

Reactive chemicals and cancer

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Epidemiologic evidence on the relation between reactive chemicals and cancer is reviewed. These highly reactive chemicals (acrylonitrile; bis[chloromethyl]ether and chloromethyl methyl ether; 1,3-butadiene, ethylene oxide; formaldehyde; mustard gas; sulfuric acid; and vinyl chloride) vary in use and exposure. All are animal carcinogens that also have received considerable epidemiologic attention. Acrylonitrile is a chemical of current economic importance. The epidemiologic evidence is quite weak, but the available studies were very small. Epidemiologic studies clearly demonstrate that bis (chloromethyl) ether and chloromethyl methyl ether cause lung cancer. Continued follow-up of exposed workers is encouraged to provide information on risks for other cancers. Results from epidemiologic studies of butadiene-exposed workers are somewhat inconsistent, but the largest study with the best exposure assessment found the largest relative risk for leukemia. The failure of several larger studies to replicate the early Swedish findings of a very strong association between leukemia and ethylene oxide has not been adequately explained. Epidemiologic studies of formaldehyde provide limited evidence for an association with cancer of the nasopharynx and possibly with nasal cancer. These very rare tumors, however, are difficult to study epidemiologically. Mustard gas is a well-established lung carcinogen, but a recent follow-up of the English cohort suggests that other sites also may be affected. Sulfuric acid appears to cause laryngeal cancer. A suggested relationship with lung cancer in a few studies is of concern because of the widespread opportunity for exposure from ambient air pollution. Vinyl chloride causes angiosarcoma of the liver, but a large, multi-country study provided no clear evidence that other sites are affected. *Cancer Causes and Control* 1997, 8, 473-490

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Introduction

In this paper we evaluate human data regarding cancer and exposure to several substances (*acrylonitrile, bis[chloromethyl]ether and chloromethyl methyl ether, 1,3-butadiene, ethylene oxide, formaldehyde, mustard gas, sulfuric acid, and vinyl chloride*). With the exception of formaldehyde and sulfuric acid, current exposures to these chemicals occur primarily at the workplace. These substances have widely different chemistry and use. They are of interest because they are known or suspected carcinogens and they are highly reactive chemicals.

Acrylonitrile

Background

Acrylonitrile is a colorless liquid with a number of important commercial uses. It is a major ingredient in the production of acrylic and modacrylic fibers, which are used in many plastic products. It also is used in the manufacture of acrylonitrile-butadiene-styrene and styrene-acrylonitrile resins and as a fumigant.¹ The epidemiology of acrylonitrile was last reviewed by the

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International Agency for Research on Cancer (IARC) in 1987² and more recently by Rothman.³ Acrylonitrile is carcinogenic in animals.² It causes a variety of cancers including brain, stomach, Zymbal gland, tongue, small intestine, and mammary gland. It is taken up readily by inhalation or through the skin.⁴ A number of different metabolites are known: 2-cyanoethylene oxide is thought to be the major carcinogenic species.⁵ Animal experiments also relate inhalation exposure with mutagenicity in the urine⁶ and hemoglobin adducts.⁷

Epidemiologic investigations

A number of epidemiologic studies have evaluated cancer risks from occupational exposure to acrylonitrile. Most

are cohort studies. Siemiatycki,⁸ however, evaluated individuals working with acrylic and modacrylic fibers in case-control studies of several cancers in Montreal, Canada. He observed a significant excess for cancer of the rectum (odds ratio [OR] = 3.5) among those with substantial exposure and a nonsignificant excess for prostate cancer (OR = 1.5). Results from nine cohort studies of acrylonitrile-exposed workers have been reported (Table 1). There was no clear evidence of any cancer excess. Some cancers could not be evaluated fully because several studies provided information on only selected cancers. Standardized mortality ratios (SMR) for lung or respiratory cancer, however, were available from all investigations. In four studies, the SMR for lung cancer

Table 1. Epidemiologic results from cohort studies of workers exposed to acrylonitrile

Author (ref.) Year	Industry/product	Country	Cohort size/no. deaths	Exposure assessment	Confounders considered	Cancer findings (no. observed)
Kisselbach <i>et al</i> ⁹ 1979	Production/processing	Germany	884/58	Duration of exposure	None	Stomach, PMR = 1.18 (4) Respiratory, PMR = 0.87 (6)
Thiess <i>et al</i> ¹⁰ 1980	Acrylonitrile resins	Germany	1,469/89	Ever exposed	None	Lung, SMR = 1.96 (11) Lymphopoietic, SMR = 2.35(4)
Werner <i>et al</i> ¹¹ 1981	Acrylic fibers	UK	1,111/68	Ever exposed	None	Stomach, SMR = 2.50 (5) Lung, SMR = 1.20 (9) Brain, SMR = 2.00 (1)
Delzell & Monson ¹² 1982	Nitrile rubber industry	US	327/74	Duration of employment	None	Lung, SMR = 1.50 (9) Lymphopoietic, SMR = 2.30(4)
O'Berg <i>et al</i> ^{13,a} 1985	Acrylic fibers	US (SC)	1,345/155	Cumulative exposure	Wage/salary	Lung, SMR = 1.21 (14) Prostate, SMR = 1.00 (1) ^b Bladder, SMR = 5.00, (3) Lymphopoietic, SMR = 1.08(4)
Chen <i>et al</i> ¹⁴ 1987	Acrylic fibers	US (WV)	1,083/92	Cumulative exposure (but not presented)	None	Digestive, SMR = 0.67 (4) ^c Lung, SMR = 0.60 (5) Prostate, SMR = 1.11 (1) ^d Lymphopoietic, SMR = 1.48(4) All cancer = 0.77 (18)
Collins <i>et al</i> ¹⁵ 1989	Acrylonitrile, acrylic fibers	US (FL/LA)	2,671/237	Cumulative exposure	Smoking	Lung, SMR = 1.00 (15) Prostate, SMR = 1.49 (2) Brain, SMR = 0.56 (1) Lymphopoietic, SMR = 1.04(5)
Swaen <i>et al</i> ¹⁶ 1992	Production, acrylic fibers, rubber, others	Netherlands	2,842/134 exposed 3,961/572 unexposed	Duration, cumulative, and peak exposures	Other workplace chemicals	Stomach, SMR = 0.46 (2) ^e Colon, SMR = 1.41 (4) Lung, SMR = 0.82 (16) Prostate, SMR = 1.64 (2) Brain, SMR = 1.75 (3)
Mastrangelo <i>et al</i> ¹⁷ 1993	Acrylic fibers	Italy	671/32	Duration of exposure	Smoking, other chemicals	Stomach, SMR = 3.39 (2) ^f Colon, SMR = 10.5 (4) Lung, SMR = 0.77 (2) Brain, SMR = 2.63 (1)

^a Study also included incident cancers identified through the Dupont Tumor Registry.

^b Observed 6 incident cases of prostate cancer *cf* 1.8 expected.

^c Expected mortality based on US population rates for all SMRs shown here.

^d One incident case *cf* 0.5 expected based on Dupont Tumor Registry rates.

^e All SMRs for workers exposed to acrylonitrile.

^f Unexposed workers and those also exposed to vinyl chloride or benzidine were excluded.

SMR = standardized mortality ratio.

PMR = proportional mortality ratio.

was greater than 1.0; it was less than 1.0 in four studies, and exactly 1.0 in one study. Rothman³ performed a meta-analysis on eight of the cohorts⁹⁻¹⁶ and found 85 lung cancer deaths occurred *cf* 79.4 expected. Brain cancer was elevated in three of the four studies that reported on this site, but only six deaths were involved. The excess of prostate cancer cases observed at a Dupont plant¹³ was not seen in the mortality analysis at the same plant, or in other studies.

