ANGIOSARCOMA

ATTACHED ARE THE IARC MONOGRAPHS TIED TO THE STATED OCCUPATIONAL FIREFIGHTING CANCER

IARC SUPPLEMENT 7

PAGES 137 (1,3 BUTADIENE*KNOWN CARCINOGEN FOUND IN SMOKE), 204 (ETHYLENE DIBROMIDE WITH WIKIPEDIA ATTACHED)

IARC 19

PAGES 384, 385, 398 AND 399 (VINYLE CHLORIDE* KNOWN CARCINIGEN IN SMOKE)

IARC 98

PAGES 399-401 PRODUCTS OF COMBUSTION AND PROCESS

IARC 100F

PAGES 148, 269, 451, 456, 457, 458 ABD 472 (VINYL CHLORIDE*)

Overview of Firefighter

"Occupational Angiosarcoma Cancer"

This packet is designed to aide a treating physician in making an educated diagnosis of a Firefighter Occupational Cancer. The following studies and documents below support the claim through research and science that this specific cancer is tied to the occupation of firefighter.

Included are multiple studies and conclusions, along with NIOSH and International Agency on the Research of Cancer (IARC). Also included is Chapter 607 of the Texas Local Government Code, which states the requirements of attaining a presumption for firefighters in Texas who develop cancer. Of specific note are the following points.

1. IARC Supplement 7- page 137 states 1,3-Butadiene as a cause of Angiosarcoma by inhalation. Page 204 states "Ethylene Dibromide", a known chemical used in flame retardants (wiki attached) produced Angiosarcoma.
2. IARC 19- 384,385,398 and 399, show the relation of "Vinyl Chloride" (a known product of combustion, see Chemical list attached).
3. IARC 98- Page 399, 400, points out the components of smoke. These state that ethylene oxide is present in the smoke of fires.
4. IARC 100F- Pages 269 links 'Benzene" and pages 451, 456, 457, 458, and 472 link "Vinyl Chloride' (both are known products of combustion ; see attached Chemicals List)

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

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

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

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

C. Other relevant data

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

References

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

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

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

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

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

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

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

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

ETHYLENE DIBROMIDE (Group 2A)

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

In one study, the mortality of 161 men exposed to ethylene dibromide in two factories since the mid-1920s and 1942, respectively, was investigated. By 1 January 1976, 36 workers had died, seven of them from cancer (5.8 expected)[1]. In another study, the mortality of 2510 male workers employed at a chemical plant was investigated. Ethylene dibromide was one of several chemicals used and was apparently a minor component of the mixed exposure. No statistically significant excess of cancer at any site was found[2]. An excess of lymphoma was detected in a mortality study of grain workers in the USA who may have had exposure to ethylene dibromide, among other compounds[3].

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

Ethylene dibromide has been tested for carcinogenicity by oral administration and by inhalation in mice and rats and by skin application in mice. Following its oral administration, it produced squamous-cell carcinomas of the forestomach in animals of each species, an increased incidence of alveolar/bronchiolar lung tumours in mice of each sex, liver carcinomas in female rats, haemangiosarcomas in male rats and oesophageal papillomas in female mice[4-6]. Following its inhalation, ethylene dibromide produced adenomas and carcinomas of the nasal cavity, haemangiosarcomas of the spleen, mammary tumours, subcutaneous mesenchymal tumours, an increased incidence of alveolar/bronchiolar lung tumours in animals of each species[7-9], and an increased incidence of peritoneal mesotheliomas in male rats[7]. Ethylene dibromide induced skin and lung tumours in mice after skin application[10].

C. Other relevant data

Ethylene dibromide did not induce chromosomal aberrations or sister chromatid exchanges in exposed pine-tree sprayers and fruit packers[11].

Ethylene dibromide did not induce dominant lethal mutations in mice or rats or chromosomal aberrations or micronuclei in bone-marrow cells of mice treated *in vivo*; however, a weak sister chromatid exchange response was observed. It bound covalently to DNA in rat hepatocytes and induced DNA strand breaks in mouse and rat hepatocytes and in rat testicular cells in studies of rodents treated *in vivo*. Sister chromatid exchanges, mutation and unscheduled DNA synthesis were induced in human cells *in vitro*, and chromosomal aberrations, sister chromatid exchanges, mutation, DNA strand breaks and unscheduled DNA synthesis in rodent cells *in vitro*. Ethylene dibromide induced sex-linked recessive lethal mutations in *Drosophila* and chromosomal aberrations and mutation in plants. It was mutagenic to fungi and bacteria and produced DNA damage in bacteria. Ethylene dibromide bound covalently to isolated DNA[11].

References

[1]Ott, M.G., Scharnweber, H.C. & Langner, R.R. (1980) Mortality experience of 161 employees exposed to ethylene dibromide in two production units. *Br. J. ind. Med.*, *37*, 163-168

1,2-Dibromoethane

From Wikipedia, the free encyclopedia

1,2-Dibromoethane, also known as **ethylene dibromide** (EDB), is the organobromine compound with the chemical formula $(CH_2Br)_2$. Although trace amounts occur naturally in the ocean, where it is formed probably by algae and kelp, it is mainly synthetic. It is a colorless liquid with a sweet odor, detectable at 10 ppm, is a widely used and sometimes-controversial fumigant.[4]

Contents

Preparation and use

It is produced by the reaction of ethylene with bromine, in a classic halogen addition reaction:

$$CH_2{=}CH_2 + Br_2 \rightarrow BrCH_2CH_2Br$$

Historically, 1,2-dibromoethane was used as an anti-knock additive in leaded fuels. It reacts with lead residues to generate volatile lead bromides, thereby preventing fouling of the engine.[5]

Pesticide

It has been used as a pesticide in soil and on various crops. The applications were initiated after the forced retirement of 1,2-dibromo-3-chloropropane (DBCP).[4] Most of these uses have been stopped in the U.S. It continues to be used as a fumigant for treatment of logs for termites and beetles, for control of moths in beehives.[6]

