Squamous Cell Cancer

IARC SUPPLEMENT 7

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WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISKS TO HUMANS

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

SUPPLEMENT 7

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ACETALDEHYDE (Group 2B)

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

In a survey of chemical plants (without prior hypothesis) in the German Democratic Republic, nine cancer cases were found in a factory where the main process was dimerization of acetaldehyde and where the main exposures were to acetaldol, acetaldehyde, butyraldehyde, crotonaldehyde and other higher, condensed aldehydes, as well as to traces of acrolein (see p. 78). Of the cancer cases, five were bronchial tumours and two were carcinomas of the oral cavity. All nine patients were smokers. The relative frequencies of these tumours were reported to be higher than those expected in the German Democratic Republic[1]. The study is inconclusive because of mixed exposure, the small number of cases and the poorly defined exposed population.

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

Acetaldehyde was tested for carcinogenicity in rats by inhalation and in hamsters by inhalation and by intratracheal instillation. It produced tumours of the respiratory tract following its inhalation, particularly adenocarcinomas and squamous-cell carcinomas of the nasal mucosa in rats[1,2] and laryngeal carcinomas in hamsters[1]. In hamsters, it did not result in an increased incidence of tumours following intratracheal instillation[1]. Inhalation of acetaldehyde enhanced the incidence of respiratory-tract tumours induced by intratracheal instillation of benzo[*a*]pyrene in hamsters[1].

C. Other relevant data

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

Acetaldehyde increased the incidence of sister chromatid exchanges in bone-marrow cells of mice and hamsters treated *in vivo* and induced chromosomal aberrations in rat

[3]Thiess, A.M., Link, R. & Wellenreuther, G. (1982) *Mortality study of employees exposed to auramine.* In: El-Attal, M., Abdel-Gelil, S., Massoud, A. & Noweir, M., eds, *Proceedings of the 9th International Conference of Occupational Health in the Chemical Industry, Cairo, 1981*, pp. 197-208

[4]Gubéran, E., Raymond, L. & Sweetnam, P.M. (1985) Increased risk for male bladder cancer among a cohort of male and female hairdressers from Geneva. *Int. J. Epidemiol., 14*, 549-554

[5]*IARC Monographs, Suppl. 6*, 83-85, 1987

AZATHIOPRINE (Group 1)

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

Two large prospective epidemiological studies have shown that renal transplant patients, who usually receive azathioprine as an immunosuppressant, become at high risk for non-Hodgkin's lymphoma, squamous-cell cancers of the skin, hepatobiliary carcinomas and mesenchymal tumours. While this is true for each of the various etiological entities resulting in the need for a transplant, these patients also have in common heavy exposure to foreign antigens[1]. Other patients who have received azathioprine as an immunosuppressant, including those with rheumatoid arthritis, systemic lupus and other 'collagen' disorders, inflammatory bowel disease and certain skin and renal diseases, have also been studied: the same array of malignancies was found to be in excess, although to a lesser extent[1,2]. For these patients, however, the picture is still not completely clear, because patients with rheumatoid arthritis constituted the largest category in the latter study[2], and some[3], but not all studies[4], have found that this disease conveys a risk for non-Hodgkin's lymphoma in the absence of treatment.

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

Suggestive evidence was obtained that lymphomas were induced in mice after intraperitoneal, subcutaneous or intramuscular injection of azathioprine, and that thymic lymphomas and squamous-cell carcinomas of the ear duct were induced in rats after oral administration, but there were limitations in the design and reporting of these studies[1,5].

C. Other relevant data

There are conflicting reports of effects on the incidence of chromosomal aberrations in lymphocytes and bone-marrow cells of patients treated with azathioprine. In one study, the incidence of sister chromatid exchanges in lymphocytes of treated patients was not increased[6].

In animals treated *in vivo*, azathioprine induced dominant lethal mutations in mice, chromosomal aberrations in rabbit lymphocytes and Chinese hamster bone-marrow cells, and micronuclei in mice, rats and hamsters; it did not induce sister chromatid exchanges in

[4]Wang, H.H. & MacMahon, B. (1979) Mortality of workers employed in the manufacture of chlordane and heptachlor. *J. occup. Med., 21*, 745-748

[5]Ditraglia, D., Brown, D.P., Namekata, T. & Iverson, N. (1981) Mortality study of workers employed at organochlorine pesticide manufacturing plants. *Scand. J. Work Environ. Health, 7 (Suppl. 4)*, 140-146

[6]Shindell, S. & Ulrich, S. (1986) Mortality of workers employed in the manufacture of chlordane: an update. *J. occup. Med., 28*, 497-501

[7]Williams, G.M. & Numoto, S. (1984) Promotion of mouse liver neoplasms by the organochlorine pesticides chlordane and heptachlor in comparison to dichlorodiphenyltrichloroethane. *Carcinogenesis, 5*, 1689-1696

[8]*IARC Monographs, Suppl. 6*, 145-147, 328-330, 1987

α-CHLORINATED TOLUENES (Group 2B)

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

Six cases of respiratory cancer were reported in two small factories in Japan where benzoyl chloride (see p. 126) and chlorinated toluenes were produced[1]. A mortality study in the UK of 163 workers exposed to benzoyl chloride and chlorinated toluenes showed excesses for cancers of the respiratory tract (5 observed, 1.8 expected) and digestive system (5 observed, 1.2 expected). The limited data did not, however, allow any differential risk estimation for the individual chlorinated toluenes[2].

B. Evidence for carcinogenicity to animals (*limited* for benzyl chloride and benzal chloride; *sufficient* for benzotrichloride)

Benzyl chloride was tested in mice by skin application and in rats by subcutaneous injection. Sarcomas at the injection site were observed in rats; a few skin carcinomas were observed in some mice, but their incidence was not statistically significant[1]. When mice and rats were administered benzyl chloride in corn oil by gavage, increased incidences of papillomas and carcinomas of the forestomach were observed in mice of each sex, and the incidence of thyroid C-cell tumours was increased in female rats but decreased in male rats; a few neoplasms of the forestomach were observed in male rats[3].

In one experiment in which benzal chloride was tested by skin application to female mice, it produced squamous-cell carcinomas of the skin. In a concurrent experiment in which it was tested for a shorter duration, a low incidence of skin papillomas was observed[1].

Benzotrichloride was tested in three studies by skin application to female mice. It produced squamous-cell carcinomas of the skin and lung tumours in all three experiments; upper digestive-tract tumours were also observed in two of the three experiments. Increases in the incidence of tumours at other sites were reported[1]. In a mouse-lung tumour bioassay, benzotrichloride increased the incidence of lung adenomas[4].

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

1,2-Dibromo-3-chloropropane has been tested by oral administration and inhalation in mice and rats. After oral administration, it produced squamous-cell carcinomas of the forestomach in animals of each species and adenocarcinomas of the mammary gland in female rats[3]. After inhalation, it induced nasal cavity and lung tumours in mice, and nasal cavity and tongue tumours in rats of each sex and adrenal cortex adenomas in females[4].

C. Other relevant data

Several reports indicate that occupational exposure to 1,2-dibromo-3-chloropropane may result in azospermia[5].

1,2-Dibromo-3-chloropropane induced dominant lethal mutations in rats, but not in mice, and DNA strand breaks in rat testicular cells and unscheduled DNA synthesis in mouse testicular cells, but not abnormalities in sperm morphology in mice treated *in vivo*. In studies *in vitro*, it induced chromosomal aberrations and sister chromatid exchanges in Chinese hamster cells and DNA strand breaks in rat testicular cells. In *Drosophila*, it induced aneuploidy and sex-linked recessive lethal mutations; heritable translocation was seen in one study but not in another, although crossing-over was found in the latter. It was mutagenic to bacteria but did not cause DNA damage[5].

References

[1]Hearn, S., Ott, M.G., Kolesar, R.C. & Cook, R.R. (1984) Mortality experience of employees with occupational exposure to DBCP. *J. occup. Med.*, *39*, 49-55

[2]Wong, O., Brocker, W., Davis, H.V. & Nagle, G.S. (1984) Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, Tris, PBB, and DDT. *Br. J. ind. Med.*, *41*, 15-24

[3]*IARC Monographs*, *20*, 83-96, 1979

[4]National Toxicology Program (1982) *Carcinogenesis Bioassay of 1,2-Dibromo-3-chloropropane (CAS No. 96-12-8) in F344 Rats and B6C3F$_1$ Mice (Inhalation Studies) (NTP Technical Report 206; NIH Publ. No. 82-1762)*, Research Triangle Park, NC

[5]*IARC Monographs*, *Suppl. 6*, 219-221, 1987

ortho-DICHLOROBENZENE (Group 3) and *para*-DICHLOROBENZENE (Group 2B)

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

One report of a series of five cases has suggested an association between leukaemia and exposure to dichlorobenzenes[1].

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

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].

(0.6-<2.4 mg/m^3) and 4% a TWA of >2.0 ppm (>2.4 mg/m^3)[4]. On the basis of the job held that incurred the highest level of exposure, the distribution among British chemical workers was: nil/background, <0.1 ppm (<0.12 mg/m^3), 25%; 0.1-0.5 ppm (0.12-0.6 mg/m^3), 24%; 0.6-2.0 ppm (0.7-2.4 mg/m^3), 9%; >2.0 ppm (>2.4 mg/m^3), 35%; and unknown, 6%[6].

Excesses of cancers of the buccal cavity and pharynx have been reported in five studies[2,8,11-13], with a statistically significant excess for cancer of the buccal cavity based on three deaths[11] in one study and statistically significant excesses for cancer at both sites in another study, based on two deaths[2]. Interpretation of the results of the last study is difficult because the deaths were not obtained systematically from the entire workforce, but rather were ascertained from worker reports and obituaries. The occurrence of cancer of the nasopharynx was elevated in a cohort study of industrial workers[4] and in case-control studies[8,9,14]. Among industrial workers exposed to formaldehyde-containing particulates, standardized mortality rates (SMRs) for nasopharyngeal cancer rose with cumulative exposure to formaldehyde: 192 (one death) for <0.5 ppm(<0.6 mg/m^3)-years, 403 (two deaths) for 0.5-<5.5 ppm(0.6-<6.7 mg/m^3)-years and 746 (two deaths) for >5.5 ppm(>6.7 mg/m^3)-years. There was a similar trend with duration of exposure to formaldehyde, and all five cases held jobs in which hourly exposures exceeded 4.0 ppm formaldehyde[15]. A rising relative risk (RR) for nasopharyngeal cancer was seen by type of exposure to formaldehyde: 1.7 for occupation alone, 2.8 for living in mobile homes and 6.7 for both occupational and mobile-home exposures. These risks were unaffected by potentially confounding factors such as smoking, alcohol use and socioeconomic status[8,9]. An excess of nasopharyngeal cancer was reported in one study among women (RR, 2.6) exposed to formaldehyde, but not among men (RR, 0.7)[14]. Several other studies showed no excess[5,6,11,16], but no death from this tumour was reported in any of these studies.