Several groups have investigated biologic measures of acrylonitrile exposure and damage. Urinary levels of acrylonitrile or its metabolites are significantly correlated with airborne levels¹⁸⁻²⁰ indicating that exposure estimates based on industrial hygiene measurements may be reasonable approximations of dose.

Conclusions and recommendations

The major limitation of these cohort studies of acrylonitrile exposed workers is that they were very small. Exposure-response analyses were attempted in only four investigations, but the small number of deaths diminished their value. IARC² considered the epidemiologic evidence to be limited, as did Rothman.³ The epidemiologic data, although limited, are too thin to provide much confidence that no excess occurs. What is needed is a study large enough to have reasonable power to identify excesses of cancers of primary interest, *e.g.*, lung, brain, and prostate, with a design that allows careful evaluation of relative risks by some quantitative estimate of exposure.

A new investigation and extensions of other cohorts are underway which should clarify the situation. The United States National Cancer Institute and the National Institute for Occupational Safety and Health are conducting an investigation of workers from eight acrylonitrile producing or using plants in the US. Approximately 25,000 workers are included. The study includes an extensive exposure-reconstruction effort undertaken with assistance from management and labor at the plants.^{21,22} Results are expected in 1997. Extended follow-up of the established cohorts of Dupont workers^{13,14} and Dutch workers¹⁶ also are expected in the near future.

Bis(chloromethyl)ether and chloromethyl methyl ether

Background

Bis(chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME) are used primarily in the preparation of anion exchange resins.²³ Since the 1970s,²³ their use has been restricted and safer handling procedures developed.²⁴ BCME produced sarcomas and lung tumors from injection and lung and nasal-cavity tumors by inhalation.²³ CMME caused sarcomas by subcutaneous administra-

tion, and lung tumors by inhalation.²³ BCME appears to be a more potent animal carcinogen than CMME.²⁵

Epidemiologic investigations

Large relative risks (RR) for respiratory cancer have been observed in epidemiologic studies of workers exposed to BCME/CMME in several countries including Germany,²⁶ the US,^{27,28} and France.²⁹ SMRs ranged from 2.8 to 5.0. All studies showed strong exposure-response gradients with RRs ranging from 7.0 to 18.0 in the highest exposure category. The largest RRs occurred 10 to 19 years after exposure and began to diminish after 20 years,^{27,28} a somewhat shorter latent period than is observed for many occupationally related cancers. Other striking features about lung cancer among BCME/CMME workers include early age at death, and a high frequency of small-cell or oat cell carcinomas.^{28,29} Few investigations presented data on cancers other than lung. Weiss³⁰ reported two cases of laryngeal cancer (*cf* 0.3 expected), which generates an RR as high as found for lung cancer. Maher and DeFonso²⁸ also reported a nonsignificant excess of laryngeal cancer (SMR = 3.0 based on two deaths), as well as excesses for cancers of the esophagus (SMR = 2.4, two deaths), colon (SMR = 2.3, six deaths), and prostate (SMR = 2.2, two deaths).

Conclusions and recommendations

Workers exposed to BCME/CMME have striking excesses of lung cancer. IARC classifies these chemicals as human carcinogens.² These chemicals are classic occupational carcinogens in that RRs are very high, there is a strong exposure-response gradient, cancers occur at a younger age among exposed than nonexposed workers, and there is high frequency of small or oat-cell carcinomas. There is some suggestion that excesses may occur for cancers other than lung. The cohorts that have been assembled are small, each with less than 2,000 exposed workers. A meta-, or pooled, analysis of the available data could be informative regarding cancers other than lung. Continued mortality follow-up of these cohorts is needed to provide more information on the time frame of the epidemic. Studies of more recent employees in the industries using these chemicals would provide information on the effectiveness of the exposure reduction efforts.

1,3-butadiene

Background

Butadiene is used primarily in the production of polymers for the manufacture of styrene-butadiene rubber for tires; nitrile rubber for hoses, gaskets, adhesives, and footwear; acrylonitrile-butadiene-styrene polymers for parts, pipes, and various appliances; and styrene-butadiene latexes for

paints and carpet backing.³¹ Butadiene also is used as an intermediate in the production of a number of chemicals. Butadiene causes tumors at multiple sites in laboratory animals, including hemangiosarcomas of the heart, malignant lymphomas, lung, forestomach, liver, and mammary tumors. Exposure-response gradients occur and tumors were induced at exposure levels ranging from 6.25 to 8,000 ppm.³¹ Butadiene is a potent mutagen that requires metabolic activation in bacterial systems.³² It apparently is metabolized to an epoxide (butadiene monoepoxide), which is thought to be the major carcinogenic metabolite. Species differ in the rate of this reaction. Mice activate butadiene to butadiene monoepoxide 15 times faster than rats. Humans resemble rats more than mice with regard to metabolic rates.³²

Epidemiologic investigations

Several investigations have included workers from plants producing styrene-butadiene rubber and two studies included workers from butadiene production facilities. Most studies have been of an industrial cohort design, or a case-control study nested within an industrial cohort (Table 2). Siemiatycki,⁸ using a case-control design, observed a significant OR of 2.0 for kidney cancer for subjects with *any* contact with styrene-butadiene rubber production, and an OR of 2.9 among those with *substantial* exposure. Cancer of the esophagus was elevated slightly (the OR was 1.8 for any exposure and 1.5 for substantial exposure). The ORs for non-Hodgkin's lymphoma, the only lymphatic and hematopoietic cancer studied, were 0.9 for any exposure and 1.5 (based on two cases) for substantial exposure. Lymphatic and hematopoietic cancers tend to be elevated in cohort studies of workers with potential exposure to butadiene (Table 2). Sometimes lymphoma was elevated,^{34,36} and sometimes leukemia.^{34,35,37} Lung cancer, which occurred in laboratory animals exposed to butadiene, was not elevated in any study. Mortality from liver cancer, also a site occurring in bioassays, was not elevated, although only two studies reported on this site.^{35,36}

Workers employed at styrene-butadiene rubber plants may be exposed to a number of chemicals, but the typical recipe calls for about three times as much butadiene as styrene.³⁴ Only one study³⁷ attempted to evaluate disease risks from the two chemicals separately. After adjusting the OR for cancer from one chemical for the effects of the other, leukemia was found to be associated more strongly with butadiene than styrene, *i.e.*, butadiene OR = 7.6 (95 percent confidence interval [CI] = 1.6-35.6) and styrene OR = 2.9 (CI = 0.8-10.3). Exposure to both butadiene and styrene yielded an OR essentially like that observed for butadiene, *i.e.*, OR = 7.4 (CI = 1.3-41.3). In this same population, a significant excess of lymphatic and hematopoietic cancer was observed among Black

male production workers (SMR = 5.1, CI = 1.9-11.1). Meinhard *et al*³⁴ found an excess of leukemia at one of the two plants studied. Most cases occurred among individuals who began working during the start up of the plant in the early 1940s. The excess of lymphatic and hematopoietic cancers observed by Divine³⁶ in the butadiene production plant tended to occur among workers with shorter latency or duration. Matanoski *et al*³⁵ found no overall association with duration or latency of exposure, and also that the largest SMRs occurred among the long latency, short duration group. Numbers of deaths in most studies were generally too small for such stratified analyses as by Matanoski *et al*.

Conclusions and recommendations

Experimental animals developed several tumors including hemangiosarcomas of the heart, malignant lymphomas, lung, forestomach, liver, and mammary tumors.

