in comparison to other methods. Enzymes extracted from microbes can show PCB activity. In 2005, *Shewanella oneidensis* biodegraded a high percentage of PCBs in soil samples.[121] A low voltage current can stimulate the microbial degradation of PCBs.[122]

### Fungal

There is research showing that some ligninolytic fungi can degrade PCBs.[123]

## Homologs

For a complete list of the 209 PCB congeners, see PCB congener list. Note that biphenyl, while not technically a PCB congener because of its lack of chlorine substituents, is still typically included in the literature.

| PCB homolog | CASRN | Cl substituents | Number of congeners |
|---|---|---|---|
| Biphenyl (not a PCB) | 92-52-4 | 0 | 1 |
| Monochlorobiphenyl | 27323-18-8 | 1 | 3 |
| Dichlorobiphenyl | 25512-42-9 | 2 | 12 |
| Trichlorobiphenyl | 25323-68-6 | 3 | 24 |
| Tetrachlorobiphenyl | 26914-33-0 | 4 | 42 |
| Pentachlorobiphenyl | 25429-29-2 | 5 | 46 |
| Hexachlorobiphenyl | 26601-64-9 | 6 | 42 |
| Heptachlorobiphenyl | 28655-71-2 | 7 | 24 |
| Octachlorobiphenyl | 55722-26-4 | 8 | 12 |
| Nonachlorobiphenyl | 53742-07-7 | 9 | 3 |
| Decachlorobiphenyl | 2051-24-3 | 10 | 1 |

## See also

- Bay mud
- Organochlorine compound
- Polybrominated biphenyl
- *Zodiac*, a novel by Neal Stephenson which involves PCBs and their impact on the environment.

## References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## External links

- ATSDR Toxicological Profile (http://www.atsdr.cdc.gov/toxprofiles/tp17.pdf) U.S. Department of Health and Human Services
- IARC PCB Monograph (http://monographs.iarc.fr/ENG/Monographs/suppl7/suppl7.pdf)
- PCBs (http://www.epa.gov/pcb/) at the US EPA
- National Toxicology Program technical reports searched for "PCB" (http://ntpsearch.niehs.nih.gov/texis/search/?query=PCB&pr=ntp_web_entire_site_all&mu=Entire+NTP+Site)
- Polychlorinated Byphenyls: Human Health Aspects (http://www.inchem.org/documents/cicads/cicads/cicad55.htm) by the WHO
- Current Intelligence Bulletin 7: Polychlorinated (PCBs) (http://www.cdc.gov/niosh/docs/1970/78127_7.html)—NIOSH/CDC (1975)
- It's Your Health - PCBs (http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/pcb-bpc-eng.php) (Health Canada)

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# 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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In further analyses of the Exxon refineries and chemical plants in Baton Rouge, LA, Baytown, TX, and Bayway/Bayonne, NJ, mortality was examined by occupation and work site (Hanis *et al.*, 1985b). Directly adjusted death rates for each subgroup of interest and for the total US population were calculated using the age, sex, race and calendar year distribution of the total cohort as a standard; thus, direct comparisons could be made between mortality rates in cohort subgroups and in the US population by calculating ratios of the directly adjusted rates. Workers were classified as having been 'potentially exposed' or 'unexposed' on the basis of their longest-held job. The 'exposed' category included those who had worked as process operators, mechanical workers and labourers (75% of the study population); while the 'unexposed' category included primarily white-collar office workers (22% of the population). Cause-specific cancer rates were higher among potentially exposed workers than among the unexposed for every cancer site except brain, but none of the site-specific rate ratios was significantly different from 1.0. Directly adjusted death rates were consistently greater than those for the total US population only for renal cancer in each of the three plants. The death rates for pancreatic cancer were higher than the US rates among employees at the Baton Rouge and Baytown plants only, and elevated rates of large intestinal cancer occurred at the Baytown and Bayway/Bayonne plants.

A series of investigations of mortality has been performed among members of the Oil, Chemical and Atomic Workers international union (OCAW) in Texas (Thomas *et al.*, 1980, 1982a,b, 1984). In all of these reports, proportionate mortality among male members of the OCAW was compared with that among US men, adjusting for age, race and calendar period.

The first report concerned 3105 Union members in Texas whose deaths in 1947–77 while actively employed were reported to OCAW and whose death certificates could be located (90%; Thomas *et al.*, 1980). Of the white OCAW members, 1722 had held blue-collar jobs in petroleum refineries and petrochemical plants, primarily in maintenance and production (Thomas *et al.*, 1982a), and had significant excess frequencies of deaths from cancers of the digestive and respiratory systems, skin and brain (ICD8 191, 192).

Subsequent analyses were limited to three petroleum refineries located in the Beaumont/Port Arthur area of the Texas Gulf Coast (Thomas *et al.*, 1982a,b, 1984) and included 1194 retired workers as well as those who had died while actively employed between 1943 and 1979. Among 2509 deceased men who had been employed by the three refineries combined (Thomas *et al.*, 1982a,b), the adjusted PMRs using national rates for all causes of death were significantly elevated for all cancers as well as for cancers of the stomach, pancreas, skin (ICD8 172, 173), prostate and brain (ICD8 191, 192) and for leukaemia. Nine deaths from multiple myeloma were observed and 4.6 were expected, but the PMR was not significant. When national cancer rates were used to calculate proportionate cancer mortality ratios (PCMRs), these ratios were also elevated but significantly so only for brain and leukaemia in whites. When county cancer mortality rates were used, none of the PCMRs was significantly raised. A detailed examination of brain tumour mortality in whites indicated that OCAW members had had elevated frequencies of mortality from benign and unspecified tumours of the brain as well as those specified on death certificates as malignant. [The Working Group noted that, of the 2509 deaths studied,

Mortality from leukaemia was significantly elevated in two refinery cohorts; in one of these, mortality increased with duration employed and also with time since first employment. Nonsignificant excess mortality from leukaemia was reported among two additional cohorts; in one of these, the excess was significant for boiler makers and pipe fitters. Elevated mortality from unspecified lymphatic leukaemia, unspecified myeloid leukaemia and acute monocytic leukaemia, but not other cell types, was reported in a subset of workers in the British cohort whose exposures included benzene. A significantly elevated incidence of lymphocytic leukaemia was reported in a large cohort study which included many of the refineries in the USA. Excess mortality from 'cancer of other lymphatic tissues' (multiple myeloma, polycythaemia vera and non-Hodgkin's lymphoma, excluding lymphosarcoma and reticulum-cell sarcoma), which was not significant, was reported in five refinery cohorts. One report indicated significant excess mortality from leukaemia and 'cancer of other lymphatic tissues' combined.

Mortality from malignant neoplasms of the brain was elevated in six of the refinery cohorts, but this was significant in only one of the studies and only for workers with short duration of employment. The elevated mortality was seen in operators and in maintenance and laboratory workers. A case-control study of astrocytic brain tumours showed a decreasing trend in risk with duration employed among men who had ever worked in petroleum refining during their lifetime. Another case-control study showed a significantly elevated risk for malignant neoplasms of the brain among men employed in petroleum refining.

Stomach cancer mortality was elevated among six refinery cohorts, significantly so in only one, among labourers, riggers and fire and safety workers; it was associated with lubricating oil production in one refinery and with solvent dewaxing in another. Mortality increased with increasing duration of employment in one of the studies.

Kidney cancer mortality was elevated, but not significantly so, among three petroleum refinery cohorts, particularly among operators, labourers and maintenance workers. Kidney and bladder cancer mortality combined was elevated in one refinery cohort. Five case-control studies of bladder cancer showed excess risk associated with employment in petroleum refining; the results were significant in two of these.

Pancreatic cancer mortality was reported to be elevated in four petroleum refining cohorts, and was associated with employment in the petroleum refining industry in one case-control study; however, none of these results was significant.

Excess mortality from cancer of the prostate, which increased with duration of employment, was reported in two refinery cohorts, and an overall excess was reported in two others. The only result that attained significance was found for men employed for 20 years or more in one of the refineries.

Lung cancer mortality was elevated in two refinery cohorts but not significantly so. There was a significant excess of lung cancer among workers with daily exposure to petroleum and its products in one of these cohorts. In five cohort studies, significant deficits in mortality from lung cancer were seen. In a case-control study, refinery maintenance workers and operators had a significantly elevated risk for lung cancer.