Sinonasal cancer was associated with employment in jobs in which there is potential contact with formaldehyde in case-control studies in Denmark (RR, 2.8 in men and women)[14,17] and in the Netherlands (RR, 2.5 and 1.9 from two independent classifications of exposure)[10]. Risk for this tumour increased with level of exposure in the Netherlands[10] and with duration of exposure in Denmark[14]. Excess risks persisted in both studies when analyses were restricted to persons without exposure to wood dust (an established risk factor for this tumour, see p. 380), although they were no longer statistically significant. In one of the studies[10], the excess of sinonasal cancer from exposure to formaldehyde was found to be limited primarily to squamous-cell carcinoma, further differentiating the formaldehyde-associated excess from that caused by wood dust, with which adenocarcinoma predominates. In another of the studies[17], however, the excess was not confined to squamous-cell carcinoma. No excess of sinonasal cancer was found in industrial workers (SMR, 91), but only two deaths occurred[4]. Sinonasal cancer was not associated with occupational or residential exposure to formaldehyde in another study[8,9]. None of the other studies reported any death from sinonasal cancer. The RRs for sinonasal cancer in the studies of Hayes[10] and Vaughan[8,9] were adjusted for smoking habits.

two studies, based on 14 deaths (SMR, 142)[4] and on one death[11]. The risk of Hodgkin's disease rose with level of formaldehyde exposure among wage and salaried workers alike, although each stratum had small numbers[4].

Although excess occurrence of a number of cancers has been reported, the evidence for a possible involvement of formaldehyde is strongest for nasal and nasopharyngeal cancer. The occurrence of these cancers showed an exposure-response gradient in more than one study, but the numbers of exposed cases were often small and some studies did not show excesses. The nose and nasopharynx could come into direct contact with formaldehyde through inhalation. Excess mortality from leukaemia and cancer of the brain was generally not seen among industrial workers, which suggests that the excesses for these cancers among professionals is due to factors other than formaldehyde. The slight excesses of cancer of the lung noted in several studies generally did not display the patterns of increasing risk with various measures of exposure (i.e., latency, duration, level or cumulative) usually seen for occupational carcinogens. No other cancer showed a consistent excess across the various studies.

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

Formaldehyde was tested for carcinogenicity by inhalation in two strains of rats and in one strain of mice. Significant increases in the incidence of squamous-cell carcinomas of the nasal cavity were induced in both strains of rats but not in mice[1,25]. A slight increase in the incidence of nasal cavity polypoid adenomas was also observed in male rats[25]. The tumours in the nasal cavity of rats were localized precisely: in the anterior portion of the lateral aspect of the nasoturbinate and adjacent lateral wall[26]. Experiments in which rats were exposed to both hydrogen chloride and formaldehyde showed that the carcinogenic response to formaldehyde does not result from the presence of bis(chloromethyl)ether (see p. 131), which is formed from the mixture of gases[27]. Another study in mice and one in hamsters by inhalation, one in rats by subcutaneous administration and one in rabbits by exposure in oral tanks were considered inadequate for evaluation[1,28].

C. Other relevant data

In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings[29].

No increase in the frequency of micronuclei or chromosomal aberrations was observed in rodents treated with formaldehyde *in vivo*; assays for dominant lethal mutations and DNA damage gave inconclusive results. Formaldehyde induced sperm-head anomalies in rats. It induced DNA-protein cross-links, unscheduled DNA synthesis, chromosomal aberrations, sister chromatid exchanges and mutation in human cells *in vitro*. It induced transformation of mouse C3H 10T1/2 cells and chromosomal aberrations, sister chromatid

surface haematite miners[1-11]. Haematite mining with low-grade exposure to radon daughters and silica dust was not associated with excess lung cancer in a relatively large cohort[12]. The importance of exposure to radon daughters in the occurrence of lung cancer in haematite miners is also suggested by the time trend of lung cancer rates in a mining population[4]. One mining population with an increased lung cancer risk but with current low exposure to radon daughters might have had higher exposures in the past due to poorer ventilation[13,14].

Some studies of metal workers exposed to ferric oxide dusts have shown an increased incidence of lung cancer[1,15], but the influence of factors in the workplace other than ferric oxide, i.e., soots (see p. 343), silica (see p. 341) and asbestos (see p. 106) in foundry work, cannot be discounted. In other studies of metal and chemical workers exposed to ferric oxide, the incidence of lung cancer has generally not been increased[1,16].

B. Evidence for carcinogenicity to animals (*inadequate* for haematite; *evidence suggesting lack of carcinogenicity* for ferric oxide)

No conclusive carcinogenic effect was observed in mice, hamsters or guinea-pigs given ferric oxide intratracheally or by inhalation[1]. Repeated intratracheal instillation to hamsters of benzo[*a*]pyrene bound to fine ferric oxide dust particles induced squamous-cell and anaplastic carcinomas[17]. There was no increase in tumour yield in hamsters administered a constant dose of benzo[*a*]pyrene and increasing amounts of ferric oxide intratracheally, indicating that, beyond a certain ratio of benzo[*a*]pyrene to ferric oxide, the latter does not affect tumour yield[18]. Administration of ferric oxide particles alone occasionally induced interstitial fibrosis, indicating that ferrous oxide particles act as cofactors in this system, mainly as carriers[19]. In one study, intrapleural inoculation of the respirable fraction of iron ore mine dust to female BALB/c mice resulted in an increased incidence of lung adenomas; in a second study, an increased incidence of lymphoma/leukaemia was observed in female C57BL/6J mice exposed chronically to the same dust. In neither study was the number of animals specified, nor whether the mice were killed serially or died; in the second study, the type of exposure was not specified[20]. In several studies in hamsters, ferric oxide was not carcinogenic when given alone but enhanced lung and nasal-cavity carcinogenesis induced by *N*-nitrosodiethylamine and *N*-nitrosodimethylamine, respectively[21-23].

C. Other relevant data

No data were available on the genetic and related effects of ferric oxide in humans. It did not induce transformation of Syrian hamster embryo cells[24].

References

[1]*IARC Monographs, 1*, 29-39, 1972

[2]Damber, L. & Larsson, L.-G. (1985) Underground mining, smoking, and lung cancer: a case-control study in the iron ore municipalities in northern Sweden. *J. natl Cancer Inst., 74*, 1207-1213

[10]Fitzsimons, C.P., Long, J. & MacKie, R.M. (1983) Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. *Lancet, i*, 235-236

[11]Kripke, M.L., Morison, W.L. & Parrish, J.A. (1982) Induction and transplantation of murine skin cancers induced by methoxsalen plus ultraviolet (320-400 nm) radiation. *J. natl Cancer Inst., 68*, 685-690

[12]Nagayo, K., Way, B.H., Tran, R.M. & Song, P.S. (1983) Photocarcinogenicity of 8-methoxypsoralen and aflatoxin B_1 with longwave ultraviolet light. *Cancer Lett., 18*, 191-198

[13]Young, A.R., Magnus, I.A., Davies, A.C. & Smith, N.P. (1983) A comparison of the phototumorigenic potential of 8-MOP and 5-MOP in hairless albino mice exposed to solar simulated radiation. *Br. J. Dermatol., 108*, 507-518

[14]Gibbs, N.K., Young, A.R. & Magnus, I.A. (1985) A strain of hairless mouse susceptible to tumorigenesis by TPA alone: studies with 8-methoxypsoralen and solar simulated radiation. *Carcinogenesis, 6*, 797-799

[15]Hannuksela, M., Stenbäck, F. & Lahti, A. (1986) The carcinogenic properties of topical PUVA. A lifelong study in mice. *Arch. dermatol. Res., 278*, 347-351

[16]*IARC Monographs, Suppl. 6*, 380-385, 1987

METHYL BROMIDE (Group 3)

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

Two cohort studies mention exposure to methyl bromide. In both study populations, exposure to a great number of other chemical compounds occurred, and, therefore, the slight excesses of some cancers found cannot be interpreted in terms of exposure to methyl bromide[1].

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

In one 90-day study by oral administration in rats, methyl bromide was reported to produce squamous-cell carcinomas of the forestomach[1]. In a second, 25-week study, it was found that early hyperplastic lesions of the forestomach regressed after discontinuation of treatment; one early carcinoma (1/11) developed after 25 weeks of continuous treatment by gavage[2].

C. Other relevant data

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

Micronuclei were induced in the bone-marrow and peripheral blood cells of rats and mice following exposure to methyl bromide by inhalation. After treatment of mice with methyl bromide by different routes, DNA methylation of liver and spleen was observed. Methyl bromide induced sister chromatid exchanges in human lymphocytes *in vitro* and mutation in mouse lymphoma cells *in vitro*. It did not induce unscheduled DNA synthesis in

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

MNNG has been tested for carcinogenicity in mice, rats, hamsters, rabbits and dogs, producing tumours at many sites. It has a predominantly local carcinogenic effect and is carcinogenic in single-dose experiments. Following its oral administration, papillomas and squamous-cell carcinomas of the oesophagus and forestomach, adenocarcinomas of the stomach, small intestine and large bowel, and sarcomas of the gastrointestinal tract were reported[3]. These findings have been extended in more recent studies after oral administration to rats[4–7], hamsters[8,9] and dogs[10,11]. After subcutaneous injection of mice, it produced lung and liver tumours and haemangioendotheliomas[12]; after intrarectal instillation in rats and guinea-pigs[13–15] and after intrauterine and intravaginal application to rats, it produced local tumours[16].

C. Other relevant data

MNNG is an alkylating agent[17]. No data were available to evaluate the genetic and related effects of this compound in humans.

MNNG induced DNA strand breaks in various organs of rats treated *in vivo*. It did not cause dominant lethal mutations in mice, but it gave positive results for mutation in the mouse spot test; it induced chromosomal aberrations and micronuclei in bone-marrow cells of mice and sister chromatid exchanges in bone-marrow cells of mice and Chinese hamsters treated *in vivo*. It induced chromosomal aberrations, sister chromatid exchanges, DNA strand breaks and unscheduled DNA synthesis in human and rodent cells *in vitro* and induced mutation in cultured rodent cells. It gave positive results in several assays for cell transformation. MNNG induced somatic and sex-linked recessive lethal mutations in *Drosophila*. It caused chromosomal aberrations, sister chromatid exchanges and mutation in plants and recombination and mutation in fungi. It was mutagenic to and caused DNA damage in bacteria, and gave positive results in host-mediated assays using bacteria or yeast as indicators and mice as hosts[17].