In epidemiologic studies, only lymphatic and hematopoietic cancers give any suggestion of an association with butadiene exposure. Although the epidemiologic data are inconsistent, the largest study with the best exposure assessment³⁷ found the greatest RR for leukemia. Every study had a deficit of lung cancer. Few studies presented data on liver cancer and too few women were included to evaluate breast cancer.

IARC concluded that 1,3-butadiene was probably carcinogenic to humans based on sufficient evidence in experimental animals and limited evidence in humans.³¹ Cole *et al*,³⁹ in their review, appear to rank the epidemiologic data lower than the 'limited evidence' for carcinogenicity classification by IARC, although they did not use the IARC categories to describe their conclusion. With one exception,³⁵ completed investigations have had very limited power to evaluate risks for less common tumors and exposure assessment is weak or absent in most studies. Only one study³⁵ attempted to separate butadiene exposure from styrene and risks by cumulative exposure are lacking. Studies employing quantitative exposure assessments are needed.

Experimental studies on metabolic activation of butadiene and the differences between species indicates that human studies focusing on interaction between exposure and important genetic polymorphisms could contribute much to our understanding of cancer risks associated with exposure to this chemical.

Ethylene oxide

Background

Ethylene oxide was first produced on a commercial scale by the chlorohydrin process. Since the 1930s, ethylene has been oxidized directly to ethylene oxide with air and

Table 2. Epidemiologic studies of workers potentially exposed to 1,3-butadiene

Author (ref.) Year	Industry/product	Country	Design	Study size	Exposure assessment	Confounders considered	Cancer findings (no. obs. and/or 95% confidence interval)
McMichael <i>et al.</i> ³³ 1976	Styrene-butadiene rubber	US	Nested case-control	1,482 deaths ^a	Employment in synthetic rubber plant; duration	None	Lymphatic/hematopoietic ^b SMR = 6.2(4.1-12.5) [†] Lymphatic leukemia SMR = 3.9(2.6-8.0) [†] Lung (no deaths) Plant A Lymphopoietic SMR = 2.12(9) [†] Lymphoma SMR = 2.24 (3) Leukemia SMR = 2.78 (5) [†] Lung SMR = 0.94 (13)
Meinhardt <i>et al.</i> ³⁴ 1982	Styrene-butadiene rubber	US	Cohort	1,662 plant A; 1,094 plant B	Employed at plants	None	Plant B Lymphopoietic SMR = 0.78 (2) Lymphoma SMR = 1.32 (1) Leukemia SMR = 1.01 (1) Lung SMR = 0.76 (5) <u>White men</u> Lymphopoietic SMR = 0.92 (48) Lymphosarcoma SMR = 0.56 (6) Leukemia SMR = 0.86 (18) Other lymphatic SMR = 1.10 (15) Liver SMR = 0.75 (8) Respiratory SMR = 0.83 (157) <u>Black men</u> Lymphopoietic SMR = 1.46 (7) Lymphosarcoma SMR = 1.32 (1) Leukemia SMR = 2.18 (4) Liver SMR = 1.44 (3) Respiratory SMR = 0.93 (20) Non-Hodgkin's lymphoma OR = 1.5 (2) (0.4-5.1) ^c Lung OR = 0.6 (2)(0.2-2.0) Kidney RR = 2.9 (3)(1.0-8.3) Lymphopoietic SMR = 1.30 (25)(0.84-1.92) Lymphosarcoma SMR = 2.29 (9)(1.04-4.35) Leukemia SMR = 1.02 (8)(0.44-2.00) Liver SMR = 0.24 (1)(0-1.31) Lung SMR = 0.80 (53)(0.60-1.05) Lymphopoietic OR = 2.09 (59)(0.85-5.17) Leukemia OR = 6.82 (26)(1.10-42.2) Lymphosarcoma OR = 0.75(6)(0.06-9.17) Other lymphoma OR = 1.22 (18)(0.3-5.02) Lymphopoietic (0 deaths; 1.2 expected) Lung SMBR = 0.42 (2)(0.05-1.51) ^e
Matanoski <i>et al.</i> ³⁵ 1990	Styrene-butadiene rubber	US and Canada	Cohort	12,110	Work area	None	
Siemiatycki <i>et al.</i> ⁸ 1990	Styrene-butadiene rubber	Canada	Case-control	4,263 cancers	Estimated level	Smoking, income, a few others for selected cancers	
Divine <i>et al.</i> ³⁶ 1990	Butadiene production plant	US	Cohort	2,582	Duration and qualitative level	None	
Santos-Burgoa <i>et al.</i> ³⁷ 1992	Styrene-butadiene rubber - same population as in ³⁶	US and Canada	Nested case-control	59 lymphopoietic cancers; 193 controls	Level and duration	Styrene	
Cowles <i>et al.</i> ³⁸ 1994	Butadiene production	US	Cohort	614	Employed at plant	Smoking ^d	

^a Exact number of controls not provided, but apparently about 25% of the 6,678 person cohort.
^b RR for this study are for persons employed at least 5 years in the styrene-butadiene rubber plant.
^c All RR for this study are for subjects with 'substantial' exposure to styrene-butadiene rubber.
^d Did not directly adjusted RR, but did have information on smoking among butadiene exposed and other workers.

^e SMBR = standardized morbidity ratio.
[†] SMRs statistically significant; SMR = standardized mortality ratio.

a silver catalyst.⁴³ It is used widely as a sterilant, disinfectant, and pesticide, but also serves as a raw ingredient in making resins, films, and antifreeze. Human exposure occurs in hospitals, in the production of certain chemicals, and in the manufacture of plastics and drugs.

Ethylene oxide is carcinogenic in laboratory animals. Oral administration caused tumors of the forestomach in rats. Exposure by inhalation caused lung and Harderian gland tumors in male and female mice and lymphomas and cancers of the uterus and mammary gland in females. In rats, inhalation caused leukemia and brain cancer in both genders and mesotheliomas near the testis and subcutaneous fibromas in males.⁴⁰ High doses in the inhalation experimental studies were 100 or 200 ppm. Ethylene oxide rapidly enters the body through the lungs and is distributed uniformly throughout the body.⁴⁰ Urinary excretion of ethylene oxide metabolites (N-acetyl-S-(2-hydroxyethyl) cysteine, S-(2-hydroxyethyl) cysteine, S-(carboxymethyl) cysteine, and ethylene glycol differ markedly between mice, rats, and rabbits.⁴¹ In animals, it causes hemoglobin and DNA adducts, chromosomal aberrations, micronuclei, and gene mutations.⁴⁰

Epidemiologic investigations

The 1979 report by Hogstedt *et al*⁴² of three cases of hematopoietic cancer among workers at a factory sterilizing hospital equipment raised concern about human exposure to ethylene oxide. A series of reports on studies of exposed populations in Sweden⁴³⁻⁴⁵ further raised concern. Since these initial observations, several larger cohort studies have been conducted in several countries. The data in Table 3 show no clear association between ethylene oxide and any cancer. Few statistically significant excesses occur and for each cancer; there are generally as many SMRs below 1.0 as above 1.0. Shore *et al*⁵⁵ found no excesses of any cancer in a meta-analysis and no trend with level of exposure was observed.

For leukemia, however, there was a slight trend with duration of exposure. Analyses by subgroups in a few studies provide some support for an association. Gardner *et al*⁴⁶ found a larger SMR for leukemia (3.5) among workers classified as definitely exposed than among other groups. The study in Italy⁵³ found larger SMRs for lymphatic and hematopoietic cancers among workers licensed to handle only ethylene oxide than among those also licensed to handle other chemicals. The recent study of mostly women⁵⁴ found a significant excess of breast cancer. No other study could assess risk among exposed women. The largest study,^{50,51} which also included a quantitative exposure assessment effort, showed a nonsignificant positive trend between lymphoid (lymphatic leukemia and lymphoma) tumors and cumulative exposure to ethylene oxide among men. The exposure-response trend was inverse among women.