# DIESEL FUELS

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

*Diesel fuel (general)*

*Chem. Abstr. Services Reg. No.*: 68334-30-5
*Chem. Abstr. Name*: Diesel oil
*IUPAC Systematic Name*: –
*Synonyms*: Auto diesel; automotive diesel oil (ADO); derv; diesel; diesel fuel oil; diesel oil; gas oil

*Diesel fuel No. 1*

*Chem. Abstr. Services Reg. No.*: not assigned (essentially equivalent to kerosene, 8008-20-6)
*Synonyms*: Diesel fuel oil No. 1; diesel oil No. 1; No. 1 diesel (These designations are not used in European terminology. Where fuels similar to US diesel fuel No. 1 are available in Europe (Scandinavia), they are commonly referred to as kerosine or Arctic diesel. In some cases, non-descriptive terminology applies, e.g., dipolar in Sweden for special kerosene fuels used in urban areas.)

*Diesel fuel No. 2*

*Chem. Abstr. Services Reg. No.*: 68476-34-6 (applicable for specific viscosity limits)
*Chem. Abstr. Name*: No. 2 diesel fuel
*Synonyms*: Diesel fuel; diesel fuel oil No. 2; diesel oil No. 2; No. 2 diesel (term not used in Europe) In the UK, distillate fuels are frequently categorized as Class A1 (road diesel) and A2 (off-highway diesel).

*Diesel fuel No. 4*

*Chem. Abstr. Services Reg. No.*: not assigned
*Synonyms*: Marine diesel fuel; distillate marine diesel fuel

## 1.2 Description

The diesel engine and diesel fuel which provides the energy to run the engine derive their names from Rudolf Diesel, the German engineer who patented the engine design in 1892 (Anon., 1966). He operated his first successful engine in 1897 (Lane, 1980).

In its early history, the diesel engine was exploited for its versatility and ability to use a variety of cheap fuels. More recently, the requirements of efficiency and economics have prompted the development of fuel standards to meet desired performance characteristics, particularly for transportation service. Diesel fuels are appreciably less volatile than gasoline. They are classed as middle distillates and are more dense than gasoline, thus providing more energy per unit volume than gasoline. The product definition for diesel oil in the US Chemical Substances Inventory under the Toxic Substances Control Act is:

> *Diesel Oil* (CAS No. 68334-30-5) — A complex combination of hydrocarbons produced by the distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of $C_9$—$C_{20}$ and boiling in the range of approximately 163—357°C.

In Europe, carbon numbers up to 28 and final boiling-points up to 390°C can be found for automotive diesel oil (CONCAWE, 1985).

The US definition encompasses both diesel fuel No. 1 and diesel fuel No. 2. There is no US Chemical Substances Inventory description for diesel fuel No. 1 or the equivalent European kerosene grade; however, in practice, this product is generally a straight-run petroleum distillate with a boiling range consistent with that of kerosene [5] (refer to Table 2 and Figure 1 of the monograph on occupational exposures in petroleum refining and to the monograph on jet fuel for the processing history of kerosene). Kerosene, and hence diesel fuel No. 1, consists of hydrocarbons with carbon numbers predominantly in the range of $C_9$—$C_{16}$ and boiling in the range of approximately 150-300°C. Fuel oil No. 1 (heating) and kerosene used in Europe for heating applications have similar boiling ranges and are described in the monograph on fuel oils.

Diesel fuel No. 2 manufactured in the USA is generally a blend of straight-run and catalytically cracked streams, including straight-run kerosene [5], straight-run middle distillate [6], hydrodesulfurized middle distillate [6A] and light catalytically [24] and thermally cracked [30] distillates. The boiling range is generally approximately 160—360°C. The major component streams in European diesel fuels are presented in Table 1.

Diesel fuel No. 4 for low- and medium-speed engines, also characterized as a marine diesel fuel, is approximately similar to fuel oil No. 4 (CAS No. 68476-31-3), discussed in the monograph on fuel oils. As indicated in Table 2, American Society for Testing and Materials (ASTM) No. 4-D grade is more viscous than diesel fuel No. 2 and allows higher levels of ash and sulfur in the product. A No. 4 grade oil is generally classed as a residual fuel. It may be made either as a refinery stream which contains high boiling material classed as residual oil [8, 21, 31] or by blending residual fuel oil with a lighter material such as diesel fuel No. 2. In either case, it normally contains up to 15% residual oil components (CONCAWE, 1985). Some engines have been designed to operate on two different fuels,

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

## VOLUME 98

## Painting, Firefighting, and Shiftwork

**Table 2.1. Cohort, linkage and proportionate mortality studies of painters published since Monograph Volume 47, 1989**

| Reference, location, time period | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure categories | No. of cases/ deaths | RR (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Yin *et al.* (1987) China | 13 604 benzene-exposed workers in China employed in factories ≥ 0.5 yrs during 1972-81; leukaemia mortality follow-up 1972-81; controls were 28 257 workers not occupationally exposed to benzene | Information on occupational history, history of benzene poisoning, working conditions and workplace atmospheric benzene concentrations were collected from factory records. | Leukaemia | | | Mortality rate ratio = 7.9 | None; controls had similar age and sex distributions | Compared to benzene-unexposed workers |
| | | | | Painters (not including paint producers) | 14 | Mortality rate: 15.9/100 000 person-years | | |
| | | | | Benzene-unexposed workers | 4 | Mortality rate: 2.01/100 000 person-years | | |
| Hrubec *et al.* (1995) USA 1954–80 | 1178 painters were followed during 1954–80 within a cohort assembled from a roster of approximately 300 000 white male WWI veterans who served in the US Armed Forces some time during 1917–40 and who held active government life insurance policies | Mailed questionnaire that inquired about tobacco use, usual industry of employment and occupation, coded using 1950 Census Occupation and Industry codes | Respiratory system | Construction and maintenance painters | 36 | **SMR (90% CI)** 1.1 (0.84–1.47) | Smoking, age, calendar time | Usual occupation was recorded |
| | | | Stomach | | 6 | 0.8 (0.42–1.61) | | |
| | | | Colon | | 18 | 1.0 (0.69–1.51) | | |
| | | | Rectum | | 8 | 1.6 (0.89–2.86) | | |
| | | | Prostate | | 10 | 0.5 (0.27–0.78) | | |
| | | | Lymphoma | | 7 | 0.9 (0.48–1.67) | | |
| | | | Leukaemia | | 9 | 1.2 (0.69–2.10) | | |

## 1.2 Composition of fire smoke

### 1.2.1 *Fire chemistry*

Smoke from fires comprises suspended liquid and solid particulate matter, gases and vapours that result from the combustion or pyrolysis of material. There is a very large number of toxic components in smoke (for reviews, see Tuve, 1985; Meyer, 1989; DiNenno *et al.*, 2002; Côté, 2003). The basic form of the overall combustion reaction of organic (carbon-containing) compounds is illustrated by the burning of methane:

$$CH_4 + 2O_2 + \text{Energy of activation} \rightarrow CO_2 + 2H_2O + \text{Heat of combustion} + \text{Light}$$

Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide ($CO_2$).

Complete combustion is approached only under carefully controlled conditions. Uncontrolled or unintentional combustion tends to be "fuel rich" and therefore incomplete. The combustion of methane ($CH_4$) illustrates the formation of free radicals in an 11-step chain reaction, the first two of which are:

$CH_4 \rightarrow CH_3^{\bullet} + H^{\bullet}$

$H^{\bullet} + O_2 \rightarrow OH^{\bullet} + O^{\bullet}$

The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

Most polymers found in buildings will burn or thermally degrade to simpler monomers. Thermal degradation products include methane, ethane, ethylene, benzene, toluene, and ethylbenzene in addition to the following monomers: ethylene, vinyl chloride, acrylonitrile, tetrafluoroethylene, styrene, methyl methacrylate, ethylene glycol, terephthalic acid, phenol, formaldehyde, hexamethylenediamine, adipic acid, propene, vinyl chloride, vinyl acetate, vinylidene chloride, chloroprene, 1,3-butadiene, ethyl acrylate, ethylene oxide, methylacrylate, urea, phenol, and isoprene.