References

[1]Pleven, C., Audran, R., Falcy, M., Efthymiou, M.-L. & Philbert, M. (1983) Glioblastomas and chemical mutagenesis in biology laboratories. Report of 3 deaths in the same institute (Fr.). *Arch. Mal. prof.*, *44*, 411-418

[2]Pleven, C., Falcy, M., Audran, R., Philbert, M. & Efthymiou, M.L. (1984) Occurrence of glioblastomas in people working in research laboratories using nitroso compounds (Fr.). *J. Toxicol. méd.*, *4*, 249-257

[3]*IARC Monographs*, *4*, 183-195, 1974

[4]Martin, M.S., Martin, F., Justrabo, E., Michiels, R., Bastien, H. & Knobel, S. (1974) Susceptibility of inbred rats to gastric and duodenal carcinomas induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. *J. natl Cancer Inst.*, *53*, 837-840

[5]Kartasheva, L.A. & Bykorez, A.I. (1975) Induction of adenocarcinomas of the stomach in rats by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (Russ.). *Vopr. Onkol.*, *21*, 50-55

[10]Cavaliere, A., Bacci, M. & Vitali, R. (1984) Induction of mammary tumors with metronidazole in female Sprague-Dawley rats. *Tumori, 70*, 307-311

[11]Sloan, D.A., Fleiszer, D.M., Richards, G.K., Murray, D. & Brown, R.A. (1983) Increased incidence of experimental colon cancer associated with long-term metronidazole therapy. *Am. J. Surg., 145*, 66-70

[12]A-Kareem, A.M., Fleiszer, D.M., Richards, G.K., Senterman, M.K. & Brown, R.A. (1984) Effect of long-term metronidazole (MTZ) therapy on experimental colon cancer in rats. *J. surg. Res., 36*, 547-552

[13]*IARC Monographs, Suppl. 6*, 399-402, 1987

MINERAL OILS:
UNTREATED AND MILDLY-TREATED OILS (Group 1)
HIGHLY-REFINED OILS (Group 3)

A. Evidence for carcinogenicity to humans (*sufficient* for untreated and mildly-treated oils; *inadequate* for highly-refined oils)

Exposure to mineral oils that have been used in a variety of occupations, including mulespinning, metal machining and jute processing, has been associated strongly and consistently with the occurrence of squamous-cell cancers of the skin, and especially of the scrotum[1]. Production processes for these oils have changed over time, and with more recent manufacturing methods highly-refined products are produced that contain smaller amounts of contaminants, such as polycyclic aromatic hydrocarbons.

Excess mortality or morbidity from gastrointestinal malignancies was seen in two out of three cohort studies of metal workers (stomach cancer in two studies, large-bowel cancer in one); however, the only significant excess was for the sum of stomach cancer plus large-bowel cancer in one study. Four cases of scrotal cancer were detected in one relatively small cohort study of metal industry workers[1]. Among 682 turners with five or more years of exposure to mineral oils, five cases of squamous-cell carcinoma of the skin (four of the scrotum) occurred, with 0.3 expected[2]. In a case-control study, a relative risk of 4.9 was reported for the association of scrotal cancer with potential exposure of metal workers to mineral oils. Neither the actual levels of exposure nor the classification of the mineral oil to which the machine workers were potentially exposed was available in the reports of the epidemiological studies[1].

In a case-control study, an excess of sinonasal cancers was seen in toolsetters, set-up men and toolmakers[1]. In a series of 344 cases of scrotal cancer from 1936 to 1976, 62% had held occupations in which exposure to mineral oils was likely to have occurred. The median latent period was 34 years[3].

An examination of the incidence of second primary cancers among men with scrotal cancer demonstrated excesses of respiratory, upper alimentary tract and skin cancers; when the occupations were grouped, the excess was largely confined to those with exposure to oil[1].

[see p. 120] and ethylene chlorohydrin), there was no statistically significant excess of cancer deaths. The study is uninformative in relation to the carcinogenicity of propylene oxide[1].

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

Propylene oxide was tested by oral gavage in rats and produced local tumours, mainly squamous-cell carcinomas and papillomas of the forestomach[1]. When tested by inhalation in mice and in rats, it produced haemangiomas and haemangiosarcomas of the nasal submucosa in mice and an increased incidence of papillary adenomas of the nasal turbinates in rats[1,2]. In one experiment by inhalation in male rats, an increased incidence of adrenal pheochromocytomas and of peritoneal mesotheliomas was observed[1]. Propylene oxide was also tested by subcutaneous administration in mice, inducing local sarcomas, mainly fibrosarcomas[1].

C. Other relevant data

Propylene oxide is structurally related to ethylene oxide.

No data were available on the genetic effects of propylene oxide in humans. Haemoglobin alkylation was observed in exposed workers[3].

Propylene oxide induced micronuclei in mice but did not cause dominant lethal mutations in mice or rats exposed *in vivo*. It induced chromosomal aberrations in human cells *in vitro* and DNA strand breaks, mutation, sister chromatid exchanges and chromosomal aberrations in rodent cells *in vitro*. It induced sex-linked recessive lethal mutations in *Drosophila*, mutation in fungi and bacteria and DNA damage in bacteria[3].

References

[1] *IARC Monographs, 36*, 227-243, 1985

[2] Renne, R.A., Giddens, W.E., Boorman, G.A., Kovatch, R., Haseman, J.E. & Clarke, W.J. (1986) Nasal cavity neoplasia in F344/N rats and (C57BL/6 × C3H)F_1 mice inhaling propylene oxide for up to two years. *J. natl Cancer Inst., 77*, 573-582

[3] *IARC Monographs, Suppl. 6*, 482-484, 1987

PROPYLTHIOURACIL (Group 2B)

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

In one survey of 331 hyperthyroid patients treated with antithyroid drugs, including propylthiouracil, and later with thyroidectomy, four thyroid cancers (an excess of unspecified proportion) were diagnosed more than one year after the beginning of drug therapy[1]. There has been one case report of acute myeloblastic leukaemia following propylthiouracil treatment[2].

gold mine, no excess lung cancer risk was seen[1,6]. The contribution of radon has not in general been assessed.

Coal miners appear not to be at increased risk of lung cancer[1].

Studies of foundry workers (see p. 224) have consistently shown moderate increases in mortality from lung cancer[1,7]. The Nordic register study also showed lung cancer risk to be elevated for foundry workers in all Nordic countries[4]. However, several contaminants other than silica dust occur in the foundry environment, including polycyclic aromatic hydrocarbons.

Epidemiological studies of both exposed populations and silicotics give indications of the carcinogenicity of a working environment contaminated with crystalline silica, particularly in combination with other exposures. In most industries studied, such an effect cannot be separated from those of other concomitant carcinogenic exposures, but in the granite and stone industry the exposure to silica is fairly pure. Few studies provide data on smoking. It is not clear whether the mechanisms of a possible carcinogenic effect of crystalline silica requires a fibrotic process.

No adequate epidemiological study or case report was available to evaluate the carcinogenicity of amorphous silica to humans.

B. Evidence for carcinogenicity to animals (*sufficient* for crystalline silica; *inadequate* for amorphous silica)

Various forms and preparations of crystalline silica produced adenocarcinomas and squamous-cell carcinomas of the lung in rats after inhalation or repeated intratracheal instillation. Thoracic and abdominal malignant lymphomas developed in rats after single intrapleural and intraperitoneal injections of suspensions of several types of quartz. Malignant lymphomas developed after intrapleural injection of cristobalite and tridymite. No tumorigenic response was observed in hamsters after repeated intratracheal instillation of quartz dusts or in a mouse-lung adenoma assay with one sample of quartz[1].

Tests of different preparations of amorphous silica administered by various routes to mice and rats either gave negative results or were inadequate. In two limited tests (one by intraperitoneal injection and one by inhalation) in mice, increased incidences of lymphosarcomas in the abdominal cavity and of lung tumours, respectively, were observed[1].

C. Other relevant data

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

Quartz did not induce micronuclei in mice treated *in vivo*. In Syrian hamster embryo cells *in vitro*, it induced cell transformation and micronuclei; it did not induce sister chromatid exchanges in Chinese hamster cells. Quartz did not inhibit intercellular communication in Chinese hamster cells *in vitro*. Silica was not mutagenic to bacteria[8].

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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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distillates [24] and one intermediate catalytically cracked distillate [25] were tested in mice by skin application and induced skin tumours.

Several high-boiling distillates [26] and residues [27] of catalytically cracked oils and several thermally cracked residues [31] were tested in experiments in mice by skin application, producing high incidences of benign and malignant skin tumours.

Thermally-cracked residues [31] originating from two different sources were tested by skin application in rabbits, producing some skin tumours, but the study was considered inadequate for evaluation. In one study in mice, skin application of water-quench pyrolysis fuel oil or oil-quench pyrolysis fuel oil (steam-cracked residues [34]) produced carcinomas and papillomas of the skin.

Effluents

Two studies on petroleum refinery effluents were inadequate for evaluation.

4.3 Human data

Taking into consideration the overlap in cohort studies conducted in the USA, ten separate, company-specific cohorts were studied. Two industry-wide study cohorts from the USA comprised various combinations of these cohorts. The cohorts mentioned hereafter refer to the ten separate US cohorts, two from Canada and one from the UK.

Information on specific jobs or exposures was available in only a few of the epidemiological studies of petroleum refinery workers. Some caution should be applied in interpreting the relative risks for cancer in cohort studies of petroleum refinery workers. As for most cohorts of actively employed persons, the overall risk for cancer in all of the cohort studies reviewed here was lower than that in the general population. Yet, it is the cancer experience of the general population that has been conventionally used, in published papers, in evaluating the rates of specific cancers in refinery workers. Significant deficits were reported for cancers at some sites in certain studies; such findings are mentioned in this summary only when a consistent pattern emerged. Caution should also be applied in interpreting the findings from those case-control studies conducted within the general population setting. Most of the studies reported had positive findings, and are likely to be an incomplete selection of case-control studies in which occupational exposures have been investigated.

One case report and one case series describe clusters of skin cancer cases (squamous-cell carcinoma) among wax pressmen who had been exposed to crude paraffin wax saturated with aromatic oils. Significant excess mortality from skin cancer was reported among three refinery cohorts, one of which included the wax pressmen from the case series. In a second cohort, the overall excess was due to an elevated risk for malignant melanoma. In the third, excess skin cancer risk was experienced primarily by maintenance workers. Skin cancer mortality was elevated in three additional cohorts, but the increase was not significant. A case-control study showed a significantly elevated risk for malignant melanoma among men employed in the coal and petroleum products industry, with a cluster of cases employed in petroleum refineries.

(ii) *Testicular cancer*

Mills *et al.* (1984) studied 347 hospital patients with histologically confirmed germ-cell tumour of the testis in the USA and matched them by age, sex, race and residence with 347 hospital controls, most of whom had tumours other than cancer of the testis. The ascertainment period was from 1 January 1977 to 31 August 1980. Occupational histories were extracted from medical records; when the type of industry was not apparent in the record, this was ascertained from the employer. An excess risk for testicular cancer was observed among petroleum and natural gas extraction workers (odds ratio, 2.3; 95% CI, 1.0–5.1). [The Working Group noted that information was obtained only on current occupation.]

Sewell *et al.* (1986) conducted a population-based study in New Mexico, USA, in which cases were identified at the New Mexico Tumor Registry. In order to be included in the study, the cases had to have had histologically confirmed testicular cancer registered in 1966–84, to have been 15 years old or more at the time of diagnosis and to have died of the disease. Controls consisted of persons who had died from other cancers, matched by age, year of diagnosis, race and sex. A total of 81 cases and 311 controls was identified. The source of occupational data was either death certificates (99%) or information on file at the tumour registry (1%). No excess risk for testicular cancer was observed among petroleum and gas workers (odds ratio, 0.57; 95% CI, 0.16–2.0). The authors noted the limited power of the study, that an association might have been obscured by the restriction to fatal cases and that information on exposure was limited.