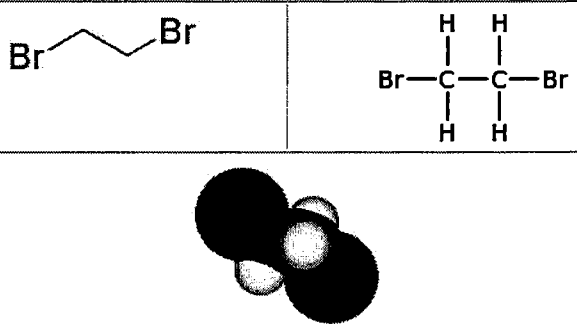
Reagent

Ethylene bromide has wider applications in the preparation of other organic compounds. It is used to make vinyl bromide, a precursor to some fire retardants.[4]

In the laboratory, 1,2-dibromoethane is used in organic synthesis as a source of bromine, e.g., to brominate carbanions and to activate magnesium for certain Grignard reagents. In the latter process, the 1,2-dibromoethane is converted to ethylene and magnesium bromide, exposing a freshly etched portion of magnesium to the substrate.[7]

Health effects

1,2-Dibromoethane



Names	
IUPAC name	
1,2-Dibromoethane[1]	
Other names	
Ethylene dibromide[1]	
Ethylene bromide[2]	
Glycol bromide[2]	
Identifiers	
CAS Number	106-93-4 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=106-93-4) ✓
3D model (Jmol)	Interactive image (http://chemapps.stolaf.edu/jmol/jmol.php?model=BrCCBr)
Abbreviations	EDB
Beilstein Reference	605266
ChEBI	CHEBI:28534 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=28534) ✓
ChemSpider	7551 (http://www.chemspider.com/Chemical-Structure.7551.html) ✓
ECHA InfoCard	100.003.132 (https://echa.europa.eu/substance-information/-/substanceinfo/100.003.132)
EC Number	203-444-5
KEGG	C11088 (http://www.kegg.jp/entry/C11088) ✓
MeSH	Ethylene+Dibromide (https://www.nlm.nih.gov/cgi/mesh/2014/MB_cgi?mode=&term=Ethylene+Dibromide)
PubChem CID	7839 (https://pubchem.ncbi.nlm.nih.gov/compound/7839)
RTECS number	KH9275000
UNII	1N41638RNO (http://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=1N41638RNO) ✗
UN number	1605
InChI	
SMILES	
Properties	

The effects on people of breathing high levels are not known, but animal studies with short-term exposures to high levels caused depression and collapse, indicating effects on the brain. Changes in the brain and behavior were also seen in young rats whose male parents had breathed 1,2-dibromoethane, and birth defects were observed in the young of animals that were exposed while pregnant. 1,2-Dibromoethane is not known to cause birth defects in humans.[8] Swallowing has caused death at 40 mL doses[6]

It is a known carcinogen, with pre-1977 exposure levels ranking it as the most carcinogenic substance on the HERP Index.[9]

References

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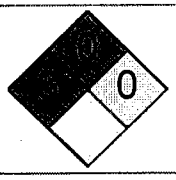
2. "NIOSH Pocket Guide to Chemical Hazards #0270". National Institute for Occupational Safety and Health (NIOSH).
3. "Ethylene dibromide". *Immediately Dangerous to Life and Health*. National Institute for Occupational Safety and Health (NIOSH).
4. Dagani, M. J.; Barda, H. J.; Benya, T. J.; Sanders, D. C. (2005), "Bromine Compounds", *Ullmann's Encyclopedia of Industrial Chemistry*, Weinheim: Wiley-VCH, doi:10.1002/14356007.a04_405
5. Seyferth, D. (2003). "The Rise and Fall of Tetraethyllead. 2". *Organometallics*. **22** (25): 5154–5178. doi:10.1021/om030621b.
6. "Toxicological Profile for 1,2-Dibromoethane" (PDF). Archived from the original (PDF) on 2009-11-22. Retrieved 2009-11-22.
7. Maynard, G. D. (2004). "1,2-Dibromoethane". In L. Paquette. *Encyclopedia of Reagents for Organic Synthesis*. New York: J. Wiley & Sons. doi:10.1002/047084289.
8. http://www.atsdr.cdc.gov/mmg/mmg.asp?id=1062&tid=131
9. "Ranking Possible Cancer Hazards on the HERP Index" (PDF). Archived from the original (PDF) on 2011-05-11. Retrieved 2010-10-14.

External links

- National Pollutant Inventory 1,2-Dibromoethane Fact Sheet (http://www.npi.gov.au/database/substance-info/profiles/31.html)
- Congressional Research Service (CRS) Reports regarding Ethylene Dibromide

Chemical formula	$C_2H_4Br_2$
Molar mass	187.86 g·mol^{-1}
Appearance	Colorless liquid
Odor	sweet[2]
Density	2.18 g mL^{-1}
Melting point	9.4 to 10.2 °C; 48.8 to 50.3 °F; 282.5 to 283.3 K
Boiling point	129 to 133 °C; 264 to 271 °F; 402 to 406 K
Solubility in water	0.4% (20 °C)[2]
log P	2.024
Vapor pressure	1.56 kPa
Henry's law constant (k_H)	14 μmol Pa kg^{-1}
Refractive index (n_D)	1.539
Thermochemistry	
Specific heat capacity (C)	134.7 J K^{-1} mol^{-1}
Std molar entropy (S°_{298})	223.30 J K^{-1} mol^{-1}
Std enthalpy of combustion ($\Delta_c H^\circ_{298}$)	−1.2419–−1.2387 MJ mol^{-1}
Hazards	
Main hazards	carcinogen[2]
GHS pictograms	
GHS signal word	**DANGER**
GHS hazard statements	H301, H311, H315, H319, H331, H335, H350, H411
GHS precautionary statements	P261, P273, P280, P301+310, P305+351+338
EU classification (DSD)	 T N
R-phrases	R45, R23/24/25, R36/37/38, R51/53
S-phrases	S45
NFPA 704	
Flash point	> 104 °C (219 °F; 377 K)
Lethal dose or concentration (LD, LC):	
LD_{50} (median dose)	55.0 mg kg^{-1} (oral, rabbit) 79.0 mg kg^{-1} (oral, chicken) 110.0 mg kg^{-1} (oral, guinea pig) 130.0 mg kg^{-1} (oral, quail) 300.0 mg kg^{-1} (dermal, rabbit)

