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

expected number was 0.52. There was also a statistically significant excess of deaths from stomach cancer (5 observed, 0.6 expected; in addition, a sixth incident case was reported). These excesses were confined to the workers exposed all day[1,2]. It should be noted that these workers had been exposed to a mixture of chemical compounds, including dichloromethane (see p. 194), ethylene chlorohydrin and small amounts of bis(2-chloroethyl)ether[1].

A third Swedish cohort consisted of 355 workers exposed at a plant producing ethylene oxide through oxygenation of ethylene. Of these, 128 workers had had almost pure exposure to ethylene oxide. Eight deaths occurred compared with 11.6 expected. There was one case of myelogenous leukaemia (0.16 expected) and one of lung cancer among men with mixed exposure[2].

The total number of leukaemias observed in the three Swedish studies was thus eight, with 0.83 expected. Stomach cancer occurred in excess in one plant only (six cases in a group of 89 workers)[2].

In a cohort study of 767 ethylene oxide production workers in the USA, no case of leukaemia was found. However, there was only low potential exposure to ethylene oxide among the workforce and an unusually large deficit in total deaths compared to the number expected, indicating diluting errors in the design of the study[1].

A cohort study of 602 factory workers in the Federal Republic of Germany exposed to ethylene oxide, propylene oxide (see p. 328), benzene (see p. 120) and ethylene chlorohydrin showed a deficit of all deaths compared with four different expected figures. There were 14 deaths due to cancer (16.6 expected from national statistics), one of which was a myeloid leukaemia (0.15 expected) and four of which were stomach cancers (2.7 expected). The expected numbers used were not calendar period-specific over the whole observation period, however, and it is not clear whether they were computed on the basis of the 92% of identified workers or the full cohort[1].

In the light of these data, a causal relationship between exposure to ethylene oxide and leukaemia is possible, but the five small epidemiological studies so far available suffer from various disadvantages, especially confounding exposures, which make their interpretation difficult.

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

Ethylene oxide was tested by intragastric intubation in rats and produced local tumours, mainly squamous-cell carcinomas, of the forestomach. When rats were fed diets fumigated with ethylene oxide, no increased incidence of tumours was observed[1]. In two experiments in which rats of one strain were exposed by inhalation, ethylene oxide increased the incidences of mononuclear-cell leukaemia, brain tumours and proliferative lesions of the adrenal cortex in animals of each sex and of peritoneal mesotheliomas in males[1,3,4]. In mice, inhalation of ethylene oxide resulted in increased incidences of alveolar/bronchiolar lung tumours and tumours of the Harderian gland in animals of each sex and of uterine adenocarcinomas, mammary carcinomas and malignant lymphomas in females[5]. Ethylene oxide was also tested by subcutaneous injection in mice, producing local tumours, which were mainly fibrosarcomas[1].

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

# IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 98

Painting, Firefighting, and Shiftwork

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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:

$$CH_4 + 2O_2 + \text{Energy of activation} \rightarrow CO_2 + 2H_2O + \text{Heat of combustion} + \text{Light}$$
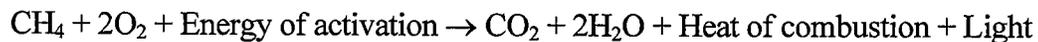
Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide (CO_2).

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:

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

$H^{\bullet} + O_2 \rightarrow OH^{\bullet} + O^{\bullet}$
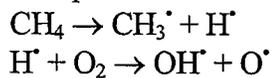
The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

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.

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

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

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

2.2   Case–control studies

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

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

[The Working Group noted that evaluation of the possible risks for lymphatic and haematopoietic cancer was hampered by inconsistencies in the histopathological classification of diagnoses over time. The interpretation of results for these malignancies was constrained by the diagnostic groupings that had been used by researchers when the studies were conducted.]