(iii) *Multiple sites*

In a large case-control study of cancer at many sites conducted in Montreal, Canada, which is described in detail in the monograph on gasoline, p. 185, an association was seen between exposure to crude oil and rectal cancer (five cases; adjusted odds ratio 3.7; 90% CI, 1.3–10.6) and squamous-cell lung cancer (seven cases; adjusted odds ratio, 3.5; 90% CI, 1.5–8.2) (Siemiatycki *et al.*, 1987). It was indicated, however, that these associations might only be apparent since they are based on very small numbers. The authors suggested that one of the main groups exposed to crude oil, namely seamen, would probably have had life styles very different from those of the rest of the study population.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Crude oil, which may be broadly characterized as paraffinic or naphthenic, is a complex mixture of alkanes, cycloalkanes and aromatic hydrocarbons containing low percentages of sulfur, nitrogen and oxygen compounds and trace quantities of many other elements. Worldwide, about 500 000 workers are employed in crude oil exploration and production. Occupational exposures during drilling, pumping and transportation of crude oil, including maintenance of equipment used for these processes, may involve inhalation of volatile

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

4.2 Experimental data[1]

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

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

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

4.3 Human data

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

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

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

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

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

the monograph on occupational exposures in petroleum refining. Studies on residues of thermally cracked oils [31], which may be used in diesel fuel No. 4, are also described in that monograph.

Skin application

Mouse: Groups of 49 or 50 male and 50 female B6C3F1 mice, eight weeks old, were administered 250 or 500 mg/kg bw marine diesel fuel in 0.1 ml acetone by application to clipped interscapular dorsal skin on five days per week for 103 weeks or 84 weeks (high-dose group terminated due to severe ulceration of the skin), respectively. A control group received the vehicle only. The diesel fuel was a mixture of petroleum-derived hydrocarbons containing 12.7% paraffins and 87.3% aromatic compounds. Survival at 84 weeks was 26/50 and 29/50 among high-dose males and females, respectively; at 104 weeks, survival was 20/49 and 12/50 in low-dose males and females, and 30/50 and 40/50 among vehicle-control males and females, respectively. There was a significant increase in the incidence of squamous-cell papillomas and carcinomas at the application site in males (controls, 0/49; low-dose, 0/49; high-dose, 3/49 (two carcinomas; $p = 0.019$). The incidences of these tumours at the adjacent inguinal site in males were: controls, 1/50 (papilloma); low-dose, 2/49 (carcinomas); high-dose, 0/50. The incidences of squamous-cell carcinomas at the application site in females were: controls, 0/50; low-dose, 1/45; high-dose, 2/48; no papilloma occurred, and no tumour was found at the adjacent inguinal region. Although no data on historical controls were available for acetone-treated animals of this strain, the background rate for skin neoplasms among untreated mice is quite low (<1%). The incidences of hepatocellular adenomas in males were: control, 5/50; low-dose, 10/48; high-dose, 10/49. The total numbers of male mice with hepatocellular tumours (adenomas and carcinomas combined) were: controls, 9/50; low-dose, 17/48; high-dose, 14/49 ($p = 0.035$). The incidence of hepatocellular tumours did not differ significantly from that in historical controls (540/1784; 30 ± 8%; National Toxicology Program, 1986).

3.2 Other relevant data

(*a*) *Experimental systems*

Absorption, distribution, excretion and metabolism

No data on the absorption, distribution, excretion and metabolism of diesel fuel in laboratory animals were available to the Working Group. One study has been reported on gulls and ducks (McEwan & Whitehead, 1980).

Toxic effects

The oral LD_{50} of diesel fuel [unspecified] in rats was 7.5 g/kg bw. No mortality was induced in acute dermal toxicity studies in rats dosed at 5 g/kg bw (Beck *et al.*, 1984).

Groups of male and female B6C3F1 mice were administered 2000–40 000 mg/kg bw 100% marine diesel fuel by dermal application for 14 consecutive days. No animal treated with 20 000 or 40 000 mg/kg survived. Skin lesions were similar in all dosed groups —

3.3 Epidemiological studies and case reports of carcinogenicity to humans

The studies reviewed in the monograph on gasoline often involved subjects or occupational groups with mixed exposures, particularly to gasoline and diesel fuel. It was often not possible to separate the effects of the two types of fuel. Studies that primarily addressed the risk associated with exposure to combustion products of diesel fuel are not considered here but are the subject of *IARC Monographs* Vol. 46 (IARC, 1989).

In a case-control study of cancer at many sites in Montréal, Canada, described in detail in the monograph on gasoline (p. 185), an increased risk for cancer of the prostate, with an adjusted odds ratio of 1.9 (90% confidence interval (CI), 1.2–3.0), was observed among men exposed to diesel fuel; however, there was no evidence of a positive dose-response relationship (Siemiatycki *et al.*, 1987). There was an increased risk for squamous-cell carcinoma of the lung in men exposed to diesel fuel (adjusted odds ratio (including smoking), 1.6; 90% CI, 1.0–2.6); for men with estimated 'nonsubstantial' exposure, the odds ratio was 1.0 (0.4–2.0), and for those with 'substantial' exposure, it was 2.5 (1.3–4.7). Mechanics and repairmen, who constituted the largest group exposed to diesel fuel, had an adjusted odds ratio of 2.0 (0.9–4.2). [The Working Group noted that, in the interpretation of the lung cancer risks, no attempt was made to separate the effects of exposure to combustion products from those of exposure to the liquid itself.]

4. Summary of Data Reported and Evaluation[1]

4.1 Exposure data

Diesel fuels are complex mixtures of alkanes, cycloalkanes and aromatic hydrocarbons with carbon numbers in the range of C_9–C_{28} and with a boiling-range of 150–390°C. Kerosene-type diesel fuel (diesel fuel No. 1) is manufactured from straight-run petroleum distillates [5]. Automotive and railroad diesel fuel (diesel fuel No. 2) contains straight-run middle distillate [6], often blended with straight-run kerosene [5], straight-run gas oil [7], light vacuum distillate [19] and light thermally cracked [30] or light catalytically cracked distillates [24]. Some blended marine diesel fuels also contain heavy residues from distillation [8, 21] and thermal cracking [31] operations. In diesel fuel consisting mainly of atmospheric distillates, the content of three- to seven-ring polycyclic aromatic hydrocarbons is generally less than 5%; in diesel fuel that contains high proportions of heavy atmospheric, vacuum and light cracked distillates, the content of such polycyclic aromatic hydrocarbons may be as high as 10%. Some marine diesel fuels may contain higher levels. Saleable diesel fuel may also contain a variety of additives, such as organic nitrates, amines, phenols and polymeric substances. Exposure to diesel fuel through the skin and by inhalation may occur during its production, storage, distribution and use as well as during maintenance of diesel engines.

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[1]The numbers in square brackets are those assigned to the major process streams of petroleum refining in Table 2 of the monograph on occupational exposures in petroleum refining (p. 44).

4.2 Experimental data[1]

One sample of marine diesel fuel was tested for carcinogenicity in one strain of mice by skin application, producing a few squamous-cell carcinomas and papillomas at the application site in animals of each sex and a few carcinomas at the adjacent inguinal region in males.

Two samples of straight-run kerosene [5], one sample of light vacuum distillate [19] and three samples of light catalytically cracked distillate [24] produced skin tumours in mice. Some residues from thermal cracking [31] produced benign and malignant skin tumours in mice. (See the monograph on occupational exposures in petroleum refining.)

4.3 Human data

In a case-control study of cancer at many sites, there was evidence of an increased risk for squamous-cell carcinoma of the lung in men estimated to have had substantial exposure to diesel fuel. There was also an indication of an increased risk for cancer of the prostate. No attempt was made to separate the effects of combustion products from those of exposure to diesel fuel itself.

4.4 Other relevant data

Inhalation or ingestion of diesel fuel resulted in acute and persistent lung damage in humans.

No report specifically designed to study genetic and related effects in humans following exposure to diesel fuel was available to the Working Group.

Application of marine diesel fuel to the skin of mice resulted in ulceration.

In a single study, diesel fuel induced chromosomal aberrations in bone-marrow cells of rats; it did not induce mutation in cultured mammalian cells but was weakly mutagenic to bacteria. Another sample did not induce mutation in bacteria or algae; a sample of marine diesel fuel and aliphatic and aromatic fractions of an unspecified diesel fuel were also not mutagenic to bacteria. (See Appendix 1.)

4.5 Evaluation[2]

There is *inadequate evidence* for the carcinogenicity in humans of diesel fuels.

There is *limited evidence* for the carcinogenicity in experimental animals of marine diesel fuel.

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[1]Subsequent to the meeting, the secretariat became aware of a study in which skin tumours were reported in mice after application to the skin of petroleum diesel (boiling range, 198–343°C) [corresponding to diesel fuel No. 2] (Clark *et al.*, 1988).

[2]For definitions of the italicized terms, see Preamble, pp. 24–28.

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identified between 1990–1992 from four centres in the Selangor and the Federal Territory. Controls were selected from among the general Chinese population in the study area by randomly sampling individual houses. Participants provided information on smoking, diet, education, occupation, and housing type during an in-person interview. The OR for a 10-fold increase in exposure to paints or varnishes was 1.08 (95% CI: 0.91–1.29; 16 cases), adjusted for diet and smoking.

Boffetta *et al.* (2003) evaluated occupational exposures and cancer of the larynx and hypopharynx among men from selected areas in France, Italy, Switzerland, and Spain. Cases ($n = 1010$) were identified from cancer registries between 1980–1983. Population controls ($n = 2176$) were selected from census lists, electoral rolls, or population registries. Information on tobacco, alcohol, other risk factors, and all jobs held for at least one year since 1945 was obtained by in-person interviews. ORs were adjusted for age, study area, tobacco, and alcohol use. Construction painters had an OR of 1.36 (95% CI: 0.67–2.74; 18 cases).

Luce *et al.* (1993) indentified cases of cancers of the nasal cavity and paranasal sinuses ($n = 207$) diagnosed between 1986–1988 from 27 hospitals in France for a study of occupational exposures. A total of 409 controls were selected in two ways and pooled for analysis: one set of controls were patients with cancers other than those of the nasal cavity or sinus ($n = 323$), and the second set were individuals named by the cases ($n = 86$). Controls were matched to cases by age, sex and residence (friend controls only). Subjects were interviewed in person about socio-demographic characteristics, smoking habits, alcohol consumption, and a complete job history. Industrial hygienists assessed potential occupational exposures. ORs for specific histological types of nasal cancer were adjusted for multiple factors where appropriate. ORs for histological types of nasal cancer among men with probable or definite medium-to-high level exposure to paints, lacquers or varnishes were 0.9 (95% CI: 0.3–2.7; four cases) for squamous cell carcinoma, 12.2 (95% CI: 6.9–21.6; 35 cases) for adenocarcinoma, and 3.5 (95% CI: 1.3–9.3; six cases) for others.