LC_{50} (median concentration)	1831 ppm (rat, 30 min) 691 ppm (rat, 1 hr)[3]
LC_{Lo} (lowest published)	200 ppm (rat, 8 hr) 400 ppm (guinea pig, 3 hr)[3]
US health exposure limits (NIOSH):	
PEL (Permissible)	TWA 20 ppm C 30 ppm 50 ppm [5-minute maximum peak][2]
REL (Recommended)	Ca TWA 0.045 ppm C 0.13 ppm [15-minute][2]
IDLH (Immediate danger)	Ca [100 ppm][2]
Related compounds	
Related alkanes	Dibromomethane Bromoform Tetrabromomethane 1,1-Dibromoethane Tetrabromoethane 1,2-Dibromopropane 1,3-Dibromopropane 1,2,3-Tribromopropane
Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa). ✗ verify (what is ✓✗ ?) Infobox references	

(http://digital.library.unt.edu/govdocs/crs/search.tkl?q=ethylene+dibromide&search_crit=title&search=Search&date1=Anytime&date2=Anytime&type=form)

- ATSDR ToxFAQs (http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=725&tid=131)
- CDC - NIOSH Pocket Guide to Chemical Hazards (http://www.cdc.gov/niosh/npg/npgd0270.html)

Retrieved from "https://en.wikipedia.org/w/index.php?title=1,2-Dibromoethane&oldid=739305119"

Categories: Endocrine disruptors | Insecticides | Bromoalkanes | Fumigants | Flame retardants | Hazardous air pollutants | Fuel additives | IARC Group 2A carcinogens

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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Some Monomers, Plastics and Synthetic Elastomers, and Acrolein

VOLUME 19

IARC LYON

FEBRUARY 1979

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1,2]

(a) Oral administration

Rat: Groups of 40 male and 40 female 13-week-old Sprague-Dawley rats received gastric intubations of 0, 3.33, 16.65 or 50 mg/kg bw vinyl chloride dissolved in olive oil 4-5 times/week for 52 weeks. After 85 weeks from the initial treatment, 35, 39, 32 and 23 animals were still alive. At 120 weeks, 9 liver angiosarcomas, 2 Zymbal gland carcinomas and 3 nephroblastomas occurred in rats administered the 16.65 mg/kg bw dose; and 16 liver angiosarcomas, 2 nephroblastomas, 1 Zymbal gland carcinoma, and 1 thymic and 1 intra-abdominal angiosarcoma were found in the 50 mg/kg bw group. One intra-abdominal angiosarcoma was seen in the low-dose group, and 1 Zymbal gland tumour occurred in the control group (Maltoni, 1977a; Maltoni *et al.*, 1975).

(b) Inhalation and/or intratracheal administration

Mouse: Groups of 30 male and 30 female 11-week-old Swiss mice were exposed to concentrations of 130-26 000 mg/m^3 (50, 250, 500, 2500, 6000, or 10 000 ppm) vinyl chloride in air for 4 hours/day on 5 days/week for 30 weeks. A total of 344 mice (176 males and 168 females) died within 61 weeks. At 81 weeks (end of experiment), 176 animals (3.5, 57, 66, 57, 70 and 70% in the different groups, respectively) had adenomas and/or adenocarcinomas of the lung, 60 animals (33, 32, 24, 30, 28 and 47%, respectively) had mammary adenocarcinomas and 47 animals (2, 19, 19, 20, 5 and 16%, respectively) had angiosarcomas of the liver. Except for lung tumours, which were not increased in the group treated with 50 ppm, a significantly higher number of neoplasms occurred in all treated groups. In 80 male and 70 female untreated controls, 8 pulmonary tumours and 3 lymphomas were observed (Maltoni, 1977; Maltoni *et al.*, 1974).

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[1]The Working Group was aware of studies in progress to assess the carcinogenicity of vinyl chloride in rats by administration in the drinking-water and by administration in the diet, and of complete but unpublished studies by inhalation in rats (IARC, 1978a).

[2]In all his experiments, Maltoni used vinyl chloride that contained the following impurities (mg/kg): water, 100; acetic aldehyde, 5; acetylene, 2; allene, 5; butane, 8; 1,3-butadiene, 10; chloroprene (see also, p. 131), 10; diacetylene, 4; vinyl acetylene, 10; propine, 3; methyl chloride, 100.

Groups of 100 male and 100 female CDI Swiss/ChR mice (age unspecified) were exposed to 130, 520 or 6500 mg/m^3 (50, 200 or 2500 ppm) vinyl chloride in air (purity unspecified) for 7 hours/day on 5 days/week for 9 months and were observed for an additional 9 months. After 8 months' exposure, 49 treated animals died with tumours. A total of 42 pulmonary adenomas, 41 liver angiosarcomas and 11 mammary gland adenocarcinomas were observed (histological evaluation was carried out on grossly visible tumours only). A dose-related carcinogenic effect was evident (see Table I). At 8 months, no tumours were observed in 200 controls (100 females and 100 males). The study was still in progress at the time of reporting (Keplinger *et al.*, 1975).

Table I

Incidence of tumours in mice exposed to vinyl chloride (purity unspecified) for 8 months[1]

Exposed groups	No. of mice with tumours at death			Type and location of tumour		
				Adenomas	Angiosar-comas	Adenocar-cinomas
	Male	Female	Total	lung	liver	mammary gland
50 ppm	1	3	4	2	2	2
200 ppm	3	12	15	12	11	3
2500 ppm	6	24	30	28	28	6
Control	0	0	0	0	0	0

[1]From Keplinger *et al.* (1975), preliminary results

Two groups each of 12 male and 12 female 3-month-old NMRI outbred albino mice were exposed to either 130 or 1300 mg/m^3 (50 or 500 ppm) vinyl chloride in air for 6 hours/day on 5 days/week. The 500 ppm group was exposed for 26 weeks only (due to the poor condition of the mice); the 50 ppm group was exposed for 52 weeks, at which time the experiment was terminated. In the low-dose group, 18/24 animals had developed tumours, including pulmonary adenomas in 13/24, angiosarcomas at various sites in 15/24 and a mammary carcinoma in 1 mouse. Inhalation of 500 ppm vinyl chloride for 26 weeks induced pulmonary adenomas in all mice; in addition, 8 mice had angiosarcomas, mammary adenocarcinomas were found in 4 animals, 1 mouse had an angiosarcoma of the liver, 1 an adenoma of the kidney and 1 an angiosarcoma of brown fat. In the control group, 3/48 had tumours: 1 adenocarcinoma of the mammary gland, 1 dysgerminoma of the ovary and 1 reticulum-cell sarcoma of the spleen (Holmberg *et al.*, 1976).