2.2 Cancer of the breast

Studies from four cohorts of workers exposed to ethylene oxide provided useful information on the association between this exposure and breast cancer (Gardner et al., 1989; Hagmar et al., 1991, 1995; Norman et al., 1995; Steenland et al., 2003, 2004; Coggon et al., 2004; see Table 2.2, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table2.2.pdf). The NIOSH study (Steenland et al., 2004) and a cohort study of hospital-based sterilization workers in the United Kingdom (Gardner et al., 1989; Coggon et al., 2004) examined mortality from breast cancer and found no overall excess risk. Three studies examined the incidence of breast cancer: the NIOSH study (Steenland et al., 2003) and a cohort study from Sweden (Hagmar et al., 1991, 1995) found no overall excess risk, while another cohort study from New York State, USA, found an excess risk of about 60%, which was borderline significant (Norman et al., 1995). Internal analyses with inclusion of questionnaire data were carried out in the NIOSH study (Steenland et al., 2003) showing increased relative risks for breast cancer at the highest level of cumulative exposure to ethylene oxide (> 11620 ppm–days, 15-year lag, OR = 1.87, 95%CI: 1.12–3.10), with a significant exposure–response relationship [P for trend = 0.002), after controlling for parity and history of breast cancer in a first-degree relative.

2.3 Other cancers

Several cohort studies provided data on exposure to ethylene oxide and mortality from other cancers (stomach, brain, pancreas; see Table 2.2, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table2.2.pdf). There was no consistent evidence of an association of these cancers with exposure to ethylene oxide.

2.4 Synthesis

The Working Group found some epidemiological evidence for associations between exposure to ethylene oxide and lymphatic and haematopoietic cancers, and specifically lymphoid tumours (i.e. non-Hodgkin lymphoma, multiple myeloma and chronic lymphocytic leukaemia).

3. Cancer in Experimental Animals

Carcinogenicity studies with mice and rats exposed to ethylene oxide by inhalation, oral gavage, and subcutaneous injection were previously reviewed (IARC, 1994, 2008). Results of adequately conducted carcinogenicity studies are summarized in Table 3.1. There have been no additional carcinogenicity studies in animals reported since the previous evaluation in *IARC Monograph* Volume 97 (IARC, 2008).

3.1 Inhalation exposure

In two inhalation studies in mice, there was an increased incidence of alveolar bronchiolar carcinomas and combined adenomas and carcinomas in male and female B6C3F$_1$ mice (NTP, 1987) and of lung adenomas in strain A/J female mice (Adkins et al., 1986). Treatment-related increases in lymphomas, Harderian gland

Table 3.1 Carcinogenicity studies in experimental animals exposed to ethylene oxide by inhalation, oral gavage and subcutaneous injection

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 2 yr Lynch et al. (1984)	Inhalation 0, 50, 100 ppm 7 h/d, 5 d/wk 80/group	Brain: 0/76, 2/77, 5/79 Mononuclear-cell leukaemia 24/77, 38/79, 30/76 Peritoneal mesotheliomas 3/78, 9/79, 21/79	$P < 0.05$ (high dose) $P = 0.03$ (low dose) $P = 0.002$ (high dose)	99.7% purity
Rat, F344 (M) 2 yr Snellings et al. (1984), Garman et al. (1985, 1986)	Inhalation 0 (control I), 0 (control II), 10, 33, 100 ppm 6 h/d, 5 d/wk 120/group	Brain[b]: 1/181, 0/92, 3/85, 6/87 Mononuclear-cell leukaemia 13/97, 9/51, 12/39, 9/30 Peritoneal mesotheliomas 2/97, 2/51, 4/39, 4/30 Subcutaneous fibromas 3/97, 9/51, 1/39, 11/30	$P < 0.01$ (trend); $P < 0.05$ (high dose) $P < 0.05$ (trend) $P < 0.005$ (trend) $P < 0.001$ (high dose)	> 99.9% purity Two control groups combined. Interim sacrifices at 6 (10 rats), 12 (10 rats), and 18 mo (20 rats). Increased mortality due to viral sialodacryoadenitis at 15 mo. No increases in tumour incidence up to 18 mo. Incidence for all sites other than brain are for rats that died or were sacrificed after 18 mo.
Rat, F344 (F) 2 yr Snellings et al. (1984), Garman et al. (1985, 1986)	Inhalation 0 (control I), 0 (control II), 10, 33, 100 ppm 6 h/d, 5 d/wk 120/group	Brain[b] 0/187, 1/94, 2/90, 2/78 Mononuclear-cell leukaemia 11/116, 11/54, 14/48, 15/26	$P < 0.05$ (trend) $P < 0.005$ (trend); $P < 0.001$ (high dose)	>99.9% purity Two control groups combined. Interim sacrifices at 6 (10 rats), 12 (10 rats), and 18 mo (20 rats). Increased mortality due to viral sialodacryoadenitis at 15 mo. No increases in tumour incidence up to 18 mo. Incidence for all sites other than brain are for rats that died or were sacrificed after 18 mo.
Mouse, A/J (F) 6 mo Adkins et al. (1986)	Inhalation 0, 70, 200 ppm 6 h/d, 5d/wk 0, 200 ppm 6 h/d, 5 d/wk 30/group	Lung adenomas 8/30, 16/28, 25/29 Lung adenomas 8/29, 12/28	[$P < 0.001$, trend & high dose] NS	≥ 99.7% purity Two independent experiments; tumour multiplicities increased for high-dose vs control in both ($P < 0.05$).