The burning of plastics typically produces voluminous amounts of soot, together with higher levels of hydrogen cyanide (HCN), hydrochloric acid (HCl) and acrolein ($CH_2$=CHCHO) than the burning of materials such as wood, and fossil fuels. More smoke evolves from fires involving aromatic polymers, such as polystyrene, compared to aliphatic polymers, such as polyethylene.

In addition to the chemical agents described above, particulate matter is produced under conditions of incomplete combustion. The particulate matter is an aerosol consisting of condensed phase components of the products of combustion and finely divided carbon particulates that have not undergone combustion but remain suspended in the air. Although the particles themselves are microscopic in size (0.3–1.6 μm), they

rapidly coalesce and thereby become visible. These particles are also adsorbents (similar to activated charcoal) and are an additional vehicle for the transport and inhalation of toxic combustion products. Smouldering yields a substantially higher conversion of fuel to toxic compounds than does flaming, although it occurs more slowly (Ohlemiller, 2002).

### 1.2.2 *Modern versus pre-modern fires*

All types of fire release toxic and carcinogenic substances, including benzene, 1,3-butadiene, and formaldehyde. The focus has generally been on substances having short-term acute effects: carbon monoxide (CO), carbon dioxide, hydrogen cyanide, nitrogen oxides ($NO_x$), sulfur dioxide ($SO_2$) and hydrogen chloride. With the increasing use of polymers in building construction and furnishings, there is concern that the burning of these new materials might release large quantities of other highly toxic substances (Austin *et al.*, 2001b).

Combustion and pyrolysis products from newer building materials and furnishings were believed to be more toxic than smoke from fires in buildings built before these materials became commonplace, and more toxic than smoke from wildland fires (Betol *et al.*, 1983; Alarie, 1985). However, many of the carcinogenic products of combustion identified are volatile organic compounds and are common to most burning materials. In a more recent study, no new or unusual non-polar volatile organic compounds (VOCs) were observed in current structural fires compared to the combustion of wood (Austin *et al.*, 2001b, 2001c). Adding polyvinyl chloride (PVC) to the fire load at simulated apartment fires was observed to significantly increase levels of polychlorinated phenols (IARC Group 2B), while polycyclic aromatic hydrocarbon (PAH) levels remained essentially unchanged (Ruokojärvi *et al.*, 2000). The increases in levels of polychlorinated biphenyls (PCBs, 0.021 to 0.031 mg/m$^3$), polychlorinated benzenes (0.002 to 0.010 mg/m$^3$) and I-TEQs [or PCDD/F] (3.5 to 5.4 ng/m$^3$) as products of combustion were not significant [possibly due to the small sample size]. In another study, proportionately higher levels of ethyl benzene (IARC Group 2B) were found at an electronics factory fire when compared to levels at residential and mixed occupancy fires (Austin *et al.*, 2001b).

The emission of combustion products (in mg per kg of material burned) for the same material varies greatly depending on combustion conditions such as ventilation (oxygen supply), temperature, and heating rate. Nonetheless, the relative amounts of the various non-polar VOCs found in smoke at municipal structural fires have been found to be remarkably similar from fire to fire, namely with the same 14 of 144 target compounds, dominated by benzene (IARC Group 1), toluene and naphthalene (IARC Group 2B) (Austin *et al.*, 2001b, 2001c).

### 1.2.3 *Carcinogens found in smoke at fires*

Table 1.1 lists the agents in Groups 1, 2A, and 2B that have been detected at fires in one or more studies, together with corresponding IARC evaluations, human and animal evidence of carcinogenicity, and for the agents in Group 1, the cancer sites in humans.

# 5. Summary of Data Reported

## 5.1 Exposure data

Several types of firefighters exist, including municipal, wildland, industrial, aviation, and military firefighters. Municipal firefighters may be assigned to combat firefighting units only or to unexposed activities such as fire prevention or technical support. Firefighters may also be fire-scene investigators who are exposed during fires or shortly following a fire. Many firefighters work in shifts (see the monograph in this Volume).

Both municipal and wildland firefighting involve two phases: in an initial phase (knockdown and attack, respectively), the fire is extinguished; in a second phase (overhaul and mop-up, respectively), small fires and hot-spots are extinguished.

All fires generate an enormous number of toxic combustion products, including known and possible carcinogens, long-lived free radicals, and particulate matter. Smoke particles may serve as vehicles for adsorbed volatile organic compounds. Peak exposures to some carcinogens may be very high, notably for benzene, 1,3-butadiene, and formaldehyde. The concentrations of respirable particulate matter to which firefighters may be exposed during overhaul can reach 50 mg/m$^3$, or up to 1000 mg/m$^3$, and above in the case of coarser particles. Exposures of firefighters to volatile organic vapours have generally been in the low parts-per-million range.

Firefighters may be exposed at different levels depending on crew assignment, tasks and/or the time spent at fires. Wildland firefighters appear to spend more time at fires during a fire season than municipal firefighters spend during an entire year. In municipal firefighting, overhaul also involves pulling down ceilings and walls, which may entail exposures to substances other than combustion products. Both municipal and wildland firefighters engage in heavy work levels when combating fires, and the increased respiration rate results in an increase in absorbed dose. In recent decades, very effective respiratory protection equipment has been made available to municipal firefighters. In most jurisdictions, wildland firefighters generally do not use respiratory protection.

## 5.2 Human carcinogenicity data

The Working Group reviewed 42 studies of cancer in firefighters that included 19 cohorts, 11 case–control studies, and 14 studies that used other designs. The studies that were most relevant to the assessment of the risk for cancer among firefighters were the larger historical cohort studies.

Elevated relative risks for cancer at many different sites were identified by one or more studies, but few were observed consistently. A recent meta-analysis evaluated 32 studies and found that the risk for cancer in firefighters was significantly elevated for ten sites, four of which showed the strongest evidence of an association. Since that analysis, two more large epidemiological studies of cancer in firefighters have been

reported. Therefore, another meta-analysis that included these two studies was performed by the Working Group for the four primary cancer sites. Three types of cancer showed significant summary risk estimates: the incidence of testicular cancer was ~50% in excess based on six studies and approximately 150 cases, that of prostatic cancer was ~30% in excess based on 17 studies and approximately 1800 cases, and that of non-Hodgkin lymphoma was ~20% in excess based on seven studies and more than 300 cases.

Four cohort studies that investigated testicular cancer in firefighters yielded risk estimates that ranged from 1.2 to 2.5 and one case–control study gave odds ratios that ranged from 1.5 to 4.3. One of three studies found a positive trend between duration of exposure and the increased risk for testicular cancer.

Of 20 studies of prostatic cancer, 17 reported elevated risk estimates that ranged from 1.1 to 3.3; however, only two reached statistical significance and only one study showed a trend with duration of employment.

The studies that investigated non-Hodgkin lymphoma in firefighters used different definitions of this tumour. Five cohort and one case–control studies that evaluated non-Hodgkin lymphoma reported risk estimates that ranged from 0.9 to 2.0. Only one study evaluated exposure–response with duration and did not find a positive relationship.

Although firefighters are exposed concurrently to a multitude of chemical compounds that include numerous carcinogens, human epidemiological studies at best used indirect (poor) measurements of exposure to such agents. Also, exposures of firefighters vary considerably depending on their job activities, and only crude measures of exposure, such as duration of employment and number of runs, have been used in these studies. Despite these limitations, increased risks for some cancers were found for firefighters in the meta-analysis.

### 5.3 Animal carcinogenicity data

No data were available to the Working Group.

### 5.4 Other relevant data

Smoke is a complex mixture of suspended particulate matter, gas, and vapour. The lack of data on toxicokinetics and toxicity of the adsorption of chemical components onto particles prevents a full understanding of the effects of smoke on firefighters. The toxicokinetics of chemical mixtures are not well understood but are probably of significant importance because of the multiplicity of chemicals in smoke. For individual smoke components, inhalation was considered to be the major source of exposure; however, dermal absorption is also an important route of exposure for polycyclic aromatic hydrocarbons and polychlorinated biphenyls.

There are insufficient studies to evaluate genotoxic effects in firefighters.

There is clear evidence of chronic and acute inflammatory respiratory effects in firefighters, which provides a potential mechanism for carcinogenesis, although the major effect would be expected in the respiratory system.

