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Acetaldehyde and Formaldehyde: Is There a Cancer Risk for Man?

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Abstract
Acetaldehyde and particularly formaldehyde are genotoxic and when chronically inhaled by laboratory rodents can produce nasolaryngeal tumours, the distribution of which parallels the severity of irritation to the upper respiratory tract. The carcinogenicity of high concentrations of these compounds may result from a combination of weak tumour-initiating genotoxicity and tumour-promoting activity associated with mucosal cytotoxicity, irritation and hyperplasia. Epidemiological evidence is lacking for a cancer risk following exposure to the low concentrations of these compounds present in ambient air, although laboratory evidence suggests that risk may be increased following chronic exposure to high concentrations.

Introduction

Man is unavoidably exposed to both acetaldehyde and formaldehyde in the course of everyday living, exposure being increased by environmental, occupational and behavioural factors. The question of whether specific chemicals such as these can increase the risk of human cancer may be addressed by examining evidence that has accumulated from a range of approaches. In this review, the findings of genotoxicity, nasal carcinogenicity and irritancy to the upper respiratory tract of laboratory animals following inhalation of acetaldehyde and formaldehyde are considered alongside the outcome of epidemiological studies. The risk to man is assessed in relation to the developing concepts of environmental carcinogenesis.

Laboratory Assessment of Acetaldehyde and Formaldehyde Toxicity

Formaldehyde was evaluated for carcinogenic risk to humans by the International Agency for Research on Cancer (IARC) in 1982 [1], and acetaldehyde was similarly evaluated 3 years later [2]. In summary, both substances gave positive results in some tests for genotoxicity and both substances proved irritant for the upper respiratory tract, especially the nasal cavity, of laboratory rodents. Prolonged exposure to concentrations which caused degeneration, atrophy, hyperplasia and metaplasia of the epithelium of the nose also gave rise to nasal tumours. Most of the tumours arose near the front of the nose while the severity of irritant effects and the incidence of nasal

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Table 1. Results of tests involving inhalation exposure of hamsters to acetaldehyde

Tests	Effects	Reference
Inhalation (4,560 ppm; 7 h/day, 5 days/week; 90-day study)	Severe inflammation, hyperplasia and metaplasia in nose Mild changes in bronchi and lungs	3
Inhalation (1,500 ppm; 7 h/day, 5 days/week, 52-week study)	Severe inflammatory changes in nose No neoplasms in nose, larynx or lung No enhancement of tumour induction by known carcinogens	4
Inhalation (2,500 ppm reducing to 1,650 ppm; 7 h/day, 5 days/week, 52-week study, then observation to 81 weeks)	Nasal and laryngeal tumours No tumours of trachea, bronchi or lungs	5

Table 2. Influence of concentration of inhaled acetaldehyde on epithelial integrity in nose, larynx and lungs in rats[a] (data from Woutersen and Feron [6])

		Exposure, ppm			
		400	1,000	2,000	5,000
Nose	Degeneration	±	+	+++	++++
	Hyperplasia	0	+	+++	++++
	Metaplasia	0	+	+++	++++
Larynx		0	0	+	++++
Trachea		0	0	0	++++

0/+ = Absence/presence of lesion.

[a] Exposure for 6 h/day, 5 days/week, for 4 weeks.

tumours was much less at the back of the nose. Further down the respiratory tract (i.e. in the larynx, trachea, bronchi and lungs) irritant effects were only seen in response to prolonged exposure to very high concentrations. Acetaldehyde appears to be one or two orders of magnitude less active than formaldehyde in all these effects.

The laboratory evidence for the irritant and carcinogenic effects of inhaled *acetaldehyde* (400–5,000 ppm) in the upper respiratory tracts of hamsters and rats is summarised in tables 1 and 2, respectively. Feron et al. [5] reported 13 instances of nasal or laryngeal tumours in 58 hamsters exposed to acetaldehyde for 52 weeks, no such tumours being found in control animals. There were no striking differences in the incidence of various tumour types between male and female animals.