Teschke *et al.* (1997a) conducted a population-based case–control study of nasal cancer in British Columbia, Canada. Cases ($n = 48$) were registered at the British Columbia Cancer Agency between 1990–1992. Controls ($n = 159$) were identified from provincial voters' lists and matched to cases by age and sex. Subjects, or next-of-kin if necessary, were interviewed in person or by telephone to obtain information on a variety of factors including occupational, residential, smoking, and medical histories.

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.

Among the cases, two were employed as firefighters. Of those occupations which self-reported exposure to diesel exhaust, including truck drivers, firefighters, road workers, and mine workers (5.5 cases and 4.4 controls), the adjusted OR was 1.47 (95% CI: 0.5–4.1). For those occupations which self-reported exposure to diesel 'fumes', firefighter was not listed amongst them The authors noted that the self-reported exposure to diesel exhaust or diesel fumes may reflect uncontrolled confounding with cigarette smoking and alcohol consumption as almost all patients who reported diesel exposure were also heavy cigarette smokers, and consumed large amounts of alcohol.

Elci *et al.* (2003) examined the link between occupations and risk of lung cancer by histological types in Turkey. Cases were identified from an oncology treatment centre at one of the largest cancer hospitals, including treatment for workers, in Istanbul. After admission to hospital, all patients completed a standardized questionnaire administered by trained interviewers. There were 1354 male lung cancer cases with complete interview information identified during 1979–1984. An oncologist reviewed hospital records for diagnostic verification and classification of cancer types. When there were four or more cases per cancer type, histopathology and morphological type was examined. Patient controls "with the same sociodemographic background as the cases" were selected having the following diagnoses: cancers of the skin (non-melanoma), testis, bone, male breast, Hodgkin disease, soft-tissue sarcoma, and non-cancer patients. Of the 27 occupations, firefighting ($n = 10$ cases) had an excess risk of lung cancer, with an age- and smoking-adjusted OR of 6.8 (95% CI: 1.3–37.4). In firefighters, for squamous-cell carcinoma ($n = 4$), the age- and smoking-adjusted OR was 6.2 (95% CI: 0.8–46.2), and for peripheral tumours including bronchus and parenchyma ($n = 9$), the age- and smoking-adjusted OR was 7.0 (95% CI: 1.3–39.1).

Bates (2007) investigated cancers of the lung and bronchus in firefighters as described above under kidney cancer and in Table 2.6. There were 495 firefighters with these cancers. The adjusted OR was 0.98 (95% CI: 0.88–1.09).

2.2.4 *Cancers at other sites*

(a) Multiple myeloma, non-Hodgkin lymphoma, and leukaemia

Demers *et al.* (1993) identified cases of multiple myeloma through SEER tumour registries in four geographic locations including two counties in Washington State, two in Utah including Salt Lake City, five counties of metropolitan Atlanta, Georgia, and three metropolitan Detroit, Michigan, counties. All those potentially eligible included all incident cases diagnosed during 1977–1981. Controls were selected to be similar in age, gender, and region. In Washington State, 1683 population-based controls were selected by using two sampling units of four households. In other areas, a random-digit dialling method was used for selecting controls. Interviews were obtained from 692 (89%) of the cases or their survivors, and from 1683 (83%) of the controls.

distribution of particles is consistent with the increased rate of lung cancer seen in rats exposed to carbon black (IARC, 1996). Chemicals adsorbed onto particles can be transported deep into the lung where depending on their solubility, they can either remain or slowly desorb into the lung-lining fluid.

Impaired particle clearance due to high loading of carbon black in experiments with rats results in increased accumulation of particles and chronic active inflammation. Increased collagen deposition from proliferating fibroblasts, increased epithelial cell proliferation, and metaplasia have been found at high lung burdens of carbon black. Most assays for mutagenicity are negative for carbon black. However, in rats exposed to carbon black by inhalation, *hprt* mutant frequency was elevated in type II cells following a 12-week exposure. Studies on DNA adducts are mixed with prolonged inhalation exposure not inducing a significant increase in DNA adducts in peripheral lung tissue of rats, but increasing DNA adduct levels in type II cells (IARC, 1996).

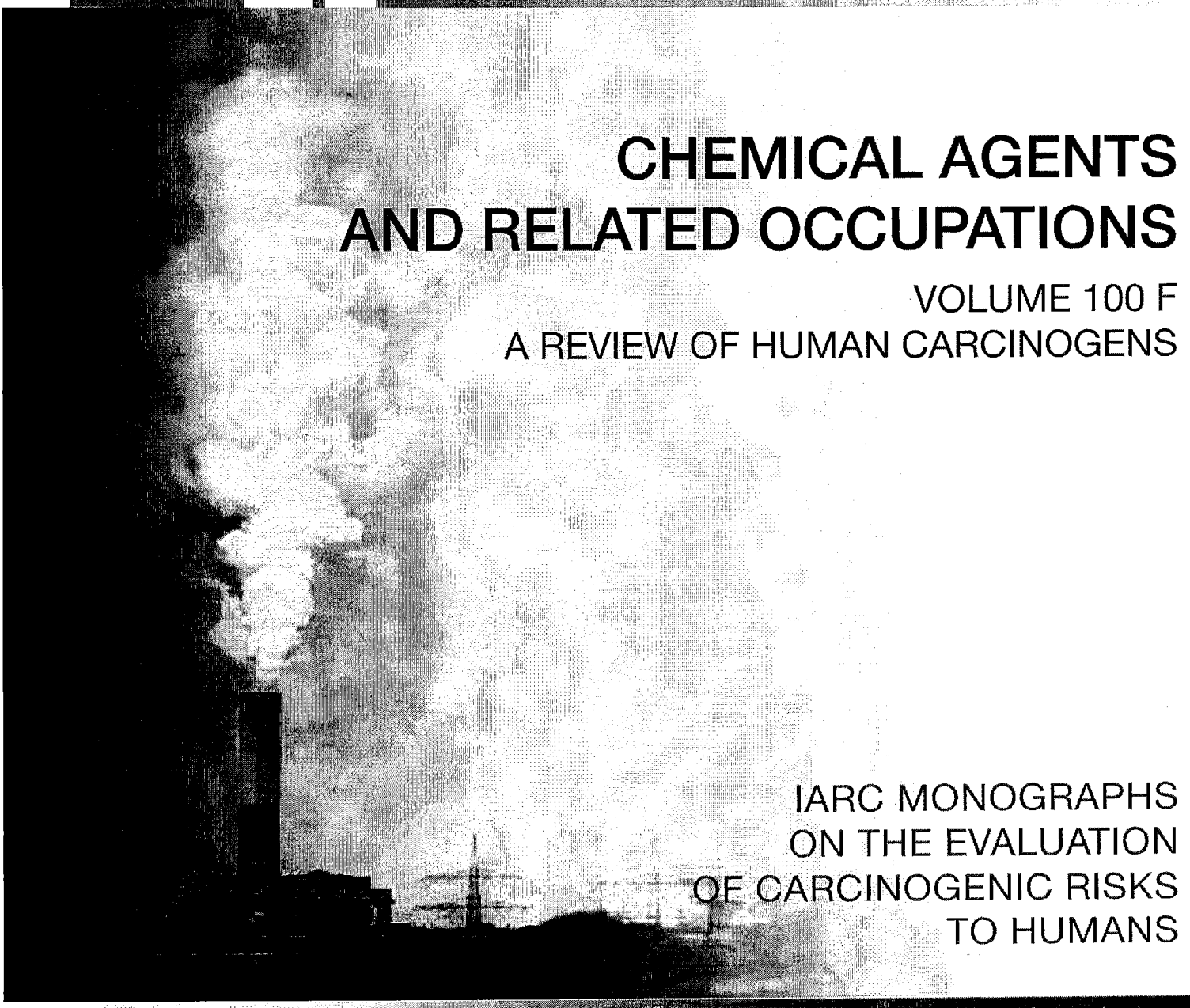
A specific exposure in firefighters consisting of mixed particulate and gas or vapour phase components is diesel exhaust, which shares many chemicals in common with wood smoke, including PAHs. Prolonged exposure of experimental animals to diesel engine exhaust leads to particle accumulation in macrophages, changes in the lung cell population, fibrotic effects, squamous metaplasia, and pathological changes in regional lymph nodes, as well as DNA adduct formation, protein adduct formation, and sister chromatid exchange. Particles or their extracts induce mutations and DNA damage in bacteria, and the gaseous phase is also mutagenic to bacteria (IARC, 1996).

In rats, a small fraction of ultrafine particles are translocated from the lungs into other organs (Kreyling *et al.*, 2002). In humans, studies of ultrafine 99mTc-labelled carbon particles also support translocation of the particles from the lung into the systemic circulation (Nemmar *et al.*, 2002). Translocation of ultrafine carbon particles from the olfactory mucosa to the brain has also been described *in vivo* (Oberdörster *et al.*, 2004).

4.1.2 *Aldehydes*

Multiple aldehydes are found in smoke, including but not limited to formaldehyde, acetaldehyde and acrolein. For all of these aldehydes, exposure is predominantly to the respiratory tract due to local metabolism. For formaldehyde, this local exposure is consistent with the human cancer data linking exposure to nasopharyngeal and sinonasal cancer (IARC, 2006). Due to this local metabolism and significant endogenous production of formaldehyde, exposure of humans, monkeys or rats to formaldehyde by inhalation has not been found to alter endogenous concentrations. No information is available on relative absorption by site within the respiratory system in humans. In monkeys, formaldehyde is absorbed in the nasopharynx, trachea and proximal regions of the major bronchi whereas in rats absorption occurs almost entirely in the nasal passages (IARC, 2006). Dermal application of formaldehyde results in a relatively low extent of absorption, so in firefighters the predominant absorption route should be through inhalation.

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

In *IARC Monograph* Volume 32 (IARC, 1983) no evaluation was made of studies of carcinogenicity in experimental animals published since 1972, but it was concluded that there is *sufficient evidence* for the carcinogenicity of benzo[*a*]pyrene in experimental animals.

Carcinogenicity studies with administration of benzo[*a*]pyrene by multiple route of exposure, reported after the initial evaluations, were subsequently reviewed in *IARC Monograph* Volume 92 (IARC, 2010) and are summarized below (Table 3.1). See Table 3.2 for an overview of malignant tumours induced in different animal species.

3.1 Skin application

In several studies in which benzo[*a*]pyrene was applied to the skin of different strains of mice, benign (squamous cell papillomas and keratoacanthomas) and malignant (mainly squamous-cell carcinomas) skin tumours were observed (Van Duuren *et al.*, 1973; Cavalieri *et al.*, 1977, 1988a; Levin *et al.*, 1977; Habs *et al.*, 1980, 1984; Warshawsky & Barkley, 1987; Albert *et al.*, 1991; Andrews *et al.*, 1991; Warshawsky *et al.*, 1993). No skin-tumour development was seen in $AhR^{-/-}$ mice that lacked the aryl hydrocarbon receptor, whereas the heterozygous and wild-type mice developed squamous-cell carcinomas of the skin (Shimizu *et al.*, 2000).