No genotoxicity studies in animals were found that involved exposure to smoke from the combustion of structural materials. Smoke causes lipid peroxidation, which may be associated with cancer. Wood smoke suspensions has been shown to cause DNA strand breakage and lipid peroxidation in cell cultures.

International Agency for Research on Cancer – *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*; Volume 98 – Painting, Firefighting, and Shiftwork

**Composition of Fire Smoke:**

Smoke from fires comprises suspended liquid and solid particulate matter, gases, and vapors that result from the combustion or pyrolysis of material.

- **ALL** types of fire release toxic and carcinogenic substances.

Overall Evaluation: The agent is described according to the wording of one of the following categories, and the designated group is given. This categorization of an agent is a matter of scientific judgment that reflects the strength of evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

| | |
|---|---|
| Group 1 | Carcinogenic to humans |
| Group 2A | Probably carcinogenic to humans |
| Group 2B | Possibly carcinogenic to humans |
| Group 3 | Not classifiable as to its carcinogenicity to humans |
| Group 4 | Probably not carcinogenic to humans |

| Carcinogens Found in Smoke at Fires | |
|---|---|
| Chemicals measured in fires | Classification |
| 1,3-Butadiene | 1 |
| 2,3,7,8-tetrachloro dibenzo-*para*-dioxin | 1 |
| Arsenic | 1 |
| Asbestos | 1 |
| Benzene | 1 |
| Benzo[*a*]pyrene | 1 |
| Cadmium | 1 |
| Formaldehyde | 1 |
| Polychlorinated biphenyls | 1 |
| Radioactivity (γ activity) | 1 |
| Radionuclides (α-particle-emitting) | 1 |
| Radionuclides (β-particle-emitting) | 1 |
| Silica (crystalline) | 1 |
| Trichloroethylene | 1 |
| Dibenz[*a*,*h*]anthracene | 2A |
| Dichloromethane (methylene chloride) | 2A |
| Lead compounds, inorganic | 2A |
| Tetrachloroethylene (perchloroethylene) | 2A |
| Acetaldehyde | 2B |

| Carcinogens Found in Smoke at Fires | |
|---|---|
| Chemicals measured in fires | Classification |
| 2-Nitroanisole | 2B |
| Benz[*a*]anthracene | 2B |
| Benzo[*b*]fluoranthene | 2B |
| Benzo[*k*]fluoranthene | 2B |
| Benzofuran | 2B |
| Carbon black | 2B |
| Chrysene | 2B |
| Ethylbenzene | 2B |
| Furan | 2B |
| Indeno-1,2,3-[*cd*]pyrene | 2B |
| Isoprene | 2B |
| Lead | 2B |
| Naphthalene | 2B |
| Polychlorophenols | 2B |
| Styrene | 2B |
| Toluene diisocyanates | 2B |
| Trichloromethane (chloroform) | 2B |
| Lead compounds, organic | 3 |
| Silica (amorphous) | 3 |
| Triphenylene | 3 |

Several studies have been conducted with the purpose of identifying the chemicals and known carcinogens found **during the overhaul phase of a structure fire.**

- *Characterization of Firefighter Exposures During Fire Overhaul* (Phoenix FD and the University of Arizona Prevention Center and Arizona State University).
- *A Study on Chemicals found in the Overhaul Phase of Structure Fires using Advanced Portable Air Monitoring available for Chemical Speciation* (Tualatin Valley Fire & Rescue – Oregon)

| Chemicals measured in overhaul environment | IARC Classification |
|---|---|
| 1,3 Butadiene | 1 |
| Arsenic | 1 |
| Asbestos | 1 |
| Benzene | 1 |
| Benzo(a)pyrene | 1 |
| Coal Tar Pitch | 1 |
| Diesel Exhaust | 1 |
| Formaldehyde | 1 |
| Vinyl Chloride | 1 |
| Dibenz(a,h)anthracene | 2A |
| N-Nitrodimethylamine | 2A |
| 1,2 Dichloroethane | 2B |
| Acetaldehyde | 2B |
| Benz(a) anthracene | 2B |
| Benzo(b)fluoranthene | 2B |
| Benzo(k)fluoranthene | 2B |
| Benzofuran | 2B |
| Ethyl benzene | 2B |
| Furan | 2B |
| Indeno(1,2,3-cd)pyrene | 2B |
| Lead | 2B |
| Napthalene | 2B |
| Styrene | 2B |
| Mercury | 3 |
| Hydrochloric Acid | 3 |
| Toluene | 3 |
| Acrolein | 3 |
| Furfural | 3 |
| Acenaphthene | 3 |
| Anthracene | 3 |
| Benzo(ghi)perylene | 3 |
| Fluoranthene | 3 |
| Fluorene | 3 |
| Phenanthrene | 3 |
| Pyrene | 3 |

***Diesel Engine Exhaust:***

On June 12, 2012, the International Agency for Research on Cancer (IARC), part of the World Health Organization and the authority on cancer, classified diesel engine exhaust as a Group 1 Carcinogen, meaning that it causes cancer in humans.

Diesel engine exhaust in fire stations has been and continues to be a serious health problem for firefighters. This exhaust is generated whenever a fire apparatus leaves or returns to the station. If not properly captured and removed, it will remain in the apparatus bay as well as enter the firefighters' living quarters. As a result, firefighters can be exposed to diesel engine exhaust for a considerable portion of their shift.

Diesel exhaust contains multiple cancer-causing chemicals such as (Source IARC Monograph 105):

| Metals | IARC Classification |
|---|---|
| Antimony Compounds | 2B |
| Arsenic and inorganic arsenic compounds | 1 |
| Beryllium and beryllium compounds | 1 |
| Cadmium and cadmium compounds | 1 |
| Chromium (VI) | 1 |
| Cobalt and cobalt compounds | 2B |
| Lead compounds (inorganic/organic0 | 2A/3 |
| Nickel (metallic/compounds) | 2B/1 |
| **Organic Chemicals** | **IARC Classification** |
| 1,3-Butadiene | 1 |
| Acetaldehyde | 2B |
| Benzene | 1 |
| Bis(ethylhexyl)phthalate | 2B |
| Ethylbenzene | 2B |
| Formaldehyde | 1 |
| Propylene oxide | 2B |
| **Halogenated and other chemicals** | **IARC Classification** |
| Dioxin/dibenzofurans | 1 |
| **Polycyclic aromatic hydrocarbons** | **IARC Classification** |
| Benz(a) anthracene | 2B |
| Benzo(b)fluoranthene | 2B |
| Benzo(k)fluoranthene | 2B |
| Benzo(a)pyrene | 1 |
| Chrysene | 2B |
| Dibenz(a,h)anthracene | 2A |
| 3,7-Dinitrofluoranthene | 2B |
| 3,9-Dinitrofluoranthene | 2B |
| 1,3-Dinitropyrene | 2B |
| 1,6-Dinitropyrene | 2B |
| 1,8-Dinitropyrene | 2B |
| Indeno(1,2,3-*cd*)pyrene | 2B |
| Napthalene | 2B |
| 3-Nitrobenzanthrone | 2B |
| 6-Nitrochrysene | 2A |
| 2-Nitrofluorene | 2B |
| 1-Nitropyrene | 2A |
| 4-Nitropyrene | 2B |
| Styrene | 2B |

career, pilots underwent yearly physical examinations, including a digital rectal examination.

Irvine and Davies (1992, 1999) studied cancer mortality in British Airways pilots using the proportional mortality ratio (PMR) method (1992), and later (1999) based on SMRs. In the PMR study, there were ten deaths due to prostate cancer. The PMR was 2.12 (95% CI: 1.02–3.89) if the reference was all-cause mortality (excluding aircraft accident), and 1.54 (95% CI: 0.74–2.83) if the reference was all-cancer mortality. [It was however evident from other studies that both overall mortality and all-cancer mortality among airline pilots is markedly below the population mortality rates. In the British Airways pilots (Irvine & Davies, 1999), the SMR was 0.61 for all causes and 0.64 for all cancers, and therefore the PMRs in Irvine & Davies (1992) did not indicate excess prostate cancer mortality among pilots compared to the average population]. In the SMR study (Irvine & Davies, 1999), there were 15 prostate cancer deaths among British Airways pilots (SMR, 1.11; 95% CI: 0.62–1.84), and three deaths among flight engineers often travelling in cockpit (SMR, 0.92; 95% CI: 0.19–2.69). In the internal analysis, the age-adjusted RR between persons flying long-haul versus mainly short-haul (European) flights was 2.47 (95% CI: 0.83–7.65). Flight engineers were assumed to operate in long-haul operations.