The laboratory data for the effects of inhaled *formaldehyde* (2–14.3 ppm) in rats and mice are summarised in tables 3 and 4, respectively. Rats appeared to be rather more sensitive to the nasal irritant and carcinogenic effects than mice.

Insofar as both acetaldehyde and formaldehyde are present in foodstuffs and beverages, and particularly since acetaldehyde is formed during the intracellular oxidation of ethanol [9], it is of interest to see whether there is any evidence that orally administered acetaldehyde or formaldehyde predispose to neoplasia. In the case of *acetaldehyde* no long-term animal studies of the effects of prolonged oral administration have been reported. However, hyperkeratosis of the forestomach epithelium was seen in rats exposed to 625 mg/kg/day acetaldehyde in the drinking water daily for 28 days [10].

Taking all the available evidence together, it is reasonable to assume that rats can be exposed to relatively high levels of orally administered acetaldehyde without risk of neoplasia at any site.

For *formaldehyde,* a far more potent irritant and carcinogen than acetaldehyde when administered by the inhalation route, Til et al. [11] have recently reported the results of a 2-year study in rats involving exposure via the drinking water to up to 82 mg/kg/day in the case of males

Table 3. Nasal cavity neoplasms and other lesions in rats exposed to formaldehyde vapour[a] (data from Swenberg et al. [7])

Exposure, ppm	0		2.0		5.6		14.3	
	M	F	M	F	M	F	M	F
Nasal cavity								
Squamous carcinoma	0	0	0	0	1	1	51	52
Undifferentiated carcinoma or carcinosarcoma	0	0	0	0	0	0	3	0
Other carcinoma	0	0	0	0	0	0	1	1
Polypoid adenoma	1	0	4	4	6	0	4	1
Inflammatory hyperplastic metaplastic and dysplastic lesions	0	0	+	+	+	+	+	+
Trachea								
Squamous metaplasia	0	0	0	0	0	0	+	+
Dysplasia	0	0	0	0	0	0	+	+

0/+ = Absence/presence of lesion.

[a] 6 h/day on 5 days/week for up to 2 years, then observed for up to 6 months (114–119 animals/sex/group).

Table 4. Nasal cavity neoplasms and other lesions in mice exposed to formaldehyde vapour[a] (data from Kerns et al. [8])

Exposure, ppm	0		2.0		5.6		14.3	
	M	F	M	F	M	F	M	F
Squamous carcinoma	0	0	0	0	0	0	2	0
Epithelial metaplasia	0	0	0	0	+	+	+	+
Epithelial dysplasia	0	0	0	0	+	+	+	+
Purulent/non-purulent thinitis	0	0	0	0	+	+	+	+
Atrophy of olfactory epithelium	0	0	0	0	+	+	+	+

0/+ = Absence/presence of lesion.

[a] 6 h/day on 5 days/week for up to 2 years, then observed for up to 6 months (119–121 animals/sex/group).

and 109 mg/kg/day in the case of females. No excess incidence of neoplasia at any site was observed, although various non-neoplastic changes (including hyperplasia, hyperkeratosis, focal ulceration and atrophic gastritis) were seen in the forestomach and glandular stomach in response to the highest dose levels. At these dose levels, food intake, water consumption and body weight gain were reduced. A no-adverse-effect level for orally administered formaldehyde of 15 mg/kg/day was established for males, the corresponding figure for females being 21 mg/kg/day.

Soffritti et al. [12] claim to have observed dose-related increases in lymphoreticular, stomach and intestinal neoplasms in Sprague-Dawley rats exposed to up to 2,500 mg/l formaldehyde via the drinking water. This is equivalent to about 250 mg/kg/day – i.e. about twice the highest daily dose studied by Til et al. [11]. However, they gave insufficient details of their experimental procedures or classification criteria, used only small numbers of animals and aggregated neoplasms of widely differing types in an unacceptable manner in their analyses.