Conclusions and recommendations

The lack of an excess of leukemia in most studies is striking given the large RR reported by Hogstedt *et al*.⁴⁵ It does not appear this inconsistency is due to differences in level of exposure because high levels are reported for other studies.^{48,49} Thus, it is reasonably clear that for most ethylene exposed populations, the risk of leukemia is not nearly as high as earlier suggested.⁴⁵ Although the epidemiologic evidence is limited, IARC⁴⁰ concluded that there was sufficient evidence for human carcinogenicity based on animal and mechanistic data. Only two investigations developed quantitative exposure assessments necessary for analysis by cumulative exposure. The large US study^{50,51} provides some evidence for an association only when this type of analysis was performed. Development of quantitative exposure estimates for the other cohorts might help clarify the issue. Given the large number of women potentially exposed, further evaluation of breast cancer is needed.

Formaldehyde

Background

Formaldehyde, a colorless gas with a pungent odor, is produced by oxidation of methanol using silver or metal oxide catalysts. It is produced in a number of countries and its widest use is in the production of urea, phenol, or melamine resins for molded products such as appliances, electric controls, and telephones; in particle-board and plywood; and in surface coatings. It is used also in the textile, leather, rubber, photographic, foundry, abrasive paper, and insulating industries.⁵⁶

In a bioassay with inhalation exposures at 0, 2.0, 5.6, and 14.3 ppm, rats developed squamous-cell carcinoma of the nasal cavities, but mice did not.⁵⁷ Among rats, most tumors occurred at the 14.3 ppm level, two at the 5.6 ppm level, and none at the 2.0 ppm level. In another experiment,⁵⁸ the nasal mucosa of some animals was damaged by electrocoagulation. Fifteen of 58 rats with damaged mucosa exposed by inhalation to 10 ppm developed nasal tumors, while only one of 26 rats with undamaged mucosa developed tumors. Formaldehyde causes the formation of DNA-protein cross-links in several species including rats and monkeys. The level of cross-linking appears to be related to concentration, but not cumulative exposure.⁵⁶ In monkeys, the cross-links showed a decreasing pattern from the middle turbinates, to lateral wall-septum, and to nasopharynx.⁵⁹ Formaldehyde also induces cell proliferation in rats at 10 ppm, but little at lower levels,⁶⁰ and in monkeys in the nasal passages, larynx, and trachea.⁵⁹

Epidemiologic investigations

Approximately 50 case-control and cohort studies have

Table 3. Epidemiologic studies of workers potentially exposed to ethylene oxide

Author (ref.) Year	Industry/product	Country	Design	Study size	Exposure assessment	Confounders	Cancer findings (no. obs. and/or 95% confidence interval)
Gardner <i>et al.</i> ⁴⁶ 1989	Chemical plants and hospitals	UK	Cohort	2,876	Probability of exposure	None	Chemical Industry Lung SMR = 1.19 (22) Breast SMR = 0 deaths NHL SMR = 1.92 (2) Leukemia SMR = 2.26 (3)
Benson & Teta ⁴⁷ 1993	Chlorohydrin unit	US	Cohort	278	Department and duration	None	Hospital Lung SMR = 1.15 (7) Breast SMR = 0.68 (4) NHL SMR = 3.51 (2) Leukemia SMR = 0 deaths Leukemia SMR = 3.5 (4)(1.0-8.9)
Kisselbach <i>et al.</i> ⁴⁸ 1990	Chemical plants	Germany	Cohort	2,658	Qualitative ranking	None	Lung SMR = 1.16 (23)(0.73-1.74) Leukemia SMR = 0.85 (2)(0.10-3.07)
Hagmar <i>et al.</i> ⁴⁹ 1991	Sterilizing of medical equipment	Sweden	Cohort	2,170	Cumulative exposure	None	Incidence Lung SMbR = 1.52 (2)(0.18-5.47) Breast SMbR = 0.64 (4)(0.18-1.65) Lymphoma and multiple myeloma SMbR = 1.54 (2) (0.19-5.56) Leukemia SMbR = 1.54 (1)(0.04-8.57)
Steenland <i>et al.</i> ⁵⁰ Slayner <i>et al.</i> ⁵¹ 1991, 1993	Sterilization facilities	US	Cohort	18,254	Quantitative estimates	None	Mortality Respiratory SMR = 1.75 (2)(0.21-6.34) Lymphoma/leukemia SMR = 1.02 (1)(0.03-5.69) Respiratory SMR = 0.94 (96)(0.76-1.15) Breast SMR = 0.85 (42)(0.61-1.14) NHL SMR = 1.20 (8)(0.57-2.37) Leukemia SMR = 0.97 (13)(0.52-1.67)
Teta <i>et al.</i> ⁵² 1993	Chemical plant	US	Cohort	1,896	Duration	None	Lymphoma SMR = 1.00 (2) Leukemia SMR = 1.06 (5)
Bisanti <i>et al.</i> ⁵³ 1993	Ethylene oxide handlers	Italy	Cohort	1,971	Duration	None	Lung SMR = 1.04 (11)(0.52-1.87) Lymphoma SMR = 6.82 (4)(1.86-17.4) Leukemia SMR = 1.93 (2)(0.23-6.99)
Norman <i>et al.</i> ⁵⁴ 1995	Sterilization of medical equipment	US	Cohort	928 women	Ever-exposed	None	Breast SMbR = 2.47 (34) ^{ab}

^a RR calculated from observed and expected numbers provided in table.

^b Statistically significant.

SMR = standardized mortality ratio; SMbR = Standardized morbidity ratio.