Embryotoxicity and teratogenicity

A significant excess of foetal deaths was reported in women whose husbands were exposed to vinyl chloride: 15.8%, or 23, foetal deaths in 139 pregnancies, as compared with 8.8% (24/273) in the age-adjusted control group. This excess of foetal deaths was shown not to be a function of chronic abortions, i.e., the association was maintained after excluding pregnancies of women who had had more than 2 abortions (Infante *et al.*, 1976a). The significance of this study was questioned because data collection methods were not specified and there was no statistical treatment of the data (Paddle, 1976). Subsequently, the data collection methods were described, showing that there had been no interviewer-respondent bias, and details of statistical analyses were specified (Infante *et al.*, 1976b).

In a registry-based study, Infante (1976) reported that an excess of central nervous system defects, of deformities of the upper alimentary and genital tracts, and of clubfoot has been observed in stillborn and live children in 3 cities in Ohio in which vinyl chloride polymerization plants are located.

In hospital-based studies in newborns in Painesville (Ohio), where there are two polyvinyl chloride plants, and in Kanawha county (West Virginia), where there is one plant, excesses of anencephaly and spina bifida were reported, but no association was made with vinyl chloride (Edmonds, 1977; Edmonds *et al.*, 1975, 1978).

Mutagenicity and other short-term tests

Chromosome aberrations were found in workers occupationally exposed to vinyl chloride in the US (Ducatman *et al.*, 1975; Heath *et al.*, 1977), Sweden (Funes-Cravioto *et al.*, 1975), the UK (Purchase *et al.*, 1975), Belgium (Léonard *et al.*, 1977), Hungary (Szentesi *et al.*, 1976) and Norway (Hansteen *et al.*, 1976). These aberrations were in most cases fragments, dicentrics and rings, and breaks and gaps.

3.3 Case reports and epidemiological studies[1]

In 1974, more than 40 years after the introduction of vinyl chloride into industry, Creech & Johnson (1974) first reported an association of exposure to this chemical with cancer in man. Three cases of liver angiosarcoma were reported in men who were employed in the manufacture of polyvinyl chloride resins (one had cleaned reactor vessels) in a single vinyl chloride polymerization plant in the US.

[1]The Working Group was aware of a study in progress on the occupational and community carcinogenic risk of vinyl chloride (IARC, 1978b).

By reviewing medical records and pathological material and by systematic medical screening, the association between exposure to vinyl chloride and angiosarcoma of the liver has been reported from a number of other countries: Canada (Delorme & Thériault, 1978; Noria *et al.*, 1976); Czechoslovakia (Lloyd, 1975); the Federal Republic of Germany (Lange *et al.*, 1974b, 1975); France (Couderc *et al.*, 1976; Ravier *et al.*, 1975; Roche *et al.*, 1978); Italy (Maltoni, 1974); Norway (Lloyd, 1975); Romania (Lloyd, 1975); Sweden (Byrén & Holmberg, 1975); the UK (Lee & Harry, 1974; Smith *et al.*, 1976b); the US (Block, 1974; Falk *et al.*, 1974a; Makk *et al.*, 1974); and Yugoslavia (Šarić *et al.*, 1976). A review of 64 reported cases in various countries as of October 1977 is available (Spirtas & Kaminski, 1978).

No history of acro-osteolysis and no evidence of exposure to hepatotoxic materials other than vinyl chloride was reported in a clinical review of 7 cases of liver angiosarcoma among US vinyl chloride polymerization workers (Heath *et al.*, 1975). In a pathological evaluation of cases of liver angiosarcoma among exposed US vinyl chloride workers, it was concluded that these tumours were often multicentric: angiosarcomas were also detected in the wall of the duodenum, in the heart and kidney, and in other organs (Thomas & Popper, 1975).

The cancer risk among a cohort of males in the US who had at least one year of occupational exposure to vinyl chloride was studied. When compared with the US male population, an excess of cancer of the digestive system, of the liver (primarily angiosarcoma), of the respiratory system, of the brain and of unknown sites, as well as lymphomas was observed in those members of the study cohort with the greatest estimated exposure to vinyl chloride (Tabershaw & Gaffey, 1974) [Vital status was undetermined for 15% of the study cohort, and only 50% had 15 or more years since onset of exposure to vinyl chloride].

In a proportional-mortality analysis of 161 deceased workers in two US plants producing and polymerizing vinyl chloride, a 50% excess of deaths due to all cancers was reported. Sites of cancer with the greatest excess were liver and biliary tract, brain, digestive tract and lung (Monson *et al.*, 1974). Falk *et al.* (1974b) questioned the authors' conclusion, on the grounds that not all deaths studied were among workers in activities directly related to vinyl chloride production or polymerization and that the study failed to include deaths among workers who had terminated employment prior to retirement or death.

The cancer mortality experience of 257 US workers (255 were traced), each of whom had been occupationally exposed to vinyl chloride for at least 5 years and observed after 10 years from onset was studied using union seniority and company employment records. Among 24 deaths from all causes, a 2.3-fold excess was observed in deaths from cancer; of the 24 deaths, 3 were due to haemangiosarcoma of the liver (Nicholson *et al.*, 1975).

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

LYON, FRANCE
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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.