Human Exposure to Acetaldehyde and Formaldehyde

Aldehydes are formed by oxidation of hydrocarbons by sunlight and by incomplete combustion of wood, gas, oil and other materials. Human exposure to *acetaldehyde* results from its presence in natural foodstuffs and in air,

both indoor and outdoor, and from its generation as the primary metabolite of ethanol [2]. Table 5 indicates the major sources contributing to the presence of acetaldehyde in the outside air (USA), the residential combustion of wood and the roasting of coffee being the most notable. The combustion of fossil fuels and incineration are the main sources of *formaldehyde* in outside air. Examples of airborne concentrations of formaldehyde in various occupational and non-occupational environments are given in table 6.

Concentrations of formaldehyde in urban air are reported to range between 0.01 and 12 μg/m^3, whereas acetaldehyde levels range between 0 and 124 μg/m^3, being mainly below 25 μg/m^3. The daily rate of loss of acetaldehyde through photolysis or reaction with hydroxyl radicals is estimated to be 80% [1, 2].

Both acetaldehyde and formaldehyde are found in tobacco smoke and although there is wide variation between brands, the daily intake from this source by smokers is likely to be negligible (table 7).

Table 5. Main sources of acetaldehyde in the outside air (USA; data from IARC [2])

	Emission (1,000 kg/year)
Residential combustion of wood	5,056
Coffee roasting	4,411
Acetic acid manufacture	1,460
Vinyl acetate manufactured from ethylene	1,094
Ethanol manufacture	58
Acrylonitrile manufacture	52
Acetic acid manufactured from butane	21

Table 6. Examples of airborne concentrations (mg/m^3) of formaldehyde in occupational and non-occupational environments

Occupational	
Embalming	up to 6.5
Sheepskin dyeing	up to 78
Resin manufacture and paper production	up to 37
Textile plants	0.25
Shoe factories	2.4
Wooden furniture plants	1.7
Adhesive plants	2.2
Foundries	3.4
Construction sites	3.5
Hospitals	0.9
Schools	0.3
Non-occupational	
Homes constructed with particle board	up to 2.25
Mobile homes	up to 3.1
Homes after urea-formaldehyde foam insulation	up to 39

Table 7. Illustrative daily intakes of acetaldehyde and formaldehyde from tobacco smoke (mg/kg/day)

	Acetaldehyde	Formaldehyde
10 cigarettes/day	0.1	0.005
20 cigarettes/day	0.2	0.01
40 cigarettes/day	< 0.4	< 0.02

Human Toxicity and Epidemiology of Acetaldehyde Exposure

Acetaldehyde is mildly irritant to the eyes and upper respiratory tract of humans under conditions of inhalation exposure for 15–30 min to airborne levels in the range of 50 ppm (90 mg/m^3) to 134 ppm (241 mg/m^3) [13, 14]. Prolonged skin exposure can lead to irritation or sensitisation. There is no actual evidence that acetaldehyde is genotoxic for humans and no reliable epidemiological data relevant to the assessment of acetaldehyde for carcinogenicity.

The Formation of Acetaldehyde from Ethanol

Acetaldehyde is the first product of ethanol oxidation in the liver. However, after its formation, its half-life is very short because it is rapidly metabolised to acetate by the enzyme aldehyde dehydrogenase. Inhibition of this enzyme by disulfiram leads to a 5- to 10-fold build-up of acetaldehyde in the blood and this leads to nausea, vomiting, headache and weakness. The distressing experience which results when ethanol and disulfiram are both present in the body is the basis for this compound's application in the treatment of chronic alcoholism.

It is not known whether acetaldehyde is implicated in the pathogenesis of cirrhosis of the liver in heavy drinkers or in the slightly increased risk of liver cancer among cirrhotics. However, it seems quite clear that, irrespective of the metabolism of ethanol to acetaldehyde, moderate indulgence in ethanol is not associated with increased risk of liver cancer. In support of this conclusion we now have the results of the study by Til et al. [11] on formaldehyde, in which the liver was not a target for any form of toxicity

in rats exposed for 2 years to high concentrations in the drinking water. Almost certainly the same would hold for orally administered acetaldehyde if it were tested in the same way.