In a large number of initiation–promotion studies in mice, benzo[*a*]pyrene was active as an initiator (mainly of squamous-cell papillomas) when applied to the skin (IARC, 2010).

3.2 Subcutaneous injection

In subcutaneous injection studies of benzo[*a*]pyrene, malignant tumours (mainly fibrosarcomas) were observed at the injection site in mice (Kouri *et al.*, 1980; Rippe & Pott, 1989) and rats (Pott *et al.*, 1973a, b; Rippe & Pott, 1989). No fibrosarcomas were observed in $AhR^{-/-}$ mice that lacked the aryl hydrocarbon receptor, whereas the heterozygous and wild-type mice did develop these tumours (Shimizu *et al.*, 2000).

In another study, male and female newborn Swiss mice that were given benzo[*a*]pyrene subcutaneously showed a significant increase in lung-adenoma incidence and multiplicity (Balansky *et al.*, 2007).

A single study in 12 strains of hamsters resulted in sarcomas at the site of injection in both sexes of all 12 strains (Homburger *et al.*, 1972).

3.3 Oral administration

After administration of benzo[*a*]pyrene by gavage or in the diet to mice of different strains (Sparnins *et al.*, 1986; Estensen & Wattenberg, 1993; Weyand *et al.*, 1995; Kroese *et al.*, 1997; Culp *et al.*, 1998; Hakura *et al.*, 1998; Badary *et al.*, 1999; Wijnhoven *et al.*, 2000; Estensen *et al.*, 2004), increased tumour responses were observed in lymphoid and haematopoeitic tissues and in several organs, including the lung, forestomach, liver, oesophagus and tongue.

Oral administration of benzo[*a*]pyrene to $XPA^{-/-}$ mice resulted in a significantly higher increase of lymphomas than that observed in similarly treated $XPA^{+/-}$ and $XPA^{+/+}$ mice (de Vries *et al.*, 1997). Benzo[*a*]pyrene given by gavage to $XPA^{-/-}/p53^{+/-}$ double-transgenic mice induced tumours (mainly splenic lymphomas and forestomach tumours) much earlier and at higher incidences than in similarly treated single transgenic and wild-type counterparts. These cancer-prone $XPA^{-/-}$ or $XPA^{-/-}/p53^{+/-}$ mice also developed a high incidence of tumours (mainly of the forestomach) when fed benzo[*a*]pyrene in the diet (van Oostrom *et al.*, 1999; Hoogervorst *et al.*, 2003).

Oral administration of benzo[*a*]pyrene by gavage to rats resulted in an increased incidence of mammary gland adenocarcinomas (el-Bayoumy *et al.*, 1995).

Table 3.2 Summary of reports of malignant tumours clearly induced in experimental animals by benzo[*a*]pyrene

Organ site/ species	Lung	Trachea	Larynx	Forestomach	Liver	Lymphoid tissue (lymphoma)	Sarcoma (injection site)	Skin	Mammary gland
Mouse	x			x	x	x	x	x	
Rat	x						x		x
Hamster	x	x	x	x			x		

3.4 Intraperitoneal injection

In a series of studies in newborn and adult mice, intraperitoneal injection of benzo[*a*]pyrene increased the incidence of liver (adenomas and carcinomas) and lung (adenomas and adenocarcinomas) tumours and, occasionally, forestomach (squamous cell papillomas and carcinomas) and lymphoreticular tumours (Vesselinovitch *et al.*, 1975a, b; Wislocki *et al.*, 1986; Lavoie *et al.*, 1987; Busby *et al.*, 1989; Rippe & Pott, 1989; Mass *et al.*, 1993; Nesnow *et al.*, 1995; Ross *et al.*, 1995; Weyand *et al.*, 1995; Rodriguez *et al.*, 1997; Von Tungeln *et al.*, 1999).

In one study in rats with a single intraperitoneal injection of benzo[*a*]pyrene, a high incidence of abdominal mesotheliomas and sarcomas was observed (Roller *et al.*, 1992).

3.5 Inhalation

In a lifetime inhalation study (Thyssen *et al.*, 1981) in male hamsters, benzo[*a*]pyrene induced dose-related increases in the incidence of papillomas and squamous-cell carcinomas in both the upper respiratory tract (nose, larynx and trachea) and the upper digestive tract (pharynx, oesophagus and forestomach).

3.6 Intrapulmonary injection

Dose-related increases in the incidence of malignant lung tumours (mainly epidermoid and squamous-cell carcinomas and a few pleomorphic sarcomas) were found after injection of benzo[*a*]pyrene into the lung of rats (Deutsch-Wenzel *et al.*, 1983; Iwagawa *et al.*, 1989; Wenzel-Hartung *et al.*, 1990; Horikawa *et al.*, 1991).

3.7 Intratracheal administration

Intratracheal administration of benzo[*a*]pyrene alone or mixed with particulates and suspended in saline with or without suspendents resulted in benign and malignant respiratory tumours in mice (Heinrich *et al.*, 1986a), rats (Pott *et al.*, 1987; Steinhoff *et al.*, 1991) and in numerous studies in hamsters (IARC, 2010). This treatment also induced forestomach tumours in hamsters (Saffiotti *et al.*, 1972; Sellakumar *et al.*, 1973; Smith *et al.*, 1975a, b, Stenbäck & Rowland, 1979). Larger benzo[*a*]pyrene particles were generally more effective than smaller ones.

Mice that lack the nucleotide excision-repair gene *XPA* (*XPA*$^{-/-}$ mice) showed a stronger lung-tumour response after intratracheal instillation of benzo[*a*]pyrene than did their similarly treated *XPA*$^{+/+}$ and *XPA*$^{+/-}$ counterparts (Ide *et al.*, 2000).

wild-type mice but not in $AhR^{-/-}$ knockout mice (Senft *et al.*, 2002). These mice were shown to be refractory to benzo[*a*]pyrene-induced carcinogenicity (Shimizu *et al.*, 2000). Benzo[*a*]pyrene induced oxidative stress in mouse lung (Rajendran *et al.*, 2008).

4.4.4 Immunosuppression mechanism

Benzo[*a*]pyrene induces immunosupression in adult mice by altering the cell-mediated responses (Wojdani & Alfred, 1984). Immune development in offspring is also altered following *in utero* exposure to benzo[*a*]pyrene (Urso & Gengozian, 1984). It is postulated that PAHs, including benzo[*a*]pyrene, act principally through their AhR-mediated CYP-derived metabolites (diolepoxides, quinones) to activate oxidative and electrophilic signalling pathways in lymphoid and nonlymphoid cells, including myeloid cells, epithelial cells, and other cell types. Furthermore, there is evidence that PAHs suppress immunity by p53-dependent pathways, by modulating signalling pathways in lymphocytes via non-genotoxic mechanisms, and by oxidative stress (Burchiel & Luster, 2001).

4.4.5 Epigenetic mechanisms

Benzo[*a*]pyrene and/or its metabolites have been shown to increase cell proliferation in several human cell lines, including terminally differentiated human bronchial squamous epithelial cells and in lung-cancer cells where increased expression of the *Cdc25B* gene (cell-division cycle 25B) was observed, along with reduced phosphorylation of Cdk1 (cyclin-dependent kinase 1) (Oguri *et al.*, 2003). Treatment with benzo[*a*]pyrene increased the number of human embryo lung-fibroblasts in the G1–S transition via the activation of c-Jun, through the p53-dependent PI-3K/Akt/ERK (phosphatidylinositol-3-kinase/protein kinase β/extracellular signal-regulated kinase) pathway (Jiao *et al.*, 2008).

Benzo[*a*]pyrene and/or its metabolites also affect apoptosis. Benzo[*a*]pyrene induced apoptosis in human MRC-5 lung fibroblasts via the JNK1/FasL (c-Jun N-terminal kinase 1/Fas Ligand) and JNK1/p53 signalling pathways (Chen *et al.*, 2005). Apoptosis induced by *anti*-benzo[*a*]pyrene-7,8-diol-9,10-epoxide in H460 human lung-cancer cells was associated with induction of Bak (BCL2-antagonist/killer) and with activation of caspase, but it was independent of Bcl-2 (Xiao *et al.*, 2007).

Altered DNA methylation has been reported to be associated with exposure to benzo[*a*]pyrene and/or its metabolites. After treatment of immortalized bronchial epithelial cells with *anti*-benzo[*a*]pyrene-7,8-diol-9,10-epoxide, the concentration of cytosine-DNA methyltransferase-1 was increased and was associated with hypermethylation of the promoters of 5–10 genes, including members of the cadherin gene-family (Damiani *et al.*, 2008).

4.5 Human exposure to PAH-rich mixtures

4.5.1 Biomarkers of exposure and effect

Molecular-epidemiological studies of cancer associated with occupational and environmental exposures to PAH have provided biomarkers that may be used to estimate internal exposure as well as to inform about molecular mechanisms that may be relevant to cancer causation, particularly in defining the early events in the carcinogenesis process. Biomarkers can be detected in the target organ, in surrogate tissues, or in tumours. These can be categorized into *biomarkers of exposure*, which are generally specific to the PAH of concern (e.g. DNA or protein adducts), *biomarkers of effect* (e.g. genotoxic and cytogenetic effects, 8-oxo-deoxyguanosine, sister chromatid exchange (SCE), micronuclei, chromosomal aberrations, mutations in oncogenes, tumour-suppressor genes, or indicator genes),

dose-dependent increase in lung cancer (epidermoid carcinomas) (Dagle *et al.*, 1990).

3.1.3 Inhalation

An aerosol generated from a Write Dust Feed packed with a raw-shale sample from Anvil Points, Colorado, and one spent-shale sample from a direct-heated retort induced lung adenomas and carcinomas in rats during 24 months of exposure, but not in hamsters during 16 months of exposure (Holland *et al.*, 1983).

3.2 Crude shale oils from low-temperature retorting

3.2.1 Skin application

Crude shale oils from a variety of locations around the world and processed by heat transfer or retort combustion at temperatures below 1000 °C consistently induced squamous cell papillomas and carcinomas when repeatedly applied to the skin of mice (Hueper, 1953; IARC, 1985). Shale-derived crude oils and a hydrotreated product induced papillomas and carcinomas in mouse skin during nearly two years of treatment (Wilson & Holland, 1988).

The inner surface of rabbit ears painted with the heavy fraction of the generator (semi-coking) oil obtained from the Estonian oil-shale in gas generators at Kohtla-Järve induced squamous cell carcinomas in 8% of the rabbits. In one surviving rabbit, metastases of the carcinomas were found in the regional lymph nodes, the liver, and the lungs (Vahter, 1959; IARC, 1985)

3.2.2 Intratracheal administration

Intratracheal administration of a crude shale oil at three dose levels significantly increased the incidence of lung tumours in mice across all dose groups (Smith & Witschi, 1983; IARC, 1985).