Table 1.1. IARC evaluations and cancer sites in humans of chemicals measured at fires

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Acetaldehyde	2B	Inadequate	Sufficient	36, Suppl. 7, 71	
Arsenic	1	Sufficient	Limited	23, Suppl. 7	Skin, lung, liver (angiosarcoma)
Asbestos	1	Sufficient	Sufficient	14, Suppl. 7	Lung, mesothelioma, larynx, gastrointestinal tract
Benz[*a*]anthracene	2B	Inadequate	Sufficient	32, Suppl. 7, 92	
Benzene	1	Sufficient	Limited	29, Suppl. 7	Leukaemia
Benzo[*b*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzo[*k*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzofuran (coumarone)	2B	No data	Sufficient	63	
Benzo[*a*]pyrene	1	No data	Sufficient	32, Suppl. 7, 92	Lung, bladder, skin
1,3-Butadiene	1	Sufficient	Sufficient	71, 97	Lymphohaematopoietic system
Cadmium	1	Sufficient	Sufficient	58	Lung
Carbon black (total)	2B	Inadequate	Sufficient	65, 93	
Chrysene	2B	Inadequate	Sufficient	3, 32, Suppl. 7, 92	
Dibenz[*a*,*h*]anthracene	2A	Inadequate	Sufficient	32, Suppl. 7, 92	
Dichloromethane (methylene chloride)	2B	Indadequate	Sufficient	71	
Ethylbenzene	2B	Inadequate	Sufficient	77	
Formaldehyde	1	Sufficient	Sufficient	88	Nasopharynx; (nasal sinuses and leukaemia, suggested)
Furan	2B	Inadequate	Sufficient	63	

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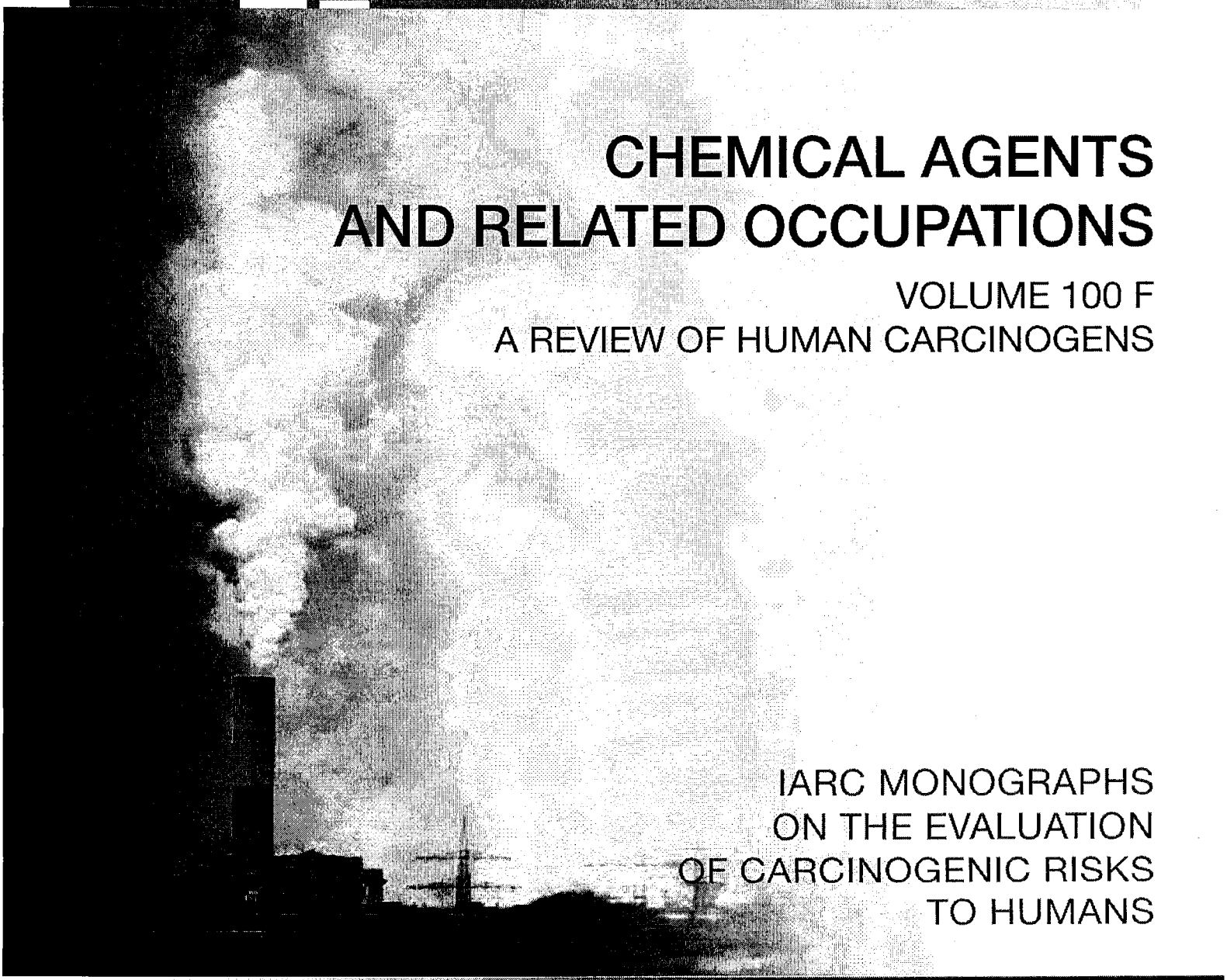

CHEMICAL AGENTS AND RELATED OCCUPATIONS

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

synthesis gas (Shadle *et al.*, 2002; Crelling *et al.*, 2005).

The moving-bed gasifiers produce tars, oils, phenols and heavy hydrocarbons, and the concentrations in the gas product are controlled by quenching and water scrubbing. Fluidized-bed gasifiers produce significantly smaller amounts of these compounds because of higher operating temperatures. Entrained-flow gasifiers that operate at even higher temperatures (in excess of 1650 °C) can achieve carbon conversions of more than 99.5%, while generating essentially no organic compounds heavier than methane (Shadle *et al.*, 2002).

In addition to PAHs, workers in coal gasification may be exposed to many compounds, including asbestos, silica, amines, arsenic, cadmium, lead, nickel, vanadium, hydrocarbons, sulfur dioxide, sulfuric acid and aldehydes (IARC, 1984).

2. Cancer in Humans

2.1 Cohort studies of coal-gasification workers

Occupational exposure during coal gasification was evaluated in *IARC Monograph* Volume 92 (IARC, 2010). There was *sufficient evidence* in epidemiological studies for the carcinogenicity of occupational exposure during coal gasification. The main body of evidence came from two cohort studies of coal-gasification workers in the United Kingdom (Doll *et al.*, 1972) and Germany (Berger & Manz, 1992), and a case–control study nested within a cohort of French gas- and electricity-production workers (Martin *et al.*, 2000; see Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-10-Table2.1.pdf). In all studies an excess of lung cancer in association with coal gasification was found, which was not likely to be explained by confounding from tobacco smoking. There was evidence supporting a lung-cancer excess in a historical record-linkage study from the United Kingdom (Kennaway & Kennaway, 1947), in two smaller cohorts (Kawai *et al.*, 1967; Hansen *et al.*, 1986), and a large but inadequately reported Chinese study (Wu, 1988).