One question remains and this concerns the association between ethanol consumption and laryngeal cancer [15]. In this context, it would be pertinent to know whether the laryngeal epithelium can metabolise ethanol to acetaldehyde and if so, whether the acetaldehyde is efficiently converted to acetate.

Human Toxicity and Epidemiology of Formaldehyde Exposure

It has long been known that formaldehyde is acutely irritant to the eyes, nose and throat of humans and that bronchospasm, dyspnoea and increased sputum production may be caused by exposure to it. Individuals appear to vary widely in the levels of formaldehyde in ambient air which they can tolerate, although 4–5 ppm is intolerable to most people. In a minority of humans formaldehyde acts as a potent allergen, and can provoke skin reactions in sensitised subjects.

Following the publication of the finding that inhaled formaldehyde causes nasal tumours in rats [7], there followed a flurry of epidemiological studies aimed at determining whether there is a cancer risk from inhaled formaldehyde in man [e.g. 16–19]. The outcome of the epidemiological studies remains inconclusive. If there is any risk at all, it is likely to be very small [20] and probably too small to be detected by available epidemiological techniques, particularly since in many studies there were confounding variables such as simultaneous exposure to wood-dust or organic solvents.

Possible Explanation for Nasal Cancer Induction by Formaldehyde and Acetaldehyde in Rodents

Although epidemiological studies have not clearly indicated a cancer risk from acetaldehyde or formaldehyde in man, the evidence of genotoxicity and nasal carcinogenicity in laboratory rodents remains. Woutersen et al. [21] have suggested an explanation for the tumour-inducing properties of these agents which raises some interesting and important points. These authors consider that the genotoxicity of formaldehyde depends upon its ability to react with single-strand DNA during cell division. Since cell turnover in intact nasal epithelium is usually low, the tumour-initiating genotoxicity of formaldehyde would therefore be low unless exposure also leads to mucosal damage and regenerative hyperplasia. Thus, the cytotoxic effect of high concentrations of formaldehyde is probably the crucial determinant in the tumour-promoting property and therefore in the nasal cancer risk of this compound. The combination of weak tumour-initiating genotoxicity combined with potent tumour-promoting activity at high levels of exposure is probably found in acetaldehyde also.

If this theory is right, then the data for these two aldehydes provide an example of the fact that evidence of genotoxicity is not necessarily indicative of carcinogenic risk and of the fact that severe irritation involving regenerative hyperplasia needs to be taken far more seriously than at present as a possible contributor to cancer risk. These important ideas are given further consideration in the following section.

Changing Views on Environmental Carcinogenesis

Observations made in the late 18th, the 19th and the early 20th centuries suggested that the development of certain cancers in man could be attributed to occupational exposure to naturally occurring and synthetic substances such as coal tar, soot, unrefined mineral oils and aniline dyes. Direct demonstration was made early this century that cancers could be produced in laboratory animals following exposure to chemical agents, and it was slowly appreciated that a high proportion of human cancer might be environmental as distinct from genetic in origin. The potential value of screening environmental chemicals for possible carcinogenic activity was not widely considered much before 1970, although persuasive evidence for the importance of environmental factors as distinct from genetic ones in relation to cancer causation came from studies on migrants from one country and culture to another. In such migrants, and particularly in their children and grandchildren, the incidences of the cancers most prevalent in the land of origin fell, while the incidences of cancers that were uncommon in the land of origin rose to be more like those in the country of adoption. This was particularly evident in migrants from Japan to the USA and Hawaii, and is forcefully demonstrated by the data shown in table 8.