3.3 Crude shale oils from high-temperature retorting

3.3.1 Skin application

Crude shale oils processed in chamber ovens above 900 °C induced squamous cell papillomas and carcinomas when applied to the skin of mice (Larionov, 1947; Bogovski, 1958, 1961; Turu, 1961; Bogovski & Vinkmann, 1979; IARC, 1985). Chamber-oven oil applied to the inner surface of rabbit ears resulted in multiple squamous-cell papillomas and keratoacanthomas and cornifying and non-cornifying squamous-cell carcinomas in 22% of the rabbits. In one rabbit, metastases in the lung and liver were found (Vahter, 1959; IARC, 1985).

3.4 Shale-oil fractions

Assessment of fractionations of shale oil were undertaken to determine the extent to which exposure to fractions containing known carcinogens such as benzo[*a*]pyrene correlates with carcinogenic activity.

3.4.1 Skin application

Chromatographic fractions of shale oil prepared by adsorption on aluminium oxide and elution with various solvents induced benign and malignant skin tumours in mice (Berenblum & Schoental, 1943; IARC, 1985). Chromatographic fractions of high-temperature (800–1000 °C, chamber-oven) shale oil were collected on silica-gel column and further fractionated into five fractions on aluminium oxide eluted with various solvents. Some of the fractions induced carcinomas and sarcomas with metastases in mice, and papillomas but not carcinomas in rabbits (Bogovski, 1961, 1962; IARC, 1985).

3.4.2 Subcutaneous and/or intramuscular administration

Intramuscular injection of various thermo-distillation products and multiple chromatography fractions of crude shale oil into the thigh of mice induced sarcomas at the site of injection (Hueper & Cahnmann, 1958; IARC, 1985). Chromatographic fractions of chamber-oven tar injected intramuscularly into the thigh of mice induced sarcomas at the injection site and lung tumours in some of the mice, which were also reported in historical controls (Bogovski, 1961, 1962; IARC, 1985).

3.5 Shale-oil distillates, blends and other commercial products

3.5.1 Skin application

Application to the skin of mice of individual distillates and blends of distillates from shale oil – including products such as 'green' oil, 'blue' oil, unfinished gas oil, machine lubricating oil, fuel oil, wood-impregnating oil, tar, bitumen, coke, and lacquer – induced papillomas, spindle-cell sarcoma, and squamous-cell carcinomas (Twort & Ing, 1928; Hueper, 1953; IARC, 1985). Heavy fractions of shale oils appeared to be more carcinogenic than light fractions. The latter induced only benign tumours while heavy fractions induced benign and malignant tumours with a shorter latency period (IARC, 1985).

Crude oil, naptha, and jet fuels derived form shale induced squamous-cell carcinomas and fibrosarcomas when applied to the skin of mice, whereas hydro-treated and diesel-distilled shale oil did not produce tumours (Clark *et al.*, 1988). Crude shale oil and industrial residue derived from a blend of shale oils induced two and three skin carcinomas (in 60 and 56 animals), respectively. No tumours were observed in controls (Bogovski *et al.*, 1990).

Tolichthtol, a product obtained from the acid residue of rectification of shale-oil aromatic fractions – containing up to 22% (w/w) sulfur compounds – did not induce tumours during 24 months after application to the skin (Vinkmann & Mirme, 1975)

3.5.2 Intratracheal administration

Shale-oil coke (a raw-shale distillation residue) did not produce tumours in Syrian golden hamsters after intra-tracheal instillation (Rowland *et al.*, 1980).

3.6 Synthesis

Inhalation of either raw oil shale or spent oil shale produced lung tumours in rats. Application of an extract of spent oil shale produced skin tumours in mice. Skin application of crude oils from both low- and high-temperature retorting induced skin tumours in mice and rabbits; the oils obtained from high-temperature retorting had higher carcinogenic activity. A low-temperature crude oil produced lung tumours in mice after intra-tracheal instillation. Various fractions of shale oils were carcinogenic when applied to the skin of mice and rabbits. Shale-oil distillates, residues, blends and commercial products of the oil-shale industry were tested in mice by dermal application, and produced skin tumours. Distillation fractions from less highly refined shale oils were more carcinogenic than the more highly refined products.

4. Other Relevant Data

4.1 Humans

Shale oil-plant workers in Estonia were examined for chromosomal damage and aneuploidy in peripheral blood cells by means of tandem-labelling fluorescence in situ hybridization. One

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,

In a retrospective study of a small group of men exposed to BCME during the period 1956–1962, six cases of lung cancer were found among 18 workers in a testing laboratory. Five of these six men were moderate smokers, one was a non-smoker. Two further cases of lung cancer were seen in a group of 50 production workers. Five of these eight cases were oat-cell carcinomas. Duration of exposure had been six to nine years, while the period from first exposure to diagnosis was 8–16 years (Thiess *et al.*, 1973; IARC, 1974).

In a five-year observational study of 125 workers exposed to CMME, four cases of lung cancer were diagnosed, representing an eight-fold higher incidence than that in a control group (n = 2804) with similar smoking history. In a retrospective follow-up, a total of 14 cases were identified, all of whom had been working in the production of CMME. In the latter group, three men were non-smokers. Duration of exposure had been 3–14 years. Histological analysis revealed that 12 of the 14 cases were oat-cell carcinomas (Figueroa *et al.*, 1973; IARC, 1974). This cohort was further reported on (Weiss & Boucot, 1975; Weiss *et al.*, 1979; Weiss, 1982, Weiss & Nash, 1997) with confirmatory results (Table 2.1, available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-20-Table2.1.pdf).

Several additional case-reports (Bettendorf, 1977; Reznik *et al.*, 1978; Roe, 1985; Nishimura *et al.*, 1990) and epidemiological studies from the USA (Collingwood *et al.*, 1987), the United Kingdom (McCallum *et al.*, 1983) and France (Gowers *et al.*, 1993) demonstrated that workers exposed to CMME and/or BCME have an increased risk for lung cancer. Among heavily exposed workers, the relative risks were ten-fold or more. An increase in risk was observed with duration of exposure and with cumulative exposure. Histological evaluation indicated that exposure resulted primarily in small-cell type lung cancer (Weiss & Boucot, 1975). The highest relative risks appeared to occur 15–19 years after first exposure (Weiss, 1982), and latency was shortened among workers with heavier exposure (Weiss & Figueroa, 1976; Pasternack & Shore, 1981).

3. Cancer in Experimental Animals

3.1 BCME

Studies on the carcinogenesis of BCME in rats, mice and hamsters after inhalation, skin application, and subcutaneous or intra-peritoneal injection have been reviewed in previous IARC Monographs (IARC, 1974, 1987b). The results of adequately conducted carcinogenicity studies are summarized in Tables 3.1, 3.2, 3.3, 3.4. There were no additional studies reported in the literature since *IARC Monographs* Supplement 7 (IARC, 1987b).

BCME was tested for carcinogenicity by inhalation exposure in five studies with rats, one study with mice and two studies with hamsters; by skin application in two studies with mice; by subcutaneous injection in one study with rats and three with mice; and by intra-peritoneal injection in one study with mice.

Exposure to BCME by inhalation caused an increased incidence of rare malignant tumours of the nose (esthesioneuroepitheliomas and squamous-cell carcinomas of the nasal mucosa) and squamous-cell carcinomas of the lung in male rats (Kuschner *et al.*, 1975; Leong *et al.*, 1981; Albert *et al.*, 1982; Sellakumar *et al.*, 1985) and of lung adenomas in male mice (Leong *et al.*, 1981). Skin application of BCME resulted in an increased incidence of skin papillomas in male and female mice (Van Duuren *et al.*, 1969; Zajdela *et al.*, 1980) and of squamous-cell carcinomas of the skin in female mice (Van Duuren *et al.*, 1969). Intra-peritoneal injection caused increased incidences of sarcomas at the site of injection in female mice (Van Duuren *et al.*, 1975). Subcutaneous injection of BCME caused strongly increased incidences of lung adenomas

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

3. Cancer in Experimental Animals

3.1 1,3-Butadiene

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

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

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

3.2 Diepoxybutane

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

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

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

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

3. Cancer in Experimental Animals

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

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

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

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

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

The carcinogenicity of mixtures of PCBs in rodents has also been clearly established through studies of various Aroclors (IARC, 1978; Mayes *et al.*, 1998; NTP, 2006c) yielding predominantly liver cancers (Cogliano, 1998). Two-year chronic exposure studies done by the US National Toxicology Program (NTP) on PCB 126 (NTP, 2006d) and PCB 118 (NTP, 2009), demonstrated tumour effects consistent with those seen for TCDD (hepatocellular adenomas, cholangiocarcinomas, gingival squamous cell carcinomas, and lung cystic keratonizing epitheliomas). Moreover, when equivalent TCDD doses where applied with the current TEF, a carcinogenic response equivalent to that predicted for TCDD from the NTP study (Walker *et al.*, 2005) was observed.

The set of DLC-28 (IARC, 1978, 1997; Milbrath *et al.*, 2009) have a long half-life similar to that of TCDD (estimated at 7.2 years in the human body) (Table 4.1). Many congeners have similar or longer half-lives (1,2,3,7,8-PeCDD, 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDD, 1,2,3,6,7,8- and 1.2.3.7.8.9-HxCDF, and PCBs 169, 114, 123, 156, 167 and 189) while most of the remaining half-lives are in excess of 1.4 years. Several authors report the presence of these compounds in human blood in the general population (Costopoulou *et al.*, 2006; Scott *et al.*, 2008; Zubero *et al.*, 2009) indicating a sustained, long-term exposure that, when coupled with the analyses for common pleiotropic response, argues in favour of the notion that all of the DLC-28s have the same carcinogenic potential in humans.

Experimental data on mechanism of carcinogenesis induced by DLC-28 are available for 2,3,4,7,8-PeCDF and PCB 126, in particular (Table 4.2), Both have been shown to bind to the AhR in humans and animals (IARC, 1978; Safe, 2001), to translocate into the nucleus and activate numerous metabolic enzymes *in vitro* (human and non-human cell lines) and *in vivo* in experimental animals (IARC, 1997; Safe, 2001; Vezina *et al.*, 2004; Haws *et al.*, 2006), to trigger changes in growth factors and signalling pathways related to cellular replication in rodents (Hemming *et al.*, 1995; Vondrácek *et al.*, 2005; N'Jai *et al.*, 2008). 2,3,4,7,8-PeCDF potential effect on cell replication is suggested in the NTP study (Walker *et al.*, 2007), and promotion in skin, liver and lung tissues is reported in initiation-promotion studies (Hébert *et al.*, 1990; Anderson *et al.*, 1991; Waern *et al.*, 1991). PCB 126 acts as a promoter of liver cancer in initiation-promotion studies (Hemming *et al.*, 1995; Haag-Grönlund *et al.*, 1998) with measured increases in cell-replication rate in the populations of initiated cells (Vondrácek *et al.*, 2005). PCB 126 and 2,3,4,7,8-PeCDF induce oxidative stress, the latter in a dose-dependent manner in brain and liver of rats (Hassoun *et al.*, 2002; Hennig *et al.*, 2002). These two compounds are carcinogenic in mixtures with TCDD (IARC, 1978; Hassoun *et al.*, 2001; NTP, 2006d) and by themselves in the NTP chronic bioassays in rats, where they increase hepatocellular adenomas, cholangiocarcinomas, gingival squamous-cell carcinomas, and, possibly, lung cystic keratonizing epitheliomas (NTP, 2006b, c, d).