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M) 102 wk NTP (1987)	Inhalation 0, 50, 100 ppm 6 h/d, 5 d/wk 50/group	Lung (alveolar/bronchiolar carcinomas): 6/50, 10/50, 16/50	$P = 0.032$ (trend), $P = 0.048$ (high dose)	> 99% purity
		Lung (alveolar/bronchiolar adenomas and carcinomas combined): 11/50, 19/50, 26/50	$P = 0.010$ (trend), $P < 0.05$ (high dose)	
		Harderian gland cystadenomas 1/43, 9/44, 8/42	$P < 0.03$ (trend), $P < 0.05$ (low and high dose)	
Mouse, B6C3F$_1$ (F) 102 wk NTP (1987), Picut et al. (2003)	Inhalation 0, 50, 100 ppm 6 h/d, 5 d/wk 50/group	Lung (alveolar/bronchiolar carcinomas): 0/49, 1/48, 7/49	$P = 0.005$ (trend), $P < 0.05$ (high dose)	> 99% purity
		Lung (alveolar/bronchiolar adenomas and carcinomas combined): 2/49, 5/48, 22/49	$P < 0.001$ (trend, high dose)	
		Harderian gland cystadenomas 1/46, 6/46, 8/47	$P < 0.05$ (trend, high dose)	
		Lymphoma: 9/49, 6/48, 22/49	$P = 0.023$ (trend), $P < 0.05$ (high dose)	
		✱ Uterine adenocarcinomas 0/49, 2/47, 5/49	$P < 0.03$ (trend)	
		Mammary gland adenocarcinomas or adenosquamous carcinomas 1/49, 8/48, 6/49	$P \leq 0.02$ (low dose)	
Rat, SD (F) 150 wk Dunkelberg (1982)	Gavage 0 (untreated), 0 (vehicle, salad oil), 7.5, 30.5 mg/ kg bw 2x/wk 50/group	Fore-stomach squamous cell carcinomas 0/50, 0/50, 8/50, 29/50	[$P < 0.01$, low and high dose]	99.7% purity Many of the fore-stomach tumours in the high-dose group metastasized or were locally invasive to other organs.

386

cystadenoma, mammary gland carcinomas and uterine adenocarcinomas were also seen in B6C3F$_1$ mice (NTP, 1987; Picut *et al.*, 2003).

In two inhalation studies in F344 rats (Lynch *et al.*, 1984; Snellings *et al.*, 1984; Garman, *et al.*, 1985, 1986), there was an increased incidence in gliomas [not further specified], mononuclear cell leukaemia and peritoneal mesotheliomas. A treatment-related increase in subcutaneous fibromas also occurred in male rats (Snellings *et al.*, 1984).

3.2 Other routes of exposure

In one study, subcutaneous injection of ethylene oxide in female NMRI mice resulted in a dose-related increase in the incidence of sarcomas at the injection site (Dunkelberg, 1981).

In one study with female Sprague-Dawley rats that received ethylene oxide by gavage, there was a treatment-related increase in fore-stomach squamous-cell carcinomas (Dunkelberg, 1982).