The 1970s also heralded the development of quick and inexpensive tests for genotoxicity, led by the view that a change from a normal cell to a cancer cell was dependent on genetic damage, so that carcinogenicity started with

Table 8. Changes in cancer risk for Japanese men and women who migrate to the USA (data from Haenszel [22])

Standardised mortality ratios (Japan = 100) for cancers of		Japanese-born	Japanese-born migrants to USA	USA-born Japanese	USA White
Men	Stomach	100	72	38	17
	Colon	100	374	288	489
	Lung	100	306	166	316
	Leukaemia	100	314	–	265
Women	Stomach	100	55	48	18
	Colon	100	218	219	483
	Breast	100	166	136	591
	Ovary	100	337	–	535
	Cervix uteri	100	52	33	48

mutagenicity. Accordingly, a genotoxic substance could be regarded as potentially carcinogenic. Materials, such as asbestos fibres, which were known to be carcinogenic in man and animals, but which consistently gave negative results in tests for genotoxicity, spurred on the development of tests for genotoxicity, without perhaps provoking the question as to whether all carcinogens are mutagens. Undeniably, there are substances which, in excessive dosage, predispose to cancer in man and/or animals but which are not demonstrably genotoxic.

Conversely, it is now clear that many naturally occurring substances, many normal body constituents, and many metabolites of normal foodstuffs are capable of causing genetic damage and that during the course of everyday life, cells are constantly suffering damage to their nuclear DNA. However, elaborate and efficient mechanisms exist for the repair of such damage, so that most of it is effectively repaired very soon after it is caused. If this defense fails, the impact of unrepaired DNA damage is reduced in tissues such as the bone marrow, the lining of the gut, and the epidermis, where there is a rapid turnover of cells. In these tissues, DNA damage to cells which are destined to die and be shed without having the chance to give rise to clones of mutant cells is of no consequence. In such tissues it is only persistent damage in the small minority of stem cells which is potentially of importance. Finally, mutant cells are apt to be recognised by lymphocytes because they exhibit abnormal proteins on their surfaces. Such recognition stimulates immune reactions which result in the elimination of the mutant cells, a third line of defence.

Although the vast majority of damage to DNA that occurs under physiological conditions or during ordinary metabolic processes is quickly and efficiently repaired, a little may not be, so that unrepaired DNA damage, or ill-repaired DNA damage, may tend to accumulate with age among the cells of multicellular organisms. It is probably this slowly accumulating DNA damage in somatic cells which is responsible both for ageing-related diseases and for increasing risk of the development of cancer with age.

During the 1970s and early 1980s, the focus of popular attention was the suggestion that most human cancers are due to exposure to man-made chemicals such as pesticides, food additives, pharmaceutical agents, industrial chemicals involved in occupational exposure, and environmental contaminants. In contrast, Doll and Peto [23], on the basis of a wide-ranging review of data of many different kinds, concluded that this list of agents contributed but little to the overall human cancer burden: food per se, smoking, alcohol and unknown factors are much more important (table 9).

Similarly, Ames, famed for his work in the area of testing for genotoxicity, has recently [24, 25] subscribed to the view that the natural environment is rich in genotoxins and that any attempt to reduce the exposure of humans to genotoxic agents must take this fact into account.

Our own research [26, 27] along with that of many others, has shown that calorie intake has a major impact on longevity, the incidence of ageing-related diseases and the incidence of many forms of cancer in laboratory rodents. Some of these findings are presented in table 10.

Carcinogenesis is clearly complex and multifactorial. However, it is reasonable to conclude that most human cancers are associated with ageing-related changes and/or prior cellular proliferation in the tissues from which they

Table 9. Proportions of cancer deaths attributed to various factors (data from Doll and Peto [23])

Factor or class of factors	Percent of all cancer deaths		
	best estimate	range of acceptable estimates	
Tobacco	30	25	40
Alcohol	3	2	4
Diet	35	10	70
Food additives	<1	-5	2
Reproductive and sexual behaviour	7	1	13
Occupation	4	2	8
Pollution	2	<1	5
Industrial products	<1	<1	2
Medicines and medical procedures	1	0.5	3
Geophysical factors	3	2	4
Infection	10?	1	?