Gundestrup & Storm (1999) studied cancer incidence among 3790 male and 87 female commercial Danish cockpit crew members, with records starting from 1921. They were followed for cancer mortality during 1943–1995. Three prostate cancer deaths were observed among both jet pilots and non-jet pilots versus 3.5–4.0 expected.

Haldorsen *et al.* (2000) published SIRs from a Norwegian cohort of 3815 authorised male pilots employed during 1946–1994. During the follow-up from 1953–1996, 25 cases of prostate cancer were observed (SIR, 1.0; 95% CI: 0.7–1.5); six were in the category of exposed to ≥ 20 mSv (SIR, 1.8; 95% CI: 0.7–4.0).

Rafnsson *et al.* (2000) studied a cohort of 458 Icelandic male pilots employed during 1937–1985, followed-up for cancer incidence from 1955–1997. There were only four cases of prostate cancer among pilots who had flown international flights (SIR, 1.41; 95% CI: 0.38–3.61), and therefore no dose–response analyses were performed for this cancer site.

The study by Hammar *et al.* (2002) reported cancer incidence both among civil and military pilots in Sweden. The incidence was about 20% above the national level in both categories, and did not vary with increasing number of block hours, high-altitude flights or long-distance flights.

Zeeb *et al.* (2002) analysed mortality data of 6061 German male pilots who had worked during 1953–1997. A total of eight deaths from prostate cancer were observed (SMR, 1.26; 95% CI: 0.53–2.59).

Zeeb *et al.* (2003) reported the combined results from cabin crew cohorts from eight European countries employed during 1921–1997 in Denmark, Finland, Germany, Greece, Iceland, Italy, Norway, and Sweden. During follow-up of 170 634 person–years for men (until 1997), five prostate cancer deaths were reported (SMR, 1.09; 95% CI: 0.35–2.68).

For most cabin crew, annual exposure to radiation ranges from 1–6 mSv, compared with approximately 2.4 mSv annually from background radiation. Cosmic radiation includes a substantial neutron component (25–50% of effective dose but less than 5% of absorbed dose). Because flight personnel are the only source of human data on the health effects of exposure to neutron radiation, it is hard to estimate how a large excess risk would be expected due to cosmic radiation. This further makes it difficult to judge how much of the observed excess could be for other risk factors such as shiftwork.

The number of flights over several time zones is used as a proxy of frequency of circadian rhythm disruptions. This number correlates with the dose of cosmic radiation, and therefore estimates of cancer risk in cumulative dose categories can also be interpreted to roughly reflect frequency of circadian rhythm disruptions. On the other hand, separation of the independent roles of these two factors is possible only in large studies with precise information on flight histories. Only one study, combining information on all pilots from the five Nordic cancer registries has been able to make this distinction to a certain extent. In general, the detailed flight histories of airline pilots are known quite well; while for cabin crew, normally only the beginning and end of employment is known. In the airline companies where the principle has been that all cabin crew members fly all routes, an approximation of the radiation dose and numbers of long flights over time zones for each person can be made based on his/her own annual numbers of flight hours, and the flight profile of the company.

All studies published on aircraft crew have been included in this evaluation, irrespective of whether they mention shiftwork or not. Only observations related to breast cancer and prostate cancer have been included in this review, because they are the only ones which have been considered to be associated with shiftwork. The observations related to breast cancer come from cabin crew personnel and those related to prostate cancer mainly from cockpit personnel, because almost all airline pilots are male, and the majority of the cabin crew, female.

In addition to the breast and prostate cancer findings presented below in detail, there is a consistent pattern of increased incidence of skin melanoma and basal cell carcinoma of the skin that are likely to be related to the more frequent sunbathing and sunburns among flight personnel in previous decades. Male cabin crew have also been shown to have a significantly increased risk of Kaposi sarcoma in most studies that included this cancer category. The risk of leukaemia, one of the main target sites in studies on effects of radiation, has been shown to be non-elevated in most studies.

### 2.3.1 *Breast cancer* (Table 2.7)

#### *(a) Cohort studies*

Pukkala *et al.* (1995) collected a cohort of 1577 all-female flight attendants who had ever worked for Finnish airline companies (first employment starting in the 1930s). This cohort was followed-up for cancer incidence during 1967–1992. The SIR for breast cancer was 1.87 (95% CI: 1.15–2.23, 20 cases), and the SIR was highest 15–19 years after

**Table 2.5. Cohort studies**

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure categories | No. of cases/ deaths | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Kubo *et al.* (2006), Japan, Japan Collaborative Cohort | Prospective cohort of 14 052 males, aged 40–65 years old enrolled from 45 areas in Japan between 1988–1990. Information on prostate cancer was obtained from cancer registries | Self-administered questionnaires at baseline included information on type of work schedule | Prostate | Day time work<br>Fixed night<br>Rotating shift | 21<br>3<br>7 | 1.0 (ref)<br>2.3 (0.6–9.2)<br>3.0 (1.2–2.7) | Age, study area, family history of prostate cancer, BMI, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level and marriage status | |
| Schernhammer *et al.* (2003) USA, American Nurses Health Study | Prospective cohort of 78 586 American nurses with a baseline question on rotating night work in 1988. Follow-up for colorectal cancer was through 1998 | Self-reported from postal questionnaires: Rotating night shift was defined as "at least 3 nights per months, in addition to evenings and afternoons in that month" | Colorectal | No rotating night shifts<br>1–14 years<br>≥15 years<br>*P* for trend 0.04 | 229<br>303<br>70 | 1.00 (ref)<br>1.00 (0.84-1.19)<br>1.35 (1.03-1.77) | Tobacco smoking, BMI, physical activity, aspirin use, colorectal cancer in relatives, endoscopy use, consumption of red meat, alcohol consumption, total calorie intake, postmenopausal hormones, menopausal status, height | No major differences in risk were seen for right or left colon, or colon and rectum separated |
| | | | Colon | No rotating night shifts<br>1–14 years<br>≥15 years<br>*P* for trend 0.26 | 137<br>169<br>41 | 1.00 (ref)<br>0.93 (0.74–1.17)<br>1.32 (0.93–1.87) | | |
| | | | Rectum | No rotating night shifts<br>1–14 years<br>≥15 years<br>*P* for trend 0.15 | 41<br>48<br>14 | 1.00 (ref)<br>0.86 (0.56–1.30)<br>1.51 (0.82–2.81) | | |

# 2. Studies of Cancer in Humans

## 2.1 Introduction

Airline personnel flying over time zones are exposed to frequent disruptions of circadian rhythm, which has similarities with exposure to shiftwork. There are studies reporting cancer risk in about ten cohorts of airline cabin crew and a similar number of studies in cockpit personnel. The cabin crew cohorts support the strong evidence of significantly increased risk of breast cancer incidence found in most independent studies. Higher diagnostic activity (screening during annual health controls) may explain part of the excess when comparing with national population rates, and it should not confound internal comparisons within differently exposed subcohorts of cabin crew. Unfortunately, the studies published so far do not demonstrate precise dose–response evaluations according to the frequency of disruptions of circadian rhythm, for which the best proxy has been duration of work as flight attendant. In most studies, the excess is observed at around 10 years after first employment, and increases weakly with increasing duration. Differences in reproductive factors explain only a small fraction of the excess, while risk attributable to radiation may explain a quarter of the excess. It is unclear whether the substantial neutron component of cosmic radiation (25–50% of the effective dose but less than 5% of the absorbed dose) increases the proportion of risk attributable to radiation – this exposure can only be studied in flight crew personnel – but it is likely that there is a major part of the excess risk in breast that must be attributable to factors others than the factors listed above. Disruptions of circadian rhythm and related hormonal effects have been repeatedly mentioned as possible causal factors, and there are no data to exclude this possibility.

Prostate cancer incidence rates from the airline pilot cohorts are above the national reference levels. This excess has decreased over decades and is likely to be related to the prostate-specific antigen tests, common among pilots much earlier they became so in the general population. In the most recent follow-up reports, the SIRs among pilots have been only slightly increased. Only one study that combined cohorts of all pilots from five Nordic countries, with detailed individual level flight histories, was able to study the independent role of the long-haul flights over time zones in an internal analysis. A significant trend in risk for prostate cancer with increasing number of long-haul flights was observed, though there were only eight cases in the highest exposure category. Hence, the evidence related to the role of circadian rhythm disruptions in causing prostate cancer is weak.