In addition to lung cancer, the study from the United Kingdom (Doll *et al.*, 1972) showed an excess of bladder cancer, and the German study (Berger & Manz, 1992) showed an excess of cancers of the stomach and colon-rectum.

No epidemiological studies of coal-gasification workers have been published since the previous evaluation (IARC, 2010).

2.2 Synthesis

In three large studies, a consistent excess of lung cancer was found in association with occupational exposure during coal gasification. This excess was not likely to be explained by tobacco smoking.

3. Cancer in Experimental Animals

Coal-tars from gas works were previously evaluated in *IARC Monograph* Volume 34 (IARC, 1984). As early as 1923 and in subsequent decades, crude coal-tars from gas-works were tested for carcinogenicity by skin application in six studies in mice and two studies in rabbits. These tars induced a high number of skin papillomas and carcinomas in all studies in mice (Deelman, 1923; Kennaway, 1925; Hieger, 1929; Woglom & Herly, 1929; Berenblum & Schoental, 1947; Grigorev, 1960) and in both studies in rabbits (Berenblum & Schoental, 1947; Grigorev, 1960). No new studies have been published since the previous evaluation.

Manufactured gas plant residues (MGP) were previously evaluated in *IARC Monograph*

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) Lifetime Maltoni *et al.* (1983, 1989), Maltoni & Scarnato (1979), Mehlman (2002)	Benzene in olive oil 0 (control), 50 or 250 mg/kg bw once/d, 4–5 d/wk for 52 wk 30 or 35/group	**Leukaemia:** M–0/28, 0/28, 4/33 F–1/30, 2/30, 1/32 **Zymbal's gland** (carcinomas): M–0/28, 0/28, 0/33 F–0/30, 2/30, 8/32*	[NS] *[$P < 0.005$] (F)	99.93% pure
Rat, Sprague-Dawley (M, F) Lifetime Maltoni *et al.* (1989) Maltoni *et al.* (1983), Mehlman (2002), Maltoni *et al.* (1982b)	Benzene in olive oil 0 (control), 500 mg/kg bw once/d, 4–5 d/wk for 104 wk Controls, 50/group Treated, 40/group	**Leukaemia:** M–3/50, 1/40 F–1/50, 3/40 **Zymbal's gland:** Carcinoma: M–1/50, 18/40 F–0/50, 16/40 **Nasal cavity:** Carcinoma: M–0/50, 3/40 F–0/50, 1/40 **Oral cavity:** Carcinoma: M–0/50, 21/40 F–0/50, 20/40 **Skin:** Carcinoma: M–0/50, 9/40 F–1/50, 0/40 **Liver:** Hepatomas: M–3/50, 3/40 F–0/50, 1/40 Angiosarcoma: M–0/50, 2/40 F–0/50, 3/40 **Forestomach:** Acanthoma/dysplasia: M–0/50, 10/40 F–0/50, 7/40 Carcinoma M–0/50, 1/40 F–0/50, 6/40 **Total Malignant tumours:** M–12/50, 68/40 F–11/50, 59/40	[NS] [$P < 0.0001$] (M, F) [NS] [$P < 0.0001$] (M, F) [$P < 0.001$] (M) [NS] [$P < 0.005$] (M, F) [$P < 0.01$] (F) -	99.93% pure

VINYL CHLORIDE

Vinyl chloride was considered by previous IARC Working Groups in 1974, 1978, 1987, and 2007 (IARC, 1974, 1979, 1987, 2008). Since that time new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

From IARC (2008) and Lide (2008)
Chem. Abstr. Serv. Reg. No.: 75-01-4
Chem. Abstr. Serv. Name: Chloroethene

$H_2C{=}CH{-}Cl$

C_2H_3Cl
Relative molecular mass: 62.5
Description: Colourless gas, with a mild, sweet odour
Boiling-point: -13.4 to -13.8 °C
Solubility: Slightly soluble in water (1.1 g/L at 25 °C); soluble in ethanol; very soluble in diethyl ether, carbon tetrachloride and benzene
Conversion factor: 1 ppm = 2.6 mg/m^3

1.2 Uses

Vinyl chloride is used primarily (> 95%) in the manufacture of polyvinyl chloride (PVC), which comprises about 12% of the total use of plastic worldwide (WHO, 1999). The largest use of PVC is in the production of plastic piping. Other important uses are in floor coverings, consumer goods, electrical applications and in the transport sector. About 1% of PVC is used to produce vinyl chloride/vinyl acetate copolymer. Minor uses of vinyl chloride (monomer) include the manufacture of chlorinated solvents (primarily 10000 tonnes per year of 1,1,1-trichloroethane) and the production of ethylene diamine for the manufacture of resins (WHO, 1999; European Commission, 2003).

Vinyl chloride has been used in the past as a refrigerant, as an extraction solvent for heat-sensitive materials, in the production of chloroacetaldehyde, as an aerosol propellant and in drugs and cosmetic products; these uses were banned in the United States of America (USA) by the Environmental Protection Agency in 1974 (IARC, 2008).

1.3 Human exposure

1.3.1 Occupational exposure

The main route of occupational exposure to vinyl chloride is by inhalation, which occurs primarily in vinyl chloride/PVC plants and in PVC-processing plants. Only few exposure

was included in the European study – indicated 12 confirmed cases of HCC (Pirastu *et al.*, 2003). The maximal overlap between these two analyses was four cases, since only four HCC from Italy were included in the multicentre cohort. In this subcohort, the incidence of HCC again increased significantly with cumulative exposure to vinyl chloride. There was suggestive evidence that the risk for HCC from vinyl chloride is substantially higher among workers who are infected with hepatitis B virus (Wong *et al.*, 2003), or who report high levels of alcoholic beverage consumption (Mastrangelo *et al.*, 2004).