4.4 Synthesis

There is strong evidence to support a receptor-mediated mechanism of action for TCDD-associated carcinogenesis in humans where the primary mechanism is the promotion of tumour development through the activation of cellular replication and the alteration in cellular senescence and apoptosis. Dioxin, through activation of an array of metabolic enzymes also increases the risk for oxidative stress, which serves as an indirect initiator of carcinogenesis. These events make dioxin a complete carcinogen. The conservation of the AhR and the related signalling pathways across species strongly support this mechanism in humans.

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local county). In a recent follow-up through 2003, Marsh *et al.* (2007a) showed elevated SMRs when both national and local county rates were used. In addition, when conducting a case–control study nested within the cohort and including seven deaths from nasopharyngeal cancer, the authors obtained information on employment outside the formaldehyde industry and showed that five of these workers had been employed as a silversmith. However, while there was some evidence of effect modification by activities as a silversmith (based on small numbers), confounding alone did not explain the relatively high number of deaths from nasopharyngeal cancer in this plant (Marsh *et al.*, 2007a).

Two analyses have been conducted to re-analyse the data from the most recent update of the NCI cohort, with a focus on solid tumours (Hauptmann *et al.*, 2004). The first included an analysis of exposure category and SMR, as well as an analysis of Plant 1, where five of nine deaths from nasopharyngeal cancer occurred, compared with all other plants in the cohort (Marsh & Youk, 2005). Using their own cut-points of exposure, the authors concluded that their analysis lent uncertainty to the findings from the NCI cohort. In another re-analysis, the authors further controlled for the effect of plant for the peak-exposure metric and performed sensitivity analyses by imputing additional cases, which showed instability in the risk estimates (Marsh *et al.*, 2007b). The authors concluded that an interaction between plant group and exposure makes generalization beyond Plant 1 difficult.

2.1.2 Case–control studies

The relationship between nasopharyngeal cancer and exposure to formaldehyde has also been investigated in seven case–control studies, five of which found elevated risks for overall exposure to formaldehyde or in higher exposure categories, although not all were statistically significant (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-24-Table2.3.pdf; Vaughan *et al.*, 1986b; Roush *et al.*, 1987; West *et al.*, 1993; Vaughan *et al.*, 2000; Hildesheim *et al.*, 2001). One study found an elevation among women, but not men (Olsen *et al.*, 1984) and one found no evidence of an association (Armstrong *et al.*, 2000). Two case–control studies were considered as the most informative because of their size, their exposure assessment, and the evaluation of potential confounders. The first, a population-based case–control study in the USA, showed a significant association for the workers whose exposure duration had been the longest (OR = 2.1; 95%CI: 1.0–4.5, P_{trend} = 0.07), but not for maximum exposure (P_{trend} = 0.57) (Vaughan *et al.*, 2000). When the analysis was limited to differentiated squamous-cell and epithelial NOS, there was a significant association in the highest exposure category for both duration and cumulative exposure with significant exposure-response trends (P_{trend} = 0.014 and 0.033, respectively). In the other study, conducted in Taiwan, China, an OR of 1.6 (95%CI: 0.91–2.9, P_{trend} = 0.08) was found in the category with the longest duration of exposure (Hildesheim *et al.*, 2001). For cumulative exposure, there was a non-significant elevation in the highest exposure category and the trend test was not significant (P = 0.10). In subanalyses that were restricted to cases and controls who were seropositive for antibodies against Epstein-Barr virus, the association between exposure to formaldehyde and nasopharyngeal cancer appeared to be stronger, with an OR for ever exposure of 2.7 (95%CI: 1.2–6.2). However, no clear dose–response pattern was observed with increasing duration of exposure, or with estimated cumulative exposure.

2.1.3 Meta-analyses

A meta-analysis published in 1997 included some but not all of the above studies, and found an overall meta-relative risk for nasopharyngeal

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

to reach the blood and circulate to the bone marrow in humans].

4.2 Toxic effects

Formaldehyde produces irritation of the nose and pharynx in humans and laboratory animals under a variety of circumstances. There appears to be a large inter-individual variation in the human response to the irritating effects of formaldehyde. Under controlled exposure conditions, symptoms of irritation were noted by healthy individuals exposed to formaldehyde concentrations of 2–3 ppm during periods that varied between 40 minute and three hours (for details, see Table 30 in *IARC Monograph* Volume 88 (IARC, 2006)).

Formaldehyde is a known cause of allergic contact dermatitis and, somewhat more controversial, of occupational asthma. Nasal biopsies of workers chronically exposed to formaldehyde showed chronic inflammation, loss of cilia, mild dysplasia, hyperplasia and squamous metaplasia, although the latter finding has been inconsistent and may have been confounded by other exposures, such as to wood dust (IARC, 2006).

The cytotoxicity of formaldehyde has been confirmed in numerous in-vitro systems. Irritation of the nasal and upper respiratory tract is also noted in animal studies. Dose-dependent pathological findings include inflammation, hyperplasia, degenerative changes, necrosis and squamous metaplasia.

Recently, a finding relevant to the possible involvement of formaldehyde in leukaemogenesis was reported by Zhang *et al.* (2010). Their study showed that colony formation by colony-forming unit-granulocyte-macrophage (CFU-GM) progenitor cells is inhibited in cell cultures exposed to formaldehyde at toxicologically relevant concentrations. Furthermore, colony formation by the more primitive CFU-granulocyte- erythrocyte-monocyte-megakaryocyte (CFU-GEMM) progenitors, which give rise to formation of all myeloid cells, showed a linear negative dose–response when treated with formaldehyde. These effects were observed at formaldehyde concentrations of 100–200 μM [3–6 μg/mL], which are toxicologically relevant since background levels of formaldehyde in human blood have been reported to be 50–100 μM [1.5–3 μg/mL] (Heck *et al.*, 1985; Casanova *et al.*, 1988). Because the CFU-GEMM multipotent myeloid progenitor cells and the pluripotent stem cells are the target cells for leukaemogenesis and are converted to leukaemic stem cells in acute myeloid leukaemia, the finding that formaldehyde damages these cells *in vitro* adds some weight to the notion that it may be associated with myeloid leukaemia.

4.3 Genetic and related effects

The genotoxicity of formaldehyde was thoroughly reviewed in *IARC Monograph* Volume 88 (IARC, 2006). Genotoxicity has been observed *in vitro* in many systems with multiple endpoints.

4.3.1 Humans

Micronucleus formation has been repeatedly reported to occur in cells of the nasal and oral mucosa of formaldehyde-exposed humans. The outcome of studies on induction of micronuclei, sister chromatid exchange and chromosomal aberrations in the lymphocytes of exposed humans – which is pertinent to the question concerning the potential of formaldehyde to cause lympho-haematopoietic cancer – has been less consistent (see Table 4.1).

DNA–protein crosslinks in circulating white blood cells were found to be higher in 12 workers exposed to formaldehyde in an anatomy department and a pathology institute than in eight controls ($P = 0.03$) (Shaham *et al.*, 1996). The number of crosslinks tended to be higher in workers who had been exposed longer (exposure duration, 2–31 years). Smoking had no effect. In a

a high incidence of tumours that were probably of olfactory neuroepithelial origin, but were formerly reported as cerebral neuroblastomas in some studies. Similar results were observed in co-exposed dams (Maltoni & Cotti, 1988). In a second study, rats were exposed to vinyl chloride for five weeks, beginning at birth. Angiosarcomas of the liver and hepatomas occurred at a high incidence in the offspring, but not in the dams that were co-exposed with the offspring (Maltoni *et al.*, 1981).

3.5 Carcinogenicity of metabolites

Chloroethylene oxide, a chemically reactive metabolite of vinyl chloride, was tested for carcinogenicity in a single study in mice by subcutaneous injection and in an initiation–promotion protocol by skin application. It caused a massive increase of fibrosarcomas at the site of injection and increased the incidence of squamous-cell papillomas and carcinomas of the skin at the site of application (Zajdela *et al.*, 1980).

4. Other Relevant Data

4.1 Kinetics and metabolism – studies in humans

Pulmonary absorption of vinyl chloride in humans appears to be rapid and the percentage absorbed is independent of the concentration inhaled. Adult male volunteers exposed for six hours to air containing 2.9–23.1 ppm [7.5–60 mg/m^3] vinyl chloride, retained on average approximately 42% of the inhaled amount (Krajewski *et al.*, 1980; cited in ATSDR, 2006). Pulmonary uptake is determined in part by the blood–air partition constant, which is 1.16 for vinyl chloride (Gargas *et al.*, 1989). Even if no data in humans were available, by assuming an identical solubility of vinyl chloride in rodent and human tissues, the tissue–blood partition constants would be twofold greater in humans (Clewell *et al.*, 2001), as a consequence of the twofold lower blood–air partition coefficient of vinyl chloride in humans compared with rats and mice.

In the postmitochondrial fractions of liver homogenates of humans and rats, large interindividual variations were noted in the metabolism of vinyl chloride, while the average activity was comparable between rat and human samples (Sabadie *et al.*, 1980). Vinyl chloride is primarily and rapidly metabolized in the liver (see Fig. 4.1), with a saturable mechanism (Reynolds *et al.*, 1975; Ivanetich *et al.*, 1977; Barbin & Bartsch, 1989; Lilly *et al.*, 1998; Bolt, 2005). The first step is oxidation in the liver, predominantly mediated by the human cytochrome P450 (CYP) isoenzyme 2E1 (WHO, 1999). Since CYP2E1 is present in several tissues at low levels – compared with concentrations in the liver – extrahepatic metabolism of systemically available vinyl chloride does occur. Inhibitors of CYP, such as 3-bromophenyl-4(5)-imidazole or 6-nitro-1,2,3-benzothiadiazole, reduce the metabolism of vinyl chloride *in vivo* (Bolt *et al.*, 1976). The primary metabolites of vinyl chloride are the highly reactive chloroethylene oxide, which is formed in a dose-dependent process and has a half-life of 1.6 minutes in aqueous solution at neutral pH (Barbin *et al.*, 1975; Dogliotti, 2006), and its rearrangement product chloroacetaldehyde (Bonse *et al.*, 1975). Both can bind to proteins, DNA and RNA and form ethenoadducts; chloroethylene oxide is the most reactive with nucleotides (Guengerich *et al.*, 1979).

Conjugation of chloroethylene oxide and chloroacetaldehyde with glutathione (GSH) eventually leads to the major urinary metabolites *N*-acetyl-*S*-(2-hydroxyethyl)cysteine and thiodiglycolic acid (Plugge & Safe, 1977). The latter compound has been reported to be the major metabolite in the urine of exposed workers (Cheng *et al.*, 2001) with concentrations in