**Table 4.1. Toxicokinetics and metabolism for selected carcinogenic products of structural and wildfire smoke**

| Chemical | Absorption | Distribution | Metabolism | Excretion | Mechanism | Cancer | Note/Reference |
|---|---|---|---|---|---|---|---|
| Particles | Inhalation (variable depending on size) | Lungs | Dependent on solubility of adsorbed chemicals | Macrophage phagocytosis followed by migration to mucociliary escalator or transport to interstitium | Inflammation | For carbon black, lung, lymphatic cancer (in presence of PAHs). For diesel exhaust, lung and bladder cancer, possibly non-Hodgkin lymphoma, multiple myeloma, and prostate cancer | IARC (2010c); Oberdörster (1992); Boffetta & Silverman (2001); Lipsett & Campleman (1999); McDuffie *et al.* (2002); Boffetta *et al.* (1988); Lee *et al.* (2003); Hansen (1993); Seidler *et al.* (1998) |
| Acetaldehyde | Inhalation (45–70%) | Predominantly peripheral blood | Acetic acid | Blood half life 3.1 min (rat) | DNA damage including acetaldehyde–DNA adducts | Nasal cancer | IARC (1999); Egle (1970); Hobara *et al.* (1985); Hardman *et al.* (1996) |
| Acrolein | Inhalation (81–84%) | Predominantly local | Conjugated rapidly with thiols | Inadequate data in humans, urinary *S*-carboxyethyl-mercapturic acid following oral exposure in rats | DNA damage in cultured mammalian cells | IARC Group 3, urinary bladder papillomas in rats | IARC (1995); Egle (1972); ATSDR (2005) |

## 2.4 Case reports

Individual firefighters have applied for, and sometimes received, workers' compensation for cancer. An apparent cluster of cancer among firefighters was reported in an investigation of a chemical waste dump fire by NIOSH (Hrubec *et al.*, 1992). However, the authors concluded it was not likely to have been related to firefighting. [Given the limitations of these reports and the large number of descriptive, cohort, and case–control studies with data on firefighters, the Working Group did not believe that case reports would contribute to the evaluation.]

## 2.5 Meta-analyses

Two meta-analyses of studies of firefighters and cancer have been conducted (Howe & Burch, 1990; LeMasters *et al.*, 2006). The most recent meta-analysis included a great majority of the studies considered by the Working Group (LeMasters *et al.*, 2006). Cancer risk was significantly elevated for ten of the 21 cancer types analysed (stomach, colon, rectum, skin, prostate, testis, brain, non-Hodgkin lymphoma, multiple myeloma, and malignant melanoma). With the exception of testicular cancer (summary RR = 2.02), the summary relative risk estimates were moderate, ranging from 1.21 for colon to 1.53 for multiple myeloma. For four of these sites (prostate, testis, non-Hodgkin lymphoma, and multiple myeloma), findings were consistent across study designs and the types of study available. However, since that analysis, two additional large studies of cancer in firefighters had been published (Ma *et al.*, 2006; Bates, 2007). Therefore, another meta-analysis was performed by the Working Group to assess the impact of these recent studies.

Inclusion criteria for studies in this meta-analysis were reported estimates of relative risk with corresponding 95% confidence intervals or information that allowed their computation by the Working Group for 'ever' versus 'never' exposure to firefighting or employment as a firefighter. For those studies that did not report for this category, the relative risks and 95% confidence intervals were estimated by the Working Group from strata-specific relative risk and corresponding number of cases, assuming a normal distribution when possible. Studies that only reported point estimates without confidence intervals were not included. Proportionate mortality studies were also excluded. Statistical heterogeneity among studies was tested with the Q statistic. Summary relative risk estimates were obtained from random-effect models for prostate cancer ($Q = 32.816$, $P = 0.005$), and fixed-effect models for testicular cancer ($Q = 3.928$, $P = 0.560$), and non-Hodgkin lymphoma ($Q = 6.469$, $P = 0.486$). All statistical analyses were performed using STATA (version 9.0; StataCorp, College Station, TX).

Based on the Working Group's meta-analysis, three of the four sites remained statistically significant. Testicular cancer was evaluated based on six studies and

## Table 2.8 (contd)

| Reference, location, name of study | Study population description | Exposure assessment | Organ site (ICD code) | Exposure categories | No. of cases/ deaths | RR/SIR/SMR (95% CI)* | Adjustement for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Blair *et al.*, (1985); Walrath *et al.* (1985); USA | Follow–up (1954–1970) of 902 USA Veterans reporting occupation as firefighter | Usual occupation from interview | | Overall, Male | | **SMR** | Age, calendar period, smoking | |
| | | | Intestine | | 8 | 1.4 [n.s.] | | |
| | | | Lung, bronchus | | 13 | 1.1 [n.s.] | | |
| Gallagher *et al.* (1989), British Columbia, Canada | Death certificate study 1950–1984. 1202 firefighter deaths | Usual occupation on death certificate | | | | **PMR** | Age, calendar period | |
| | | | All | | 197 | 1.2 (1.0–1.3) | | |
| | | | Colon | | 20 | 1.4 (0.8–2.1) | | |
| | | | Rectum | | 10 | 1.2 (0.6–2.2) | | |
| | | | Pancreas | | 19 | 1.7 (1.1–2.7) | | |
| | | | Lung | | 50 | 1.0 (0.8–1.4) | | |
| | | | Prostate | | 23 | 1.4 (0.9–2.1) | | |
| | | | Bladder | | 9 | 1.5 (0.7–2.9) | | |
| | | | Kidney | | 3 | 0.7 (0.1–2.1) | | |
| | | | Brain | | 6 | 1.2 (0.4–2.7) | | |
| | | | Non-Hodgkin lymphoma | | 7 | 1.5 (0.6–3.2) | | |
| | | | Multiple myeloma | | 2 | 0.8 (0.1–2.9) | | |
| | | | Leukaemia | | 8 | 1.3 (0.5–2.5) | | |

Hansen (1990) performed a study of Danish firefighters employed at the time of the 1970 national census. An analysis was then conducted of 57 deaths (21 from cancer) during 1970–1980 occurring among 886 males who had reported employment as firefighter. Men employed in similar occupations were used as the reference group, and an excess of lung cancer among firefighters over the age of 60 was reported, based on small numbers.

Ma *et al.* (1998) conducted a further analysis of a data set collected by Burnett *et al.* (1994) with additional years of follow-up using 1984–1993 death certificate data from 24 states in the USA. A total of 6607 deaths and 1883 cancer deaths among firefighters were identified based on the occupational titles on death certificates. Race-specific cancer mortality odds ratios (MORs) were calculated with all non-cancer deaths as the reference group. Analyses were adjusted for age and year of death. Among caucasian male firefighters, significant excesses were observed for cancers of the lip, pancreas, lung, prostate, kidney, and soft-tissue sarcoma and non-Hodgkin lymphoma. Among black male firefighters, significant excesses were observed for cancers of the nasopharynx, colon, prostate, and brain.

### 2.3.2 *Descriptive studies with firefighter results.*

There is a large body of descriptive epidemiology carried out for the purpose of occupational cancer and mortality surveillance. The results of these studies are summarized in Table 2.8.

Berg & Howell (1975) examined the risk of colorectal cancer by occupation using death certificate data from the USA and the United Kingdom and observed an excess among firefighters. [The Working Group noted that there was an overlap between the United Kingdom data included in this study and the meta-analysis by Dubrow & Wegman, 1983].

Williams *et al.* (1977) observed excesses of oral cancer, lung cancer, bladder cancer, and non-Hodgkin lymphoma based on the small number of cancers among firefighters that were included in the Third National Cancer Survey, USA. [The Working Group noted that Williams *et al.* (1977) was included in the meta-analysis conducted by Dubrow & Wegman (1983), but was unique in that occupation was ascertained by interview.]

Dubrow & Wegman (1983) summarized the results of ten early USA and United Kingdom studies and reported the results that appeared to be most consistent between the studies. Among those studies that reported results for firefighters, large intestine cancer and multiple myeloma were significantly elevated.