4. Other Relevant Data

Experimental studies on ethylene oxide have been evaluated previously in *IARC Monograph* Volumes 60 and 97 (IARC, 1994, 2008). There is an extensive body of data on the mechanism of ethylene oxide-induced carcinogenicity encompassing toxicokinetics, DNA-adduct formation, biomarkers, genotoxicity, and molecular biology. Ethylene oxide is a direct alkylating agent that reacts with nucleophiles without the need for metabolic transformation. It has been shown to have genotoxic and mutagenic activity in numerous assays in both somatic and germ cells, and prokaryotic and eukaryotic organisms (IARC, 1994, 2008). Ethylene oxide is active in a wide range of *in vitro* and *in vivo* systems. Increases in both gene mutations and chromosomal alterations, two general classes

of cancer-related genetic changes, have been observed. The direct reaction of ethylene oxide with DNA is thought to initiate the cascade of genetic and related events that lead to cancer (Swenberg *et al.*, 1990). Thus, formation of DNA adducts and resultant mutations are key steps in the mechanism of carcinogenicity for this agent.

4.1 Absorption, distribution, metabolism, and excretion

Ethylene oxide is readily taken up by the lungs and is absorbed relatively efficiently into the blood. A study of workers exposed to ethylene oxide revealed an alveolar retention of 75–80%, calculated from hourly measurements of ethylene oxide in ambient air, which ranged from 0.2 to 24.1 mg/m^3 [0.11–13.2 ppm], and in alveolar air, which ranged from 0.05 to 6 mg/m^3 [0.03–3.3 ppm] (Brugnone *et al.*, 1985, 1986). At steady-state, therefore, 20–25% of inhaled ethylene oxide that reached the alveolar space was exhaled as the unchanged compound and 75–80% was taken up by the body and metabolized. Blood samples taken from workers at four hours after the work-shift gave venous blood/ alveolar air coefficients of 12–17 and venous blood/environmental air coefficients of 2.5–3.3.

The mammalian metabolic pathways of ethylene oxide are shown in Fig. 4.1 and can be summarized as follows: Ethylene oxide is converted (a) by enzymatic and non-enzymatic hydrolysis to ethylene glycol, which is partly excreted as such and partly metabolized further via glycolaldehyde, glycolic acid and glyoxalic acid to oxalic acid, formic acid and carbon dioxide; and (b) by conjugation with glutathione (GSH) followed by further metabolism to S-(2-hydroxyethyl)cysteine, S-(2-carboxymethyl) cysteine and N-acetylated derivatives (N-acetyl-S-(2-hydroxyethyl)cysteine (also known as S-(2-hydroxyethyl)mercapturic acid or HEMA) and N-acetyl-S-(2-carboxymethyl)cysteine) (Wolfs

embalmers 1.6 (95%CI: 1.2–2.0); and for pathologists and anatomists 1.4 (95%CI: 1.0–1.9), with an overall mRR of 1.1 (95%CI: 1.0–1.2) (Collins & Lineker, 2004). In another meta-analysis, analysis was restricted to 13 cohort or proportionate mortality studies and similar results were found, with a pooled RR based on the weighted average of the SMRs for leukaemia among industrial workers of 0.9 (95%CI: 0.75–1.07), based on 122 deaths, and of 1.39 (95%CI: 1.15–1.68) among professionals, based on 106 deaths (Bosetti et al., 2008). A further meta-analysis differed from these two previous ones by excluding all proportionate mortality studies and including the most recent update of the NCI cohort (Bachand et al., 2010). For leukaemia overall, a risk estimate of 1.05 (95%CI: 0.93–1.20) was calculated for 'ever exposure', based on 15 studies with the use of a fixed-effects model. For myeloid leukaemia, the calculated mRR was 1.09 (95%CI: 0.84–1.40, based on three studies) and for lymphatic leukaemia the mRR was 1.11 (95%CI: 0.81–1.52, based on two studies).

Zhang et al. (2009) published a meta-analysis that included 15 cohort or case–control studies. The authors selected only studies where it was clear that the workers had been exposed to formaldehyde. In contrast to the other meta-analyses, this one used one exposure metric from each study and considered the highest exposure category for calculating the mRR. For leukaemia, the mRR was 1.54 (95%CI: 1.18–2.00). In addition, a separate analysis of myeloid leukaemia – for the six studies that reported it – found an mRR of 1.90 (95%CI: 1.31–2.76).