Table 4. Selected epidemiologic studies on formaldehyde and cancer

Author (ref.) Year	Industry/product	Country	Design	Study size	Exposure assessment	Confounders considered	Cancer findings (no. obs. and/or 95% confidence interval)
Blair <i>et al.</i> ^{61,63} Stewart <i>et al.</i> ⁶⁴ 1986-1990	Producers, resin makers, and other users	US	Cohort	26,561	Quantitative assessments	Smoking on a sample	White men Nasal SMR = 0.9 (2) Nasopharynx SMR = 3.0 (6) † Lung SMR = 1.1 (201)(1.0-1.3) Brain SMR = 0.8 (17)(0.5-1.3) Leukemia SMR = 0.8 19(0.5-1.2) <u>First employed before 1965</u> Nasal SMR = 0.7 (1)(0.2-3.9) Nasopharynx (0 deaths; 1.3 expected) Lung SMR = 1.2 (348)(1.1-1.4) Brain SMR = 0.9 (16) (0.5-1.5) Leukemia SMR = 0.9 (15)(0.5-1.5)
Gardner <i>et al.</i> ⁶⁵ 1993	Chemical industry	UK	Cohort	7,660	Quantitative assessments	None	
Bertazzi <i>et al.</i> ⁶⁶ 1989	Resin manufacturing	Italy	Cohort	1,330	Ever/never and duration	None	Nasal (0 deaths; 0.03 expected) Nasopharynx (not provided) Lung SMR = 1.0 (24)(0.6-1.5) Lymphatic and hematopoietic SMR = 1.4 (7)(0.6-1.5)
Stayner <i>et al.</i> ⁶⁷ 1988	Garment industry equipment	US	Cohort	11,030	Duration	None	Nasal (not provided) Nasopharynx (not provided) Lung SMR = 1.1 (39)(0.8-1.6) Brain SMR = 0.7 (5)(0.2-1.7) Leukemia SMR = 1.1 (9)(0.5-2.2)
Anjelkovich <i>et al.</i> ⁶⁸ 1995	Foundry	US	Cohort	3,929	Qualitative levels	Other occupational exposures, smoking	Nasopharynx (0 deaths among exposed) Nasal (0 deaths) Lung SMR = 1.20 (51)(0.89-1.58) Brain SMR = 0.62 (2)(0.07-2.23) Leukemia SMR = 0.43 (2)(0.05-1.57)
Hall <i>et al.</i> ⁶⁹ 1991	Pathology	UK	Cohort	4,512	None	None	Nasal (not provided) Lung SMR = 0.2 (9)(0.1-0.4) Brain SMR = 2.2 (6)(0.8-4.8) Leukemia SMR = 1.5 (4)(0.4-3.9)
Walrath and Fraumeni ⁷⁰ 1983	Embalmers and funeral directors	US	PMR	1,132	None	None	Nasal (0 deaths; expected not provided) Lung PMR = 1.1 (70)(0.9-1.9) ^a Brain PMR = 1.4 (9)(0.9-1.4) ^a Brain PMR = 2.3 (6)(0.8-5.0) ^a (embalmlers) Leukemia PMR = 1.2 (12)(0.6-2.1)
Walrath and Fraumeni ⁷¹ 1984	Embalmers and funeral directors	US	PMR	1,007	None	None	Lung PMR = 0.9 (41)(0.6-1.2) ^a Brain PMR = 1.9 (9)(P < .05) Leukemia PMR = 1.4 (12)(0.7-2.4) ^a
Levine <i>et al.</i> ⁷² 1984	Embalmers	Canada	Cohort	1,477	None	None	Nasal (0 deaths; 0.2 expected) Lung SMR = 0.9 (19)(0.6-1.5) Brain SMR = 1.2 (3)(0.2-3.4) ^a Leukemia SMR = 1.6 (4)(0.4-4.1) ^a

Continued

Table 4. Continued

Author (ref.) Year	Industry/product	Country	Design	Study size	Exposure assessment	Confounders considered	Cancer findings (no. obs. and/or 95% confidence interval)
Stroup <i>et al</i> ⁷³ 1986	Anatomists	US	Cohort	2,239	Specialty and duration	None	Nasal (0 deaths; 0.5 expected) Lung SMR = 0.3 (12)(0.1-0.5) Brain SMR = 2.7 (10)(1.3-5.0) Leukemia SMR = 1.5 (10)(0.7-2.7)
Hayes <i>et al</i> ⁷⁴ 1990	Embalmers and funeral directors	US	PMR	3,649 White men; 397 Black men	None	None	Nasopharynx PMR = 1.9 (3)(0.4-5.5), White men PMR = 4.0 (1)(0.1-22), Black men Nasal (0 deaths; expected not provided) Lung PMR = 1.0 (285)(0.9-1.1), White men PMR = 0.8 (23)(0.5-1.1), Black men Brain PMR = 1.2 (24)(0.8-1.8) White men (0 deaths), Black men Lymphatic/hematopoietic PMR = 1.3 (100)(1.1-1.6), White men PMR = 2.4 (15)(1.4-4.0), Black men OR = 0.4 (0.1-1.8)
Brinton <i>et al</i> ⁷⁵ 1984	Reported by subject	US	Nasal cases-control	160 cases 290 controls	Ever	Smoking	OR = 1.6 (0.7-3.6), adjusted for wood dust and for men probably exposed for > 10 years
Olsen <i>et al</i> ⁷⁶ 1984	Work history	Denmark	Nasal cases-control	488 cases 2,465 controls	Ever and duration	Wood dust	OR = 2.5 (1.0-5.9), IH A exp. assessments OR = 1.6 (0.8-3.1), IH B exp. assessments
Hayes <i>et al</i> ⁷⁷ 1986	Work history	Nether- lands	Nasal cases-control	91 cases 195 controls	Level	Wood dust and smoking	OR = 0.3 (0.0-1.3), medium or high occupational exposure
Vaughan <i>et al</i> ^{78, 79} 1986	Environmental/ work history	US	Nasal cases-control	53 cases 552 controls	Level	Smoking, alcohol	OR = 1.5 (0.7-3.2), > 10 years with particulateboard exposure
Rousch <i>et al</i> ⁸⁰ 1987	Work history	US	Nasal cases-control	198 cases 605 controls	Probability of exposure	None	OR = 1.5 (0.6-3.9), exposed to high level for 20 or more years
Luce <i>et al</i> ⁸¹ 1993	Work history	France	Nasal cases-control	77 cases 409 controls	Probability of exposure	Wood dust	OR = 0.8 (0.3-2.0), probably exposed for 20+ years
Vaughan <i>et al</i> ^{78, 79} 1986	Work history	US	Nasopharynx case-control	27 cases 552 controls	Level	Smoking	OR = 2.1 (0.6-7.8), high occup. exposure
Olsen <i>et al</i> ⁷⁶ 1984	Work history	Denmark	Nasopharynx case-control	266 cases; 2,465 controls	Ever and duration	Wood dust	OR = 5.5 (1.6-19), home exposure for 10+ years OR = 0.7 (0.3-1.7), men
Rousch <i>et al</i> ⁸⁰ 1987	Work history	US	Nasopharynx case-control	147 cases; 509 controls	Probability of exposure	None	OR = 2.6 (0.3-22), women OR = 2.3 (0.9-6.0), exposed to a high level for more than 20 years
West <i>et al</i> ⁸² 1993	Work history	Philippines	Nasopharynx case-control	104 cases; 205 controls	Duration	Other occup. exposures	OR = 2.7 (1.1-1.7), < 15 years OR = 1.2 (0.5-3.2), ≥ 15 years
Partanen <i>et al</i> ⁸³ 1985	Wood industry	Finland	Lung, nested case-control	151 cases; 169 controls	Level, cumulative, duration	Other occup. exposures, smoking	OR = 2.9 (1.1-7.6), first exposure > 25 years ago OR = 1.93 (9)(0.78-4.74), < 5 ppm years OR = 0.63 (2)(0.16-2.58), 5+ ppm years
Siemiatycki <i>et al</i> ⁸ 1991	Work history	Canada	Lung case-control	1,082 cases; 2,648 controls	Level, duration	Smoking, alcohol, ethnic origin	OR = 1.7 (50)(1.1-2.5), any exposure OR = 1.0 (9)(0.2-3.7), substantial exposure
Hansen & Olsen <i>et al</i> ⁸⁴ 1995	Work history	Denmark	All cancer case-control	2,041 cancers	None	None	Nasopharynx OR = 1.3 (4)(0.3-3.2) Nasal OR = 2.3 (13)(1.3-4.0) Lung OR = 1.0 (410)(0.9-1.1)

^aSMR, PMR, or confidence intervals not in paper but calculated by IARC.⁵⁶ OR = odds ratio. PMR = proportional mortality ratio. SMR = standardized mortality ratio.