Morton & Marjanovic (1984) examined the incidence of leukaemia by occupation in the Portland–Vancouver metropolitan area in North-western USA, and excesses were observed among firefighters based on very small numbers.

Mortality among a cohort of 293 958 United States military veterans was examined by occupation and industry (Blair *et al.*, 1985). Usual occupation and industry as well as smoking information was determined from questionnaires

**Table 2.7 (contd)**

| Reference, location, name of study | Study population description | Exposure assessment | Organ site (ICD code) | Exposure categories | No. of cases/ deaths | PMR/SMR/MOR (95% CI) | Adjustement for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Ma *et al.* (1998), 24 states, USA | Analysis of 1984–1993 death certificate data, 6607 firefighters identified | Usual occupation on death certificate | | Overall, caucasian males | | **MOR** | Age, year of death | |
| | | | All | | 1817 | 1.1 (1.1–1.2) | | |
| | | | Lip | | 3 | 5.9 (1.9–18.3) | | |
| | | | Colon | | 149 | 1.0 (0.9–1.2) | | |
| | | | Rectum | | 27 | 1.1 (0.8–1.6) | | |
| | | | Pancreas | | 88 | 1.2 (1.0–1.5) | | |
| | | | Lung | | 633 | 1.1 (1.0–1.2) | | |
| | | | Prostate | | 189 | 1.2 (1.0–1.3) | | |
| | | | Bladder | | 48 | 1.2 (0.9–1.6) | | |
| | | | Kidney & pelvis | | 49 | 1.3 (1.0–1.7) | | |
| | | | Brain & CNS | | 41 | 1.0 (0.8–1.4) | | |
| | | | non-Hodgkin lymphoma | | 76 | 1.4 (1.1–1.7) | | |
| | | | Multiple Myeloma | | 28 | 1.1 (0.8–1.6) | | |
| | | | Leukaemia | | 60 | 1.1 (0.8–1.4) | | |
| | | | Soft tissue sarcoma | | 14 | 1.6 (1.0–2.7) | | |
| | | | | Overall, black males | | | | |
| | | | All | | 66 | 1.2 (0.9–1.5) | | |
| | | | Nasopharynx | | 1 | 7.6 (1.3–46.4) | | |
| | | | Colon | | 9 | 2.1 (1.1–4.0) | | |
| | | | Pancreas | | 5 | 2.0 (0.9–4.6) | | |
| | | | Lung | | 15 | 0.8 (0.5–1.3) | | |
| | | | Prostate | | 16 | 1.9 (1.2–3.2) | | |
| | | | Brain & CNS | | 5 | 6.9 (3.0–16.0) | | |

* specify *P* value if no confidence interval indicated; MOR, mortality odds ratio; NJ, New Jersey; NR, not reported; n.s, not significant; PMR, proportionate mortality ratio; SMR, standardized mortality ratio

**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<br>Colorectum<br>Lung<br>Melanoma<br>Prostate<br>Testis<br>Bladder<br>Brain<br>Thyroid<br>Leukaemias<br>Non-Hodgkin lymphoma<br>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<br>Stomach<br>Colorectum<br>Caecum<br>Pancreas<br>Lung & bronchus<br>Melanoma<br>Prostate<br>Testis<br>Bladder<br>Kidney & renal pelvis cancer<br>Brain<br>Thyroid cancer<br>Leukaemias<br>Non-Hodgkin lymphoma<br>Multiple myeloma | 62<br>51<br>282<br>52<br>63<br>495<br>323<br>1144<br>70<br>174<br>101<br>71<br>32<br>100<br>159<br>37 | 1.48 (1.14–1.91)<br>0.80 (0.61–1.07)<br>0.90 (0.79–1.03)<br>1.09 (0.82–1.44)<br>0.90 (0.70–1.17)<br>0.98 (0.88–1.09)<br>1.50 (1.33–1.70)<br>1.22 (1.12–1.33)<br>1.54 (1.18–2.02)<br>0.85 ( 0.72–1.00)<br>1.07 (0.87–1.31)<br>1.35 (1.06–1.72)<br>1.17 (0.82–1.67)<br>1.22 (0.99–1.49)<br>1.07 (0.90–1.26)<br>1.03 (0.75–1.43) | SES quintile | Use of other cancer controls may have biased study toward null |

SES, socioeconomic status

Logistic regression analyses adjusted for 5-year age categories, 4-year categories from date of diagnosis, five ethnic categories and five categories of an indicator of socioeconomic status. A total of 101 firefighters with a diagnosis of cancer of the kidney or renal pelvis were assessed, and the OR was 1.07 (95% CI: 0.87–1.31), adjusted for age, calendar period of diagnosis, race, and an indicator of socioeconomic status for the census block of residence.

Krstev *et al.* (1998) investigated incident prostate cancer cases in the USA using population-based cancer registries for Atlanta Georgia and Detroit Michigan, and for ten counties in the state of New Jersey during 1986–1989. Histologically confirmed cases were identified from pathology and outpatient records at hospitals included in these registries. Cases were selected by random sampling among the total number of cases identified in each age–race category. [Three additional cancer sites were investigated but not reported including oesophagus, pancreas, and multiple myeloma, and no published articles were located regarding these cancers.] Control subjects were proportional to the age, sex, and race distribution of the cases. Controls younger than 65 years of age were selected through random-digit dialling. Older controls were systematically selected by random sampling from computerized records of the Health Care Financing Administration stratified by three age groups, and race (african american or caucasian for each geographic area). Cases and controls were interviewed in person. There were 981 cases and 1315 controls analysed using unconditional logistic regression adjusted for age (< 60, 60–69, 70+), study site, and race. A total of ten cases and five controls were classified as firefighting (SOC 512.3). The overall adjusted OR for prostate cancer was 3.85 (95% CI: 1.34–11.10), for caucasians only (nine cases and three controls) 4.75 (1.26–18.00), and for african americans (three cases and two controls), 2.64 (0.43–16.20).

Bates (2007) evaluated 1144 firefighters diagnosed with cancer of the prostate (cohort described above for cancer of the kidney), and found an adjusted OR of 1.22 (95% CI: 1.12–1.33).

Stang *et al.* (2003) examined the risk of testicular cancer or extragonadal germ cell tumours during 1995–1997 in five German regions. Cases were reported through an active reporting system. A pathologist derived histological evaluations for 95% of the cases. Interviews were conducted with 269 of the 353 eligible cases, with a response rate of 78% including the two surrogate interviews. Controls were randomly selected from mandatory registries of residence. Approximately two controls were age- and region-matched for the cases between the ages of 15–34 years. Four controls were matched for those cases aged 35–69 to increase study power related to the fewer number of cases in this older age group. The response rate in the controls was 57%, with 918 interviewed (eight surrogate) of 1982 eligible subjects. Each job held for at least 6 months was recorded including job tasks and hours per week worked. These jobs were coded according to the International Standard Classification of Occupation. Conditional logistic regression models were calculated with matching factors including 5-year age groups, and geographic region. The adjusted ORs for 'ever'

mortality from cancer. Excesses of brain tumours (SMR, 2.1; 95% CI: 1.2–3.3) and lymphatic and haematopoietic cancers (SMR, 1.3; 95% CI: 0.9–1.8) were found. Younger firefighters (< 40 years of age) showed an excess risk of cancer (SMR, 1.45; 95% CI: 0.8–2.39), primarily due to brain cancer (SMR, 3.75; 95% CI: 1.2–8.7). The risk of lymphatic and haematopoietic cancers was greatest for men with at least 30 years of exposed employment (SMR, 2.1; 95% CI: 1.1–3.6), especially for leukaemia (SMR, 2.6; 95% CI: 1.0–5.4).

Demers *et al.* (1994) further examined the incidence of cancer in a subcohort of 2447 male firefighters who were employed for at least one year during 1945–1979 in Seattle and Tacoma, who were still alive on January 1st 1974. Incident cancer cases were ascertained through the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, a population-based tumour registry. The follow-up period was from 1974 to 1989. Cancer incidence in firefighters was compared with local rates and with the incidence among 1878 policemen from the same cities. The overall risk of cancer among firefighters was found to be similar to that of both the police (SIR, 1.0; 95% CI: 0.8–1.3) and the general male population (SIR, 1.1; 95% CI: 0.9–1.2). No excesses were observed for the most common organ sites. An elevated risk of prostate cancer was observed relative to the general population (SIR, 1.4; 95% CI: 1.1–1.7), but was less elevated compared with rates in policemen (incidence density ratio [IDR], 1.1; 95% CI: 0.7–1.8), and was not related to duration of exposure. The risk of colon cancer, although only slightly elevated relative to that of the general population (SIR, 1.1; 95% CI: 0.7–1.6) and the police (IDR, 1.3; 95% CI: 0.6–3.0), appeared to increase with duration of employment.