A meta-analysis of cohort studies of vinyl choride-exposed workers published up to 2002 (Boffetta *et al.*, 2003) was based on eight independent studies, i.e. two multicentric investigations (Mundt *et al.*, 2000; Ward *et al.*, 2001) and six additional, smaller studies (Thériault & Allard, 1981; Weber *et al.*, 1981; Smulevich *et al.*, 1988; Laplanche *et al.*, 1992; Huang, 1996; Wong *et al.*, 2002) (*P*-value for the test for heterogeneity was ≥ 0.01). Six of these eight studies reported results for liver cancer, but these were considered to be too heterogeneous to be included in a meta-analysis because for 'liver cancer overall' and for 'liver cancer other than ASL', the *P*-value for heterogeneity was < 0.001. For the two multicentre studies (Mundt *et al.*, 2000; Ward *et al.*, 2001), the lack of heterogeneity allowed calculation of summary estimates for liver cancer overall (meta-SMR, 2.96; 95%CI: 2.00–4.39; random effects model; *P*-value for heterogeneity = 0.03) and for liver cancer other than ASL (meta-SMR, 1.35; 95%CI: 1.04–4.39; random effects model; *P*-value for heterogeneity = 0.7).

[The Working Group noted that the meta-analysis did not evaluate the quality of the studies and that some heterogeneity between studies may have resulted from variable quality of the data. Excluding one study from the People's Republic of China, other studies reported SMRs that ranged from 1.78 (95%CI: 1.15–2.62) to 57.1 (95%CI: 24.6–113) for liver cancer overall and from 1.27 (95%CI: 0.84–1.83) to 10.1 (95%CI: 4.37–20.0) for liver cancer other than ASL.]

2.3 Cancer of the lung

Among workers exposed to vinyl chloride, there was no overall evidence of an increased risk for lung cancer (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.2.pdf). However, in PVC-packers and -baggers, the risk for lung cancer increased significantly with cumulative exposure to vinyl chloride (Ward *et al.*, 2001). [These workers are known to have had concomitant exposure to PVC-dust; the study did not allow attribution of the association to a specific agent or combination of agents.]

2.4 Malignant neoplasms of connective and soft tissue

Suggestive evidence was found for malignant neoplasms of connective and soft tissue (ICD9-code, 171). This derived from the multicentre study in the USA (Mundt *et al.*, 2000), in which a nearly threefold statistically significant overall increase in mortality from these neoplasms was observed (SMR 2.7, 95%CI: 1.4–4.7; 12 observed, 4.4 expected). The risk was higher for workers with longer duration of employment (i.e. 10–19 *vs* > 20 years) and for those first employed before 1960. Four of the 12 observed deaths were from angiosarcomas for which the site was unknown. The increased mortality from neoplasms of connective and soft tissue persisted even after exclusion of these four angiosarcomas. [This presumes that the malignant neoplasms of connective and soft tissue were mis-classified deaths from angiosarcoma of the liver.]

The findings mentioned above were not supported by results from the European multicentre study, in which the number of deaths from connective-tissue neoplasms was too small

for an evaluation of exposure–response (Ward *et al.*, 2001): there were six observed deaths from neoplasms of connective and soft tissue (SMR = 1.9, 95%CI: 0.7–4.1), but in a re-evaluation of the diagnoses three of the six deaths coded as tumours of the connective tissue were found to be ASL. [The Working Group noted that, although a statistically significant increase in mortality from neoplasms of connective and soft tissue was found in the US study, the discrepant results with the European study and the difficulties in arriving at a correct diagnosis and coding of the tumour site for this type of neoplasm, complicate an evaluation of these findings.]

2.5 Other cancers

The Working Group did not find strong evidence for associations of exposure to vinyl chloride with cancers of the brain or the lymphatic and haematopoeitic tissues, with melanoma of the skin (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.3.pdf, Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.4.pdf, and Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.5.pdf). Although the associations found for these cancers in specific studies may reflect true increases in risk, the findings were inconsistent between studies, no clear exposure–response relationships were found in the European multicentre study (Ward *et al.*, 2001), and, for several of the sites, the numbers of observed/expected cases were small.

No conclusion could be reached for breast cancer since the available studies included too few women.

2.6 Synthesis

There is compelling evidence that exposure to vinyl chloride is associated with angiosarcoma of the liver, and strong evidence that it is associated with hepatocellular carcinoma. Together with the observation that vinyl chloride increases the risk for liver cirrhosis, which is a known risk factor for hepatocellular carcinoma, the findings from two large multicentre cohort studies provide convincing evidence that vinyl chloride causes hepatocellular carcinoma as well as angiosarcoma of the liver. There is contradictory evidence that exposure to vinyl chloride is associated with malignant neoplasms of connective and soft tissue, and inconsistent or scanty evidence that it is associated with cancers of the lung, brain, lymphohaematopoietic system, and breast, or with melanoma of the skin.

3. Cancer in Experimental Animals

The carcinogenicity of vinyl chloride has been studied intensively and repeatedly in experimental animals, with a wide range of concentrations, spanning orders of magnitude. The many studies consistently showed hepatic and extrahepatic angiosarcomas in mice and rats. Various other malignant neoplasms also occurred at several anatomical sites. However, the reporting of the results has often been incomplete, and the outcomes of many studies are available only from summary tables in the published literature, in which technical details are given in footnotes.

Studies of the carcinogenicity of vinyl chloride in experimental animals after oral administration, inhalation, subcutaneous injection, intraperitoneal injection, and transplacental and perinatal exposure have been reviewed in previous *IARC Monographs* (IARC, 1974, 1979, 1987, 2008). No studies have been published since the most recent evaluation (IARC, 2008). The

following is a summary of the available data (see also Table 3.1).