2.3 Cancer of the nasal sinuses

2.3.1 Cohort studies

An analysis of proportionate cancer incidence among industrial workers in Denmark showed an increased risk for squamous-cell carcinomas (Hansen & Olsen, 1995, 1996). No excess of mortality from sinonasal cancer was observed in the three recently updated studies of industrial and garment workers in the USA, and of chemical workers in the United Kingdom (see Table 2.1 online; Coggon et al., 2003; Hauptmann et al., 2004; Pinkerton et al., 2004).

2.3.2 Case–control studies

The association between exposure to formaldehyde and the risk for sinonasal cancer has been evaluated in six case–control studies that primarily focused on formaldehyde (see Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-24-Table2.4.pdf; Olsen et al., 1984; Hayes et al., 1986; Olsen & Asnaes, 1986; Vaughan et al., 1986a; Roush et al., 1987; Luce et al., 1993; Pesch et al., 2008). Four of these six studies reported an increased risk (Olsen et al., 1984; Hayes et al., 1986; Vaughan et al., 1986a; Luce et al., 1993).

2.3.3 Pooled analysis

Four of the cohort studies contributed to a pooled analysis that collated occupational data from 12 case–control investigations (Luce et al., 2002). After adjustment for known occupational confounders, this analysis showed an increased risk for adenocarcinoma associated with high exposure (> 1 ppm) to formaldehyde in both men (OR, 3.0; 95%CI: 1.5–5.7) and women (OR, 6.3; 95%CI: 2.0–19.7). An exposure–response trend was observed in relation to an index of cumulative exposure. There was some evidence of an association with squamous-cell carcinoma.

[Most epidemiological studies of sinonasal cancer have not distinguished between tumours that arise in the nose and those that develop in the nasal sinuses. Thus, any effect on the risk for nasal cancer specifically would tend to be diluted if there were no corresponding effect on the risk for cancer in the sinuses and could mask its detection, particularly in cohort studies that

have relatively low statistical power. However, the apparent discrepancy between the results of the case–control as compared with the cohort studies might also reflect residual confounding by wood dust in the former. Almost all of the formaldehyde-exposed cases in the case–control studies were also exposed to wood dust, which resulted in a high relative risk, particularly for adenocarcinomas.]

2.4 Other cancers

Several studies have identified statistically significant positive associations between exposure to formaldehyde and cancer at other sites, including the oral cavity, oro-and hypopharynx, larynx, lung, brain, pancreas, Hodgkin lymphoma, and multiple myeloma. However, the results are inconsistent (see Tables 2.4 and 2.5 online; Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-24-Table2.6.pdf, and Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-24-Table2.7.pdf).

2.5 Synthesis

The Working Group noted one industrial cohort study with both a strong overall association between exposure to formaldehyde and nasopharyngeal cancer, and the most elevated risks in the highest exposure category. Positive associations were also observed in many of the case–control studies, in particular those of larger size and higher-quality exposure assessment. While there was no association observed in the two other large industrial cohort studies, the expected number of cases in those studies was quite small. It is concluded that occupational exposure to formaldehyde causes nasopharyngeal cancer in humans. The Working Group noted that it was unlikely that confounding or bias could explain the observed association.

Elevated risks of leukaemia have been consistently observed in proportionate mortality studies of professionals exposed to formaldehyde (i.e. embalmers, workers in the funeral industry, pathologists and anatomists). Results from a nested case–control study of workers in the funeral industry show elevated risks for many measures of exposure, which are strongest for myeloid leukaemia. In two of the three large industrial cohort studies positive associations were observed for leukaemia, which were somewhat stronger for myeloid leukaemia. It is difficult to reconcile the lack of association observed in the third industrial cohort study with the overall positive associations in the others. However, there seems to be no strong evidence that confounding or bias explains the positive associations seen in multiple settings. On balance, the Working Group concluded that the epidemiologic evidence shows that occupational exposure to formaldehyde causes leukaemia.

Many case–control studies show positive associations for exposure to formaldehyde and sinonasal cancer, some with evidence of an exposure–response pattern. However, many of these cases were also exposed to wood dust, which was strongly associated with sinonasal cancer in these studies. The industrial cohort studies show no such association, which may be due to lack of statistical power, or could indicate that uncontrolled confounding to wood dust partially explains the observed associations in the case–control studies. The Working Group could not rule out the possibility of residual confounding in the case–control studies and noted the discordant results between the cohort and case–control studies.