Table 10. Effect of restriction of food intake (standard diet) to 80% of ad libitum (AL) on survival and incidence of certain neoplasms in rats (data from Roe [27])

		Males		Females	
		AL	80% AL	AL	80% AL
Survival, %					
≤ 24 months		72	87**	77	89**
≤ 30 months		41	69****	42	76****
Neoplasms, %					
Pancreas	islet cell	10	1***	2	1
	exocrine	5	0**	0	0
Pituitary	anterior lobe	30	14****	62	46***
	intermediate lobe	13	9	6	0***
Subcutaneous		18	6**	1	2
Mammary		0	0	37	9****
Lung		6	0**	4	0**
Mesenteric lymph node		16	8*	9	3**
Malignant neoplasm any site		30	13****	34	18****

* $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$; **** $p < 0.001$.

arise [28]. The accumulation of unrepaired or malrepaired DNA damage, and the expression of such damage in the forms of clones of cells carrying similarly defective DNA, is favoured by increased cellular metabolism, and by increased cell proliferation and increased cell turnover. This can explain why mice start to develop ageing diseases when they are only about 2 years old, whereas in humans the start date is not until they are about 60 years of age. The basal metabolic rate and the rate of cell turnover is many times faster in the mouse than in man [29, 30].

The occurrence of ageing-related changes and of cancers of particular tissues is likely to be favoured by chronic irritation leading to prolonged cellular proliferation and increased cell turnover. This would explain why excessive exposure to non-genotoxic natural hormones predisposes to increased cancer risk in hormone-responsive tissues. Also, it would explain why natural non-genotoxic food ingredients such as lactose can predispose to adrenal medullary neoplasia in rats [31]. It raises the question of which factor is more important in relation to the association between smoking and lung cancer: is it the presence of low levels of genotoxins in the smoke or could it be that irritation and resulting increased cellular proliferation in the epithelium of the respiratory tract plays a more important role? In the case of acetaldehyde and formaldehyde it seems clear that irritation and cellular proliferation are the more important.

Cancer Risks from Acetaldehyde and Formaldehyde

Are humans at increased risk of developing nasal or other cancers as a consequence of exposure to either of these substances? The answer, based on available epidemiological evidence, seems to be probably 'no'. The laboratory evidence is consistent with there being a need for severe damage to the nasal epithelium leading to necrosis and reparative hyperplasia for there to be any increased risk of cancer development. The genotoxicity of acetaldehyde and formaldehyde is by itself not enough to enhance the risk of cancer development. Thus the laboratory evidence is consistent with the conclusion that humans are not at cancer risk from low levels of acetaldehyde or formaldehyde in ambient air. Only if they were exposed to concentrations that led to severe irritation of the nasal epithelium with reparative hyperplasia is the risk of developing nasal cancer likely to be increased.