3.1 Inhalation exposure

Vinyl chloride was tested by inhalation exposure in several studies in mice (Holmberg *et al.*, 1976; Lee *et al.*, 1978; Hong *et al.*, 1981; Maltoni *et al.*, 1981; Drew *et al.*, 1983; Suzuki, 1983), in several studies in rats (Lee *et al.*, 1978; Feron *et al.*, 1979; Feron & Kroes, 1979; Groth *et al.*, 1981; Kurliandskiĭ *et al.*, 1981; Maltoni *et al.*, 1981; Drew *et al.*, 1983), and in two studies in hamsters (Maltoni *et al.*, 1981; Drew *et al.*, 1983). Male and female animals of all three species were included, although some experiments were carried out only in one sex. Vinyl chloride induced hepatic angiosarcomas in three experiments in mice and in eight experiments in rats; a dose–response was observed for hepatic angiosarcomas in both species over a wide range of exposures. Extrahepatic angiosarcomas related to treatment with vinyl chloride were observed in three studies in mice and one study in rats. Vinyl chloride increased the incidence of malignant mammary tumours in seven experiments in mice, in two experiments in one study in rats, and in one study in hamsters. Exposure to vinyl chloride increased the incidence of skin epitheliomas in one study in rats and one study in hamsters, and of skin carcinomas in another study in hamsters. It increased the incidence of Zymbal gland carcinomas in three experiments in rats, with a dose–response pattern in one experiment. In mice, vinyl chloride increased the incidence of benign lung tumours in six experiments, and of lung carcinomas in two experiments. It also increased the incidence of nasal cavity carcinomas in one study in rats, of hepatocellular carcinomas in two experiments in rats, of glandular adenomas in one study in hamsters, and of benign fore-stomach tumours in another study in hamsters.

In one study in rats, combined oral administration of ethanol and inhalation exposure to vinyl chloride increased the incidence of hepatic angiosarcomas compared with exposure to vinyl chloride alone (Radike *et al.*, 1981).

3.2 Oral administration

Vinyl chloride was tested by oral administration in four experiments in male and female rats (Feron *et al.*, 1981; Maltoni *et al.*, 1981; Til *et al.*, 1991). It induced hepatic angiosarcomas in two experiments, lung angiosarcomas in one experiment and hepatocellular adenomas and hepatocellular carcinomas in two experiments.

3.3 Subcutaneous and intraperitoneal injection

When vinyl chloride was tested in rats by subcutaneous injection and by intraperitoneal injection in single studies, no increase in tumour incidence was observed (Maltoni *et al.*, 1981).

3.4 Transplacental administration and perinatal exposure

The transplacental carcinogenicity of vinyl chloride was evaluated in one study in the offspring of rats exposed by inhalation on days 12–18 of pregnancy. A low incidence of tumours was observed in prenatally exposed offspring at several sites including the kidney (nephroblastomas) and the Zymbal gland (carcinomas). However, no angiosarcomas or hepatomas developed in the offspring (Maltoni *et al.*, 1981).

Vinyl chloride was tested by perinatal inhalation exposure in two studies in rats. In one study, rats were exposed transplacentally, as neonates, and during adulthood. Treatment with vinyl chloride induced hepatic angiosarcomas and hepatocellular carcinomas. The rats also showed

N^2,3–εG, and HO-ethanoG) may be involved in base-pair substitution and other specific mutations in cancer-related genes (i.e. *RAS* oncogenes, *TP53* tumour-suppressor gene) (WHO, 1999). The DNA lesions εA, εC and *N*2,3-εG have demonstrated miscoding potential *in vitro* and *in vivo* (Singer *et al.*, 1987; Cheng *et al.*, 1991; Mroczkowska & Kuśmierek, 1991; Singer *et al.*, 1991; Basu *et al.*, 1993). The adduct εA causes A→G transitions and A→T transversions, εC causes C→A transversions and C→T transitions and εG causes G→A transitions (Bolt, 2005). The same mutation types are observed in *TP53* and *RAS* genes in vinyl chloride-induced tumours. Mutations in K_i-*RAS* are associated with vinyl chloride-induced angiosarcomas in humans but not in rats, and to a lesser extent with vinyl chloride-induced HCC (CAA61CTA Ha-*Ras* mutation) in rats (IARC, 2008). In half of the cases, these mutations led to the incorporation of aspartate instead of glycine. *TP53* mutations associated with exposure to vinyl chloride (frequently A→T transversions) are found in approximately half of the angiosarcomas in both humans and rats. The presence of mutated p21ras and p53 proteins in the blood of a high proportion of workers exposed to vinyl chloride and the positive correlation between the occurrence of the mutated proteins and cumulative exposure to vinyl chloride, suggest that the mutation is an early event (IARC, 2008).

Various assays have been designed to explore the mutagenic properties of DNA adducts introduced into oligonucleotides or into site-specific vectors. Vector plasmids have also been treated with 2-chloroethyleneoxide or 2-chloroacetaldehyde and propagated in *E. coli* or mammalian cells. The mechanism by which adducts cause mutations still remains unclear, as misincorporation events depend on the individual mechanisms of DNA polymerases (Choi *et al.*, 2006). HO-ethanoG and 1,N^2-εG block the replication process with many different polymerases, thereby causing base misincorporation (Langouët *et al.*, 1997, 1998; Guengerich *et al.*, 1999).

The induction of extrahepatic tumours (e.g. in the brain or lung) by vinyl chloride has been established experimentally, but the mechanism is not well elucidated (Bolt, 2005). Overall, data suggest that etheno adducts are probably involved in the initiation of hepatocarcinogenesis, but the effects of the observed tissue- and cell-specificity and the variability in various biomarkers such as mutant p53 and anti-p53 antibodies are not completely clear (Trivers *et al.*, 1995; Brandt-Rauf *et al.*, 1996). One source for this variability may be explained by differences in polymorphisms in genes (i.e. *CYP2E1*, *GSTT1*, *GSTM1*, *ALDH2*) that encode metabolising enzymes or DNA-repair proteins (i.e. the *XRCC1* gene) (Li *et al.*, 2003a).

4.4 Synthesis

Numerous studies on the toxicokinetics, metabolism, genotoxicity, and molecular biology of vinyl chloride provide strong evidence that the carcinogenicity of this chamical involves a genotoxic mechanism of action, mediated by reactive metabolites. The extensive information on the mechanism underlying vinyl chloride-induced carcinogenicity has established many key events in the pathway of vinyl chloride-induced liver carcinogenesis. These key events include metabolic activation to reactive metabolites, binding of the metabolites to DNA, promutagenic action of these adducts leading to G→A and A→T transitions, and the effects of such mutations on the functioning of proto-oncogenes and tumour-suppressor genes at the gene and protein levels, with tumourigenesis as the final outcome. Many of these key events identified in experimental animals have also been demonstrated in humans.