IARC MONOGRAPHS

DIESEL AND GASOLINE ENGINE EXHAUSTS AND SOME NITROARENES

VOLUME 105

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

relative risks were 0.95 (95% CI, 0.92–0.98), 1.1 (95% CI, 1.08–1.21) and 1.3 (95% CI, 1.26–1.42) for low, medium and high intensity of exposure, respectively. Corresponding results for probability of exposure were 1.1 (95% CI, 1.04–1.13), 0.90 (95% CI, 0.86–0.94) and 1.2 (95% CI, 1.10–1.24). Fewer cases (*n* = 57) and less exposure occurred in women, and the risk for lung cancer was not increased. Among men exposed to diesel exhaust, the standardized incidence ratio for urinary bladder cancer was 1.00 (95% CI, 0.97–1.03), with no trends by intensity or probability. For men with a high probability of exposure, the standardized incidence ratios were 1.1 (95% CI, 0.96–1.28) for laryngeal cancer, 0.98 (95% CI, 0.92–1.04) for urinary bladder cancer, 1.0 (95% CI, 0.96–1.14) for kidney cancer, 1.1 (95% CI, 0.99–1.21) for oral and pharyngeal cancer, 1.1 (95% CI, 1.05–1.20) for stomach cancer and 1.1 (95% CI, 0.99–1.19) for pancreatic cancer. A significantly increased risk of oral/pharyngeal (SIR, 1.64) and cervical (SIR, 1.48) cancers was observed among women, with a suggestion of a dose–response relationship. [The Working Group noted that the lack of work histories, which prohibited analyses by duration and latency, and the lack of smoking data were factors that weakened this study.]

In a population-based study in the Netherlands, Zeegers *et al.* (2001) studied 58 279 men who answered a questionnaire on occupation in 1986 and were followed up for the incidence of urinary bladder cancer until 1992. Experts using a JEM assigned the levels of exposure to diesel exhaust as none, low, medium and high to each subject. Using a case–cohort approach (532 cases, 1630 non-cases), the relative risks for urinary bladder cancer, after adjustment for smoking, demographics and other occupational exposures, were 1.00 (95% CI, 0.65–1.54), 0.96 (95% CI, 0.60–1.53) and 1.17 (95% CI, 0.74–1.84) for low, medium and high exposure, respectively, relative to no exposure (*P* for trend = 0.76).

Lee *et al.* (2003) analysed the risk for multiple myeloma in relation to diesel exposures in a large

Swedish cohort of construction workers who were followed up from 1971 to 1999. By linkage with the Swedish National Cancer Registry, 446 cases of primary multiple myeloma were identified. A JEM was developed to classify exposure to occupational agents, including diesel exhaust, using a 1971–76 survey of occupational exposures in the construction industry and nitric oxide as a marker of exposure to diesel exhaust. However, few occupations were considered to entail exposure to diesel exhaust in the original survey: drivers, earthmoving, mountain and asphalt workers, as well as some repair and concrete workers, were classified as occupationally exposed to diesel exhaust. Tobacco smoking status, body mass index and age, as well as socioeconomic status and other occupational exposures, were considered as potential confounders. Among diesel-exposed workers, the adjusted relative risk for multiple myeloma was 1.3 (95% CI, 1.00–1.77). No evidence of a dose–response was found. [The Working Group noted that the lack of information on duration of exposure, as well as the overall low levels of exposure to diesel exhaust in exposed cohort members, were limitations of the study.]

In a study described in Section 2.2.1, Guo *et al.* (2004a) also used a Finnish JEM (FINJEM) to estimate exposures to gasoline and diesel exhaust based on job reviews, and to assign exposure to diesel exhaust to different jobs reported in the census. In FINJEM jobs were classified as diesel-exposed when nitrogen dioxide had been found in surveys, and as gasoline-exposed when carbon monoxide had been found. The overall relative risk for lung cancer was 0.99 (95% CI, 0.96–1.03) among men and 1.22 (95% CI, 0.85–1.73) among women estimated to have been exposed to diesel exhaust, and 1.05 (95% CI, 1.01–1.09) among men and 1.61 (95% CI, 1.23–2.1) among women estimated to have been exposed to gasoline exhaust. The Finnish occupational exposure database included occupation, gender, age and period-specific tobacco smoking

diesel exhaust ✗

187