evaluated cancer risks from formaldehyde exposure. A thorough review was performed by IARC in 1995.⁵⁶ The critical investigations for evaluation are presented in Table 4. These include several large cohort studies of industrial workers, cohort and proportional mortality studies of members of professional groups such as embalmers, anatomists, and pathologists, and case-control studies of nasal and nasopharyngeal cancer. A variety of study designs was employed including cohort compared with national, local, and internal referents; case-control studies using other deaths, other cancers, and population samples for controls, and proportional mortality. Exposure comes from employment in various industries and professional settings, and from off-gassing from products in residences. Several studies^{61,65,68,77,79} developed quantitative exposure estimates and evaluated cancer risk by intensity and cumulative exposure. Some studies^{8,64,68,77-79,82} collected information on potential occupational and lifestyle confounders. This range of techniques and approaches ensures that no common bias could affect all the studies. In biomarker studies, micronuclei were increased in nasal mucus cells of plywood workers exposed to formaldehyde⁸⁵ and in buccal cells, nasal cells, and blood cells among mortician students in embalming classes.⁸⁶

Conclusions and recommendations

The data are not sufficient to state conclusively that any human cancer is caused by formaldehyde exposure.^{56,87-89} Lung cancer does not appear to be associated with formaldehyde exposure. Brain cancer and leukemia tend to be elevated in professionals exposed to formaldehyde. The failure to observe excesses of leukemia and brain cancer among industrially exposed workers and the difficulty of getting formaldehyde beyond the site of contact suggests that the excesses among professionals is due to bias or some other exposure. Four case-control studies found some evidence for an association between formaldehyde and nasal cancer,^{76,77,80,82,84} but others did not.^{75,78,79,81} These data are, at best, weak evidence for a relationship between formaldehyde and nasal cancer in humans.

Several factors may make nasal cancer less likely in humans than in rodents. Formaldehyde caused cancer in the nasal passages of rats, but most nasal cancer in humans occurs in the nasal sinuses. Formaldehyde appears not to penetrate into the nasal sinuses in rodents,⁵⁶ so it may not in humans either. The strongest evidence for a cancer-formaldehyde link comes from nasopharyngeal cancer. Excesses have been observed in studies of professional workers,⁷⁴ industrial workers,⁶² and in case-control studies,^{78-80,82,84} and meta-analyses^{37,89} suggest a possible exposure-response trend. A number of studies, however, did not find an association. IARC concluded that the evidence for formaldehyde as a nasopharyngeal carcino-

gen was limited because the number of exposed cases was too small to exclude chance,⁵⁶ but that confounding and bias were not likely problems.

Future research should focus on the possible formaldehyde-nasopharyngeal cancer association. Mechanistic studies offer a possible avenue of attack. In rats, formaldehyde is absorbed almost entirely in the nasal passages.⁵⁶ The smaller and shorter nasal passages in humans suggests that the nasopharynx may be the site most likely to be affected. DNA-protein cross-links occur in the nasopharynx of exposed monkeys.⁵⁹ Experimental studies also have shown the DNA-protein cross-links in rats are related to concentration and not to cumulative exposure. Most epidemiologic studies with some quantitative estimate of exposure used cumulative exposure. Peak exposures were evaluated in one study,⁶³ but more careful attention should be paid to short-term levels.

Mustard gas

Background

Mustard gas (bis[2-chloroethyl]sulphide) was used in chemical warfare during World War I. Large numbers of soldiers were poisoned. Mustard gas is an alkylating agent and was the first chemical shown to cause mutations in fruit flies.⁹⁰ It is distributed throughout the body, but is concentrated in the liver, lungs, and kidneys.⁹¹ It causes lung cancer in mice by inhalation or intravenous injection and mammary tumors and local sarcomas by injection.⁹⁰

Epidemiologic investigations

Epidemiologic studies have included soldiers gassed during combat and chemical manufacturing workers. The earliest study⁹² compared the mortality experience of 1,267 veterans in Great Britain poisoned during World War I with two unexposed groups (1,421 with chronic bronchitis and 1,114 with wartime injuries). The number of lung cancer deaths was about twice that expected from general population rates in the poisoned and the chronic bronchitis cohorts, but about as expected in the injury group. Beebe⁹³ studied US veterans poisoned from mustard gas and follow-up of this cohort was extended through 1965 by Norman.⁹⁴ The study included 2,718 men exposed to mustard gas in 1918; 1,855 men with postinfluenzal pneumonia, and 2,578 men with wounds in the extremities as controls. The lung cancer mortality among the poisoned men compared with the injury controls was 1.3 (CI = 0.9-1.9), based on 69 deaths. The proportion of smokers was 77 percent among the exposed veterans and 73 percent among the controls.

Cancer among workers engaged in the manufacture of mustard gas has been studied in Japan and England. The mortality follow-up of both has been extended recently.

Nishimoto *et al*⁹⁵ studied 1,632 workers employed at a mustard gas factory between 1929 and 1945 and followed through 1980. SMRs were 3.9 (70 deaths) for lung cancer, 0.9 (59 deaths) for gastrointestinal cancer, and 0.7 (44 deaths) for other cancers. The risk was approximately fivefold among workers engaged in production as well as those in other jobs with direct contact with the chemical such as laboratory, repair, inspection, and incineration. SMRs by duration of employment were about 1.0 for less than six months, 2.7 for six months to five years, and 7.0 for five or more years. There also appeared to be an excess of cancers of the nasal sinuses, pharynx, and larynx, but SMRs were not presented.

In England, 3,530 workers (2,498 and 1,032 women) engaged in the manufacture of mustard gas between 1940 and 1961 were followed for mortality through 1985 and compared with the experience of England and Wales and local areas.⁹⁶ Compared with national rates, significant excesses were observed for mortality from cancer of: the gum and mouth (SMR = 3.5, four deaths); pharynx (SMR = 5.5, 13 deaths); esophagus (SMR = 1.8, 16 deaths); stomach (SMR = 1.4, 53 deaths); larynx (SMR = 2.7, 10 deaths); and lung (SMR = 2.7, 189 deaths). Nonsignificant elevations occurred for: non-Hodgkin's lymphoma (1.7, nine deaths); leukemia (SMR = 1.5, 10 deaths); and cancers of the tongue (SMR = 1.9, three deaths); salivary gland (SMR = 4.2, two deaths); small intestine (SMR = 3.7, two deaths); and nose (SMR = 2.4, two deaths). Also elevated were all causes (SMR = 1.2, 1,542 deaths) and nonmalignant respiratory disease (SMR = 1.4, 283 deaths). RRs were associated with duration of exposure for cancers of the pharynx, larynx, lung, and other upper respiratory sites. The risk of respiratory cancer was not notably larger among production workers than individuals employed in other areas of the plant.

Mechanisms of mustard gas in humans is thought to occur by DNA damage since it causes mutations and chromosome aberrations in experimental animals. Takeshima *et al*⁹⁷ found two double mutations (G:C to A:T) in the *p53* suppressor gene in lung tissues from 12 lung cancer cases exposed to mustard gas during manufacturing and none among 12 nonexposed cases. The authors suggested that this double mutation might be characteristic of mustard gas exposure.

Conclusions and recommendations

Based on the studies of manufacturers, mustard gas is clearly carcinogenic in humans, particularly for upper airway cancers. The recent follow-up of the English cohort⁹⁶ suggests that more distant sites also may be influenced including esophagus, stomach, and possibly non-Hodgkin's lymphoma and leukemia. Studies from poisoned veterans are substantially lower than workers in production, which suggests that chronic exposure is

more of a cancer hazard than a single acute exposure. Exploration of mechanisms of action for mustard gas and susceptibility factors for the various tumors could be informative.