References

1 International Agency for Research on Cancer (IARC): Some industrial chemicals and dye stuffs. Monogr Eval Carcinog Risk Chem Hum 1982;29:345–389.
2 International Agency for Research on Cancer (IARC): Allyl compounds, aldehydes, epoxides and peroxides. Monogr Eval Carcinog Risk Chem Hum 1985;36:101–132.
3 Kruysse A, Feron VJ, Til HP: Repeated exposure to acetaldehyde vapor. Studies in Syrian golden hamsters. Arch Environ Health 1975; 30:449–452.
4 Feron VJ: Effects of exposure to acetaldehyde in Syrian hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine. Prog Exp Tumor Res 1979;24:162–176.
5 Feron VJ, Kruysse A, Woutersen RA: Respiratory tract tumours in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene or diethylnitrosamine. Eur J Cancer Clin Oncol 1982;18:13–31.
6 Woutersen RA, Feron VJ: Inhalation toxicity of acetaldehyde in rats. Progression and regression of nasal lesions after discontinuation of exposure. Toxicology 1987;47:295–305.
7 Swenberg JA, Kerns WD, Mitchell RI, Gralla EJ, Pavkov KL: Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res 1980;40:3398–3402.
8 Kerns WD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA: Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res 1983;43:4382–4392.
9 Eriksson CJ: Human blood acetaldehyde concentration during ethanol oxidation (update 1982). Pharmacol Biochem Behav 1983;18 (suppl 1):141–150.
10 Til HP, Woutersen RA, Feron VJ, Clary JJ: Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking-water study in rats. Food Chem Toxicol 1988;26: 447–452.
11 Til HP, Woutersen RA, Feron VJ, Hollanders VH, Falke HE, Clary JJ: Two-year drinking-water study of formaldehyde in rats. Food Chem Toxicol 1989;27:77–87.
12 Soffritti M, Maltoni C, Maffei F, Biagi R: Formaldehyde: An experimental multipotential carcinogen; in Mehlman MA (ed): Advances in Modern Environment Toxicology. Princeton, Scientific Publications 1990, vol 17, pp 225–256.
13 Silverman L, Schulte HF, First MW: Further studies on sensory responses to certain industrial solvent vapors. J Ind Hyg Toxicol 1946; 28:262–266.
14 Sim VM, Pattle RE: Effect of possible smog irritations on human subjects. JAMA 1957; 165:1908–1913.
15 International Agency for Research on Cancer (IARC): Alcohol drinking. Monogr Eval Carcinog Risk Chem Hum 1988;44:1–378.
16 Olsen JH, Jensen SP, Hink M, Faurbok K, Breum NO, Jenson OM: Occupational formaldehyde exposure and increased nasal cancer risk in man. Int J Cancer 1984;34:639–644.
17 Hagmar L, Bellander T, Englander V, Ranstam J, Attewell R, Skerfving S: Mortality and cancer morbidity among workers in a chemical factory. Scand J Work Environ Health 1986; 12:545–551.
18 Costantini AS, Paci E, Miligi L, Buiatti G, Martelli C, Lenzi S: Cancer mortality among workers in the Tuscan tanning industry. Br J Ind Med 1989;46:384–388.
19 Blair A, Stewart PA, Hoover RN: Mortality from lung cancer among workers employed in formaldehyde industries. Am J Ind Med 1990; 17:683–699.
20 Report of the Ad Hoc Panel on Health Aspects of Formaldehyde: Epidemiology of chronic occupational exposure to formaldehyde. Universities Associated for Research and Education in Pathology. Toxicol Ind Health 1988;4:77–90.
21 Woutersen RA, Appelman LM, Van Garderen-Hoetmer A, Feron VJ: Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. Toxicology 1986;41:213–231.
22 Haenszel W: Cancer mortality among the foreign-born in the United States. J Natl Cancer Inst 1961;26:37–132.
23 Doll R, Peto R: The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66:1191–1308.
24 Ames BN: Dietary carcinogens and anticarcinogens. Oxygen radicals and degenerative diseases. Science 1983;221:1256–1264.
25 Ames BN, Profet M, Gold LS: Dietary pesticides (99.99% all natural). Proc Natl Acad Sci USA 1990;87:7777–7781.
26 Salmon GK, Leslie G, Roe FJC, Lee PN: Influence of food intake and sexual segregation on longevity, organ weights and the incidence of non-neoplastic and neoplastic diseases in rats. Food Chem Toxicol 1990;28:39–48.
27 Roe FJC: 1,200-Rat Biosure Study: Design and overview of results; in Fishbein L (ed): Proc ILSI Conf 'Biological Effects of Diet Restriction' Washington, March 1991, in press.
28 Roe FJC: Non-genotoxic carcinogenesis: Implications for testing and extrapolation to man. Mutagenesis 1989;4:407–411.
29 Ames BN, Gold LS: Too many rodent carcinogens: Mitogenesis increases mutagenesis. Science 1990;249:970–971.
30 Cohen SM, Ellwein LB: Cell proliferation in carcinogenesis. Science 1990;249:1007–1011.
31 Roe FJC, Baer A: Enzootic and epizootic adrenal medullary proliferative disease of rats: Influence of dietary factors which affect calcium absorption. Hum Toxicol 1985;4:27–52.