Giles *et al.* (1993) conducted a cancer incidence study of 2855 male firefighters employed by the fire brigade in Melbourne, Australia, during 1917–1988. All were operational personnel, who would more than likely have been called to combat fires. The follow-up period was from 1980 to 1989, and was estimated to have been 95% complete. To determine cancer incidence during the follow-up period, fire brigade employment records were linked to the Victorian Cancer Registry. SIRs were calculated by the direct method using the population of the State of Victoria as the reference group. The cohort accrued a total of 20 853 person–years, and 50 firefighters developed cancer during the period of observation. The SIR for all cancer sites and all ages combined was 1.13 (95% CI: 0.84–1.48). For firefighters under the age of 65 years, the all-site SIR was 0.84 (95% CI: 0.56–1.20); for those above 65 years of age, the all-site SIR was 2.14 (95% CI: 1.32–2.37). The only site-specific cancer that was elevated in the age group of 65 and older was colorectal cancer, with an SIR of 3.65 (95% CI: 1.13–7.94). The SIR for all other cancers in the age group 65 and above after removing colorectal cancer remained elevated, with a residual SIR of 1.83 (95% CI: 1.03–3.02).

Guidotti (1993) examined the mortality by cause of death for two cohorts totaling 3328 firefighters active during 1927–1987 in Edmonton and Calgary, Alberta, Canada. Associations were examined by cohort (before and after the 1950s) and by

### 2.1.4 *Proportionate mortality studies since IARC Monograph volume 47* (Table 2.1)

Miller *et al.* (1986), in the United States, conducted a proportionate mortality study of deaths among 1746 caucasian pictorial artists who died during 1940–1969. Proportionate cancer mortality ratios (PCMR) were significantly elevated for bladder cancer (PCMR, 2.6; 95% CI: 1.5–4.4, 14 deaths), and leukaemia (PCMR 2.3; 95% CI: 1.2–4.5, ten deaths). Terstegge *et al.* (1995) conducted a proportionate mortality study of Dutch painters among whom 9812 deaths were observed during 1980–1992. These authors found significant excesses of mortality from cancer of the lung (PMR, 1.20; 95% CI: 1.14–1.26, 1480 deaths), and all cancers (PMR, 1.07; 95% CI: 1.03–1.11, 3266 deaths). Mortality from bladder cancer was borderline significant (PMR, 1.19; 95% CI: 1.00–1.41, 132 deaths) as was mortality from non-Hodgkin lymphoma (PMR, 1.28; 95% CI: 0.99–1.64, 65 deaths). Results for most sites were provided but were generally unremarkable.

Peto *et al.* (1995) studied mesothelioma mortality among men aged 16–74 in England, Scotland and Wales during the years 1979–1980 and 1982–1990. The PMR for mesothelioma in painters was reported as 1.31 ($P < 0.05$, 100 deaths).

Wang *et al.* (1999) studied American construction workers, which included a group of painters, paperhangers, plasterers, and supervisors, who died during 1988–1994. [As noted previously with regard to Carstensen *et al.* (1988), this grouping may be relevant for paint exposures as these workers are all likely to work together and to be exposed to paint fumes.] Significantly excess mortality was seen for cancers of the of the lung (PMR, 1.18), and of the pharynx (PMR, 1.78) with significantly decreased mortality seen for cancers of the kidney, brain, colon, and leukaemia. No confidence intervals or number of cause-specific deaths were given. [This was a proportionate mortality study and the elevation of some cancer PMRs may have been artificial and due to the observed low heart disease among healthy workers in this occupation (PMR, 0.87). No correction was made via use of PCMRs.]

### 2.1.5 *Study of paint-manufacturing workers since 1989*

Paint-manufacturing workers have different exposures than painters, and were judged separately by IARC in 1989. IARC concluded in 1989 that occupation as a paint-manufacturing worker is *not classifiable as to its carcinogenicity to humans* (Group 3).

Lundberg & Milatou-Smith (1998) studied cancer incidence among 411 workers in paint manufacturing that had been exposed to organic solvents for at least 5 years during 1955–1975. This was an update of an earlier study that included follow-up from 1961–1992. A total of 83 incident cancers were observed, versus 80 expected (SIR, 1.0; 95% CI: 0.8–1.3). There were no notable cancer excesses with the exception of a borderline increased risk for multiple myeloma (SIR, 3.2; 95% CI: 0.9–8.3), and cancer of the prostate (SIR, 1.5; 95% CI: 1.0–2.2).

Brown *et al.* (2002) studied 5741 male paint- and lacquer-manufacturing workers in a record linkage study in Sweden (see description above), and found significant elevations of

government life insurance policies. Personal data on usual occupation and smoking habits were obtained by mailed questionnaire in the 1950s. SMRs were calculated using Poisson regression, using all other occupations as the reference. After adjustment for smoking, age and calendar time, 1178 construction and maintenance painters had an SMR for all cancers of 1.0 (90% CI: 0.84–1.11, based on 140 cancer deaths). Cancer mortality was not remarkable for most anatomical sites. For anatomical sites with more than five deaths, the SMRs were 0.8 (90% CI: 0.42–1.61; six deaths) for cancer of the stomach, 1.0 (90% CI: 0.69–1.51; 18 deaths) for cancer of the colon, 1.6 (90% CI: 0.89–2.86; eight deaths) for cancer of the rectum, 1.1 (90% CI: 0.84–1.47; 36 deaths) for cancer of the respiratory system, 0.5 (90% CI: 0.27–0.78; ten deaths) for cancer of the prostate, 0.9 (90% CI: 0.48–1.67; seven deaths) for lymphoma, and 1.2 (90% CI: 0.69–2.10; nine deaths) for leukaemia. A smaller number of non-construction painters ($n = 140$) provided little extra information on cancer mortality owing to the small numbers involved.

Alexander *et al.* (1996) conducted a cohort study of 2429 chromate-exposed workers in the aerospace industry, of whom 62% had ever worked as a painter. A total of 15 cases of lung cancer were observed among the entire cohort, which was less than expected based on incidence data (SIR, 0.8; 95% CI: 0.4–1.3). No exposure–response trends with hexavalent chromium was seen, although the number of cases of lung cancer were too small to draw any meaningful conclusions. There was an inverse trend of lung cancer with duration of employment for painters, although sanders and polishers (exposed to dusts rather than mists) had a somewhat positive trend with duration. None of these results were statistically significant.

van Loon *et al.* (1997) conducted a population-based cohort study in the Netherlands that prospectively followed 58 279 men, aged 55–69 years, for cancer incidence from 1986–1990. Rate ratios were estimated by a case–cohort analysis (524 cases, 1630 non-cases in the subcohort). Self-reported lifetime job history, reviewed by experts on a case by case basis, was used to create a job exposure matrix (JEM) for exposure to paint dust (none, low, high). Positive non-significant increases in lung cancer were found for the 'low' exposed group (RR, 2.29; 95% CI: 0.61–8.63) and the 'high' exposed group (RR, 2.48; 95% CI: 0.88–6.97) compared to the unexposed group, after adjustment for age, smoking, diet, and other occupational exposures; although the test for trend was significant ($P < 0.01$). [This study was limited owing to the small sample size (14 'high' and '4' low exposed lung cancer deaths) and the use of a JEM to assign exposure level based on self-reported employment information.]

Boice *et al.* (1999) conducted a retrospective cohort study among 77 965 aircraft industry employees in California (1216 painters), employed for at least one year on or after 1960, with registry-linked mortality follow-up through 1996. There was little detail available on the type of painting done, except that the paints contained chromates. There were 101 cancer deaths among painters (all cancer SMR, 0.87; 95% CI: 0.71–1.06). The SMR for cancer of the lung was 1.11 (95% CI: 0.80–1.51; 41 deaths).