Sulfuric acid

Background

Sulfuric acid is a strong acid with low volatility and is typically present in the air as a mist. The potential for human exposure is considerable from its many uses in industry and from environmental pollution. Major industrial uses of sulfuric acid include production of isopropanol, ethanol, and sulfuric acid; treatment of metals, and the manufacture of soaps, detergents, and batteries. Sulfuric acid also is formed from sulfur dioxide in moist environments including the ambient air and human respiratory system.⁹⁸ Environmental formation is a concern for human health because of large sulfur-dioxide emissions in many countries.⁹⁹

The evidence for human carcinogenicity from sulfuric acid is based almost entirely on epidemiology. In the 1992 review by IARC,⁹⁸ no data on animal carcinogenicity were available to the working group. Since then, a study of lung cancer in rats evaluated sulfuric acid exposure in combination with other chemicals.¹⁰⁰ The authors concluded that sulfuric acid, in combination with nitrogen dioxide, promoted tumor formation following earlier administration of the carcinogen N-bis(2-hydroxypropyl)nitrosamine. In donkeys and rabbits, exposure to sulfuric acid has deleterious effects on mucociliary clearance, after an initial increase in clearance rate. In monkeys, long-term administration resulted in deleterious effects on pulmonary function and histology.⁹⁸

Epidemiologic investigations

Epidemiologic studies of cancer and sulfuric acid exposures are summarized in Table 5.

Cohort mortality, cohort incidence, and case-control studies indicate that exposure to sulfuric acid mists cause lung and laryngeal cancer. Risks for laryngeal cancer are often more than doubled and rise to fourfold or more in heavily exposed workers. RRs for lung cancer are lower than for laryngeal cancer, *i.e.*, usually less than 2.0. In studies that presented information, RRs were highest 10 or 20 years after initial exposure. Several studies^{8,106,107,113-117} were able to control for smoking, alcohol, and other potential confounding factors and found that RR were little affected by such adjustments.

There is little evidence that other cancers are affected, although excesses for brain,¹⁰¹ esophagus,^{8,108,109} liver,¹⁰⁸ bladder,^{109,110} stomach,¹¹² and kidney⁸ were noted in some studies. The mechanism of action for sulfuric acid with

Table 5. Selected epidemiologic studies of sulfuric acid and cancer

Author (ref.) Year	Industry/product	Country	Design	Study size	Exposure assessment	Confounders considered	Cancer findings (no. obs. and/or 95% confidence interval)
Alderson & Rattan ¹⁰¹ 1980	Isoropropanol	UK	Cohort	262	None	None	Lung SMR = 0.78 (2) Larynx (Not provided) Lung SMR = 2.48 (4)
Enterline <i>et al.</i> ¹⁰² 1982	Isoropropanol	US	Cohort	433	None	None	Larynx SMR = 5.04 (4)
Lynch <i>et al.</i> ¹⁰³ 1979	Isoropropanol	US	Cohort	335	None	None	Lung SMR = 0.94 (22) Larynx SMR = 2.00 (2)
Teta <i>et al.</i> ¹⁰⁴ 1992	Isoropropanol	US	Cohort	1,031	Duration	None	Lung SMR = 1.64 (35)(1.14-2.28) Larynx SMR = 1.93 (2)(0.23-6.99) Larynx SIR = 2.2 (4)
Beaumont <i>et al.</i> ¹⁰⁵ 1987	Metal treatment	US	Cohort	1,165	Ever/never and duration	None	Lung SMR = 1.36 (41)(0.97-1.84) (No trend with duration) Lung PMR = 1.06 (62) Larynx PMR = 1.43 (5)
Steenland <i>et al.</i> ^{106a} 1997	Metal treatment	US	Cohort	1,156	Duration	Smoking/alcohol	Lung RR ^b = 1.03 ^c (WM); 1.03 ^c (WF) Larynx RR = 1.10 ^c (WM); 1.03 (WF)
Steenland <i>et al.</i> ^{107a} 1989	Metal treatment	US	Cohort	1,156	Duration and latency	Smoking	<u>Incidence</u> Respiratory SMR = 2.00 (56) Bladder SMR = 3.77 (5)
Blair <i>et al.</i> ¹⁰⁸ 1980	Metal plating	US	PMR	1,292	None	None	<u>Mortality</u> Lung SMR = 1.69 (5)(0.55-3.90) Larynx SMR = 1.67 (1)(0.09-11.4)
Blair and Mason ¹⁰⁹ 1980	Metal plating	US	Geographic correlation	126 counties	None	None	<u>Incidence</u> Larynx SIR = 6.94 (5)
Englander <i>et al.</i> ¹¹⁰ 1988	Sulfuric acid	Sweden	Cohort	400	Duration	None	Lung SMR = 1.24 (109)(1.02-1.50) Larynx SMR = 1.28 (6)(0.47-2.80)
Forastiere <i>et al.</i> ¹¹¹ 1987	Soap	Italy	Cohort	347	Duration	None	OR = 4.6 (0.83-25.4)-Moderate level OR = 13.4 (2.08-86.0)-High level OR = 4.27 (1)(exposed to sulfuric, hydrochloric, and nitric acids) OR = 0.76 (22)(0.42-1.35)
Cooper <i>et al.</i> ¹¹² 1985	Battery	US	Cohort	4,519	Duration	None	OR = 1.86 (0.94-3.66) Questionable exp. OR = 2.95 (1.50-5.83) Probable exp. OR = 4.32 (1.64-11.37) Substantial exp. OR = 4.03 (5)(1.05-15.51)
Soskolne <i>et al.</i> ^{113d} 1984	Chemical workers	US	Laryngeal case-control	30 cases 175 controls	Average level	Smoking, alcohol	
Zemla <i>et al.</i> ¹¹⁴ 1987	Work history	Poland	Laryngeal case-control	328 cases 656 controls	None	Lifestyle factors	
Brown <i>et al.</i> ¹¹⁵ 1988	Work history	US	Laryngeal case-control	183 cases 250 controls	IH est.	Smoking/alcohol	
Soskolne <i>et al.</i> ¹¹⁶ 1992	Work history	Canada	Laryngeal case-control	204 cases 204 controls	Level, frequency, probability	Smoking, alcohol, occup. exp.	
Yamaguchi ¹¹⁷ 1992	Work history	Japan	Lung case-control	144 cases 676 controls	Ever	Smoking	Exposed to inorganic acids Lung OR = 1.2 (1.0-1.6)
Siemiatycki ⁸ 1991	Work history	Canada	Multiple cancer case-control	4,263 cancers	Level, probability, duration	Smoking, alcohol	

^aSame cohort as studies in reference 103. ^bRR = ratio of adjusted rates between metal plating and control counties. ^cRR is statistically significant.

^dSubjects from plant studied in reference 101. ^eWF = White females, WM = White males. OR = Odds ratio. SMR = standardized mortality ratio.

regard to human cancer is not clear. The frequency of sister chromatid exchanges was increased in lymphocytes of Chinese workers exposed to sulfur dioxide in a sulfuric acid factory. Exposure to acids apparently increases mucus viscosity and reduces lung function.⁹⁸ Experimental exposure to sulfuric acid in volunteers increase clearances of particles from large airways in the lung.¹¹⁸

Conclusions and recommendations

IARC⁹⁸ concluded that epidemiologic studies provided sufficient evidence that sulfuric acids cause human cancer. Laryngeal cancer is consistently excessive among exposed workers, while the association with lung cancer is only suggestive. The possible excess of lung cancer, however, is of special concern given its frequency of occurrence

and the opportunity for human exposure to sulfur dioxide (which can form sulfuric acid in moist conditions) from air pollution. Additional information on the risk of lung cancer risk is needed, particularly for low-dose situations. Development of quantitative exposure estimates for completed occupational studies could help fill this void. Although there is little evidence that sulfuric acid causes cancers other than lung and larynx, the potential for exposure to a number of upper respiratory and digestive system sites, suggests that these tumors should not be ignored in any future evaluations. In some industrial situations, exposure to more than one acid is possible and assessment of cancer risks from individual and combined exposures also are needed.

Table 6. Epidemiologic studies of cancer from exposure to vinyl chloride

Author (ref.) Year	Country	Design	Study size	Exposure assessment	Confounders	Cancer findings (no. obs. and/or 95% confidence interval)
Jones <i>et al</i> ¹²² 1988	UK	Cohort	5,498	Occupational groupings	None	Liver SMR = 2.20 ^a (3) Lung SMR = 0.87 (81) Brain SMR = 0.65 (4)
Smulevich <i>et al</i> ¹²³ 1988	USSR	Cohort	3,232	Qualitative	None	Liver (0 deaths) Lung SMR = 1.39 (17) Brain SMR = 1.54 (4) Leukemia SMR = 5.00 ^b (5)
Wu <i>et al</i> ¹²⁴ 1989	US	Cohort/nested case-control	3,635 exp.	Cumulative exposure	None	<u>Vinyl Chloride Subcohort</u> Liver SMR = 3.33 (14)(2.02-5.21) Lung SMR = 1.15 (80)(0.95-1.39) Brain SMR = 1.45 (10)(0.79-2.48) Lymphatic/hematopoietic SMR = 0.78 (15)(0.48-1.21)
Hagmar <i>et al</i> ¹²⁵ 1990	Sweden	Cohort	2,042	Cumulative and duration of exposure	None	<u>Incidence</u> Liver SMR = 1.89 (2)(0.23-6.84) Lung SMR = 1.86 (13)(0.99-3.18) Brain SMR = 2.29 (6)(0.84-4.98)
Simonato <i>et al</i> ¹²⁶ 1991	Italy, Norway, Sweden, UK	Pooled cohort	12,706	Cumulative exposure	None	<u>Mortality</u> Liver SMR = 2.86 (24)(1.83-4.25) Lung SMR = 0.97 (144)(0.82-1.14) Brain SMR = 1.07 (14)(0.59-1.80) Leukemia SMR = 0.82(11)(0.41-1.47) <u>Incidence</u> Liver SIR = 3.03 (7)(1.22-6.23) Lung SIR = 1.52 (22)(0.95-2.30) Brain SIR = 1.59 (8)(0.68-3.12)
Laplanche <i>et al</i> ¹²⁷ 1992	France	Cohort	1,100	None	None	Liver, angiosarcoma (3 exposed; 0 unexposed) Lung (8 exposed; 6 unexposed)
Dell & Teta ¹²⁸ 1995	US	Cohort	5,945	Duration	No	Liver SMR = 1.34 (7)(0.54-2.76) Lung SMR = 1.10 (124)(0.92-1.31) Brain SMR = 0.63 (6)(0.23-1.37) Leukemia SMR = 0.98 (12)(0.50-1.70)

^a Calculated from observed and expected numbers summed across all occupational groups.

^b Statistically significant at the < 0.05 level.

SIR = standardized incidence ratio.

SMR = standardized mortality ratio.

Vinyl chloride

Introduction

Vinyl chloride, or monochloroethylene, is a colorless gas. Its major use is in polyvinyl resins for the production of plastic pipes, floor coverings, and in electrical and transportation applications.¹¹⁹ Vinyl chloride produced cancers of the mammary gland, lung, Zymbal gland, skin, and angiosarcoma of the liver in mice, rats and hamsters by oral administration and inhalation.^{2,119} Ethanol appears to enhance formation of liver tumors (including angiosarcomas) associated with vinyl chloride.¹²⁰ Chromosomal aberrations, sister chromatid exchanges, and micronuclei were increased in exposed rodents and the chemical alkylated DNA in several tissues in the mouse.²

Epidemiologic investigations

Vinyl chloride is a classic modern case of the value of observations by astute clinicians. The report of three cases of the very rare tumor, angiosarcoma of the liver, among men who worked in the manufacture of polyvinyl chloride resins conclusively established the association.¹²¹ Further surveys of medical records and pathologic material uncovered a number of additional cases of angiosarcoma of the liver.¹¹⁹

Cohort studies consistently show an excess of liver cancer among vinyl chloride-exposed populations (Table 6). Risks were very large among heavily exposed workers, *i.e.*, autoclave operators in the UK (SMR = 60)¹²² and the four-country study (SMR = 9.0).¹²⁶ The pooled analysis showed a very strong cumulative exposure-response gradient (< 2,000 ppm-years, RR = 1.0; 2,000-5,999 ppm-years, RR = 6.8; 6,000-9,999 ppm-years, RR = 24.7; 10,000+ ppm-years, RR = 45.4).¹²⁶ Leukemia and cancers of the lung, brain, larynx, and pancreas were excessive in some studies, but few were statistically significant and none showed exposure-response gradients. An interesting finding from the study in the Soviet Union¹²³ was that the RR for total cancer mortality among the heavily exposed was considerably greater among women (SMR = 4.4, 12 deaths) than among men (SMR = 1.0, 28 deaths). No breast cancers occurred among the women in this cohort. A biomarker study of workers exposed to vinyl chloride¹²⁹ evaluated the presence of p53 mutations by enzyme immunoassay. Anti-p53 antibodies occurred in five of 15 workers with angiosarcoma of the liver and in only four of 77 workers without clinically evident cancer. In two cases, the anti-p53 antibodies were detected in serum collected four months and 11 years prior to diagnosis of cancer.

Conclusions and recommendations

The epidemiologic data show a very high RR for angiosarcoma of the liver from vinyl chloride exposure. The multi-country study shows no evidence of an exposure-

response gradient for other tumors. The large size of this cohort and quality of the exposure evaluation (which was able to show a strong exposure-response relationship for angiosarcoma of the liver) suggest that vinyl chloride is not likely to be associated strongly with cancers other than liver in humans.

Overall summary

Several issues are apparent from this review of the epidemiologic literature on eight reactive chemicals. Considerable information is available from epidemiologic studies regarding the human carcinogenicity of these substances. Sufficient evidence exists for a causal relationship between cancer and BCME, mustard gas, sulfuric acid, and vinyl chloride. For the other chemicals – *i.e.*, acrylonitrile, butadiene, ethylene oxide, and formaldehyde – the epidemiologic evidence is less conclusive. Even for the substances that are clearly human carcinogens, however, a number of questions arise including how many cancer sites are affected, what is the shape of the exposure-response curve, and what mechanisms of action are involved?

Usually a clear association between an exposure and one cancer is sufficient for review groups to conclude that the chemical is a human carcinogen. Which, and how many, cancers are affected, however, is important in assessing the public health impact. Chemicals causing several common tumors would be of more concern than those causing a single, rare cancer. The epidemiologic data for several of these reactive chemicals suggests associations with multiple cancers. Unfortunately, reports do not always present information on all sites. This probably means that no other cancer showed a striking excess, but one is unsure. Many studies lack quantitative exposure assessments and this is a major limitation. Without such information it is difficult to determine whether a small overall excess is a real or a chance finding. Quantitative estimates allow exposure-response evaluations, which are an important criterion in assessing causality.

For some chemicals, there was considerable experimental and human pharmacologic and mechanistic data, which facilitates interpretation. The ability of some chemicals to cause cancers at multiple sites, however, raises the possibility that they may operate through more than one mechanism. One should be cautious in assuming that there is only one mechanism which explains all carcinogenic activity. Finally, the potential for confounding must be considered in any epidemiologic review. For the chemicals evaluated here, confounding was not much of a problem because some investigations on each chemical obtained information on major potential confounders and statistical adjustment had little effect on the estimate of relative risk.

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