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SOME FACTS AND LEGISLATION CONCERNING POLYCYCLIC AROMATIC HYDROCARBONS IN SMOKED FOODS

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Abstract - Although smoking of foods has been long established as a method for its preservation, the possibility that smoking can introduce compounds which may be carcinogenic to man poses problems for legislation relating to public health.

While evidence from industrial exposures which correlate cancer incidence and benzo a pyrene intake is strong, it must be recognized that although they have not been measured, other chemical carcinogens might be involved in the smoking of food. The most important example here would be N-nitroso compounds.

Since PAH are ubiquitous in our environment a major problem is to take decisions on levels which can be tolerated. Present evidence suggests that PAH contamination of green vegetables mainly from traffic fumes is likely to be at least as great as the contamination of smoked food where modern technology is employed. Other factors which may affect the situation are co- and anti-carcinogenic factors which may be associated with different diets of which little is at present known.

Although there is generally a reluctance to legislate specifically for carcinogens, a number of nations have introduced legislation to limit aflatoxin content in foods. As good methodology exists for the determination of PAH and the technology exists to limit their content in smoke additives, there seems no reason why PAH should not be controlled either directly in the food or in the smoke additive.

The preservation of food must have occupied the attention of man for a good deal longer than recorded history, and smoking of food is among the oldest methods known. In the light of extensive epidemiological, biological and chemical studies its practice poses questions from the public health point of view since it can introduce directly or indirectly carcinogens such as polycyclic aromatic hydrocarbons (PAH) and nitrosamines. It is therefore pertinent for national authorities charged with the responsibility for public health to assess the known facts and introduce legislation designed to safeguard the public. Let us consider firstly the facts as these are the essential details on which legislation must be based. Here by the very wealth of information already available PAH merit primary concern.

As early as 1775, John Percivall in England observed an association between

cancer of the scrotum and the exposure of chimney sweeps to soot. Pott's observation was subsequently reported by a number of other workers. Later, in 1892, Butlin observed skin cancer nad cancer of internal organs among chimney sweeps. Cancer incidence has been described in a number of occupations which bring workers into contact with PAH. Observations have been made in the rubber industry (1), the coal tar and pitch industry (2, 3) and the coal tar and gas industry (4, 5). In a recent study Doll et al (6) found a significant excess of deaths in the latter industry from lung, bladder and scrotum cancer. The shale oil industry has also been implicated in scrotum cancer (1) whilst in the spinning industry the use of shale oil as a lubricant was implicated in 575 fatal cases of scrotum cancer between 1900 and 1938 (1). High skin cancer incidence has been reported among lathe operators using cutting oils. Waterhouse (7) has shown that in the United Kingdom at least two thirds of the scrotal cancer incidence could be related to contact with this type of oil; a similar observation has been made in France (8). In the steel industry in the USA, higher levels of respiratory cancer were found among the coke plant workers than other sections of the industry (9). In the 1925 Kennaway (10) produced carcinogenic tars in the laboratory from a number of sources and found that the carcinogenicity was associated with the higher boiling fractions. The fluorescence character of these fractions led Kennaway and Heiger in 1930 (11) to isolate benzo(a)pyrene which was later shown to be carcinogenic. Since that time a large number of PAH have been identified in various smokes, tars, etc. We thus have a persistent chain of evidence from observations over a long period of time and in a variety of industries showing some relationship between incidence of certain types of cancer and exposure to PAH.

In addition to the human data there are data from a large number of animal experiments carried out both with products containing PAH and with individual compounds. In 1973 an IARC working group of experts evaluated the animal data for 13 individual PAH and 4 individual heterocyclic aromatic hydrocarbons (12) for which animal and environmental data were available as shown in Table 1. Although the Committee was extremely rigorous in discarding any uncertain data, animal studies leave little doubt that many PAH are carcinogenic and present a risk to man.

Before considering other environmental data it is pertinent to comment briefly on the analytical status of PAH analysis. There can be little argument that over the years this has been developed to a high degree of sophistication, particularly with the evolution of chromatographic techniques. PAH analysis has, in fact, given considerable leadership in the general approach to trace analysis in environmental chemistry. Gas chromatography, thin-layer chromatography and column chromatography have been applied and recent work with high pressure liquid chromatography shows that analytical developments are still taking place. PAH analysis has also been the subject of a number of successful collaborative studies. It is reasonable to conclude therefore that a good proportion of environmental data reported in the literature can be regarded as reliable. Tables 2 and 3 give ranges of values for benzo(a)pyrene which, I feel after scanning a large number of

TABLE 1. The list of Polycyclic aromatic hydrocarbons and heterocyclic compounds dealt with in the IARC programme for the evaluation of carcinogenic risk of chemicals to man

Polycyclic aromatic hydrocarbons	
	Benz(a) anthracene
	Benzo(b) fluoranthene
	Benzo(j) fluoranthene
	Benzo(a) pyrene
	Benzo(e) pyrene
	Chrysene
	Dibenz(a,h) anthracene
	Dibenzo(h,rst) pentaphene
	Dibenzo(a,e) pyrene
	Dibenzo(a,h) pyrene
	Dibenzo(a,i) pyrene
	Dibenzo(a,l) pyrene
	Indeno(1,2,3-cd) pyrene
Heterocyclic compounds	
	Benz(c) acridine
	Dibenz(a,h) acridine
	Dibenz(a,j) acridine
	7H-dibenzo(c,g) carbazole

TABLE 2. Showing ranges of values for benzo(a)pyrene in smoked meat selected to illustrate levels commonly found

Product	Benzo(a)pyrene range ug/kg	Authors
Bacon	0.2 - 4	Mannelli (1966) Lenges and Lucks (1974)
Ham	0.2 - 14	Toth (1971) Fry (1966) Lenges and Lucks (1974)
Commercial smoked meat(various)	trace - 33.5	Thorssteinsson (1969) Lucks and Lenges (1973) Hamm and Reiner (1973) Filipovic and Toth (1974)
Sausage	0.2 - 11	Dobes et al. (1954) Mannelli (1966) Lenges and Lucks (1974) Filipovic and Toth (1971) Howard and Fazio (1969)
Charcoal barbecued meat	trace - 8	Fritz (1975) Lijinski and Shubik (1964) (1965)

papers, represent those which could normally be expected in the foodstuffs shown. They exclude the high values found in areas where smoked food has been implicated in cancer incidence. Table 2 gives ranges for various smoked meat products; somewhat similar ranges could be given for smoked fish.

TABLE 3. Showing a range of values for benzo(a)pyrene found in some vegetables fruits and cereals

Products	Benzo(a)pyrene ug/kg	Authors
Green vegetables (kale, spinach, leeks, etc.).	1 - 24.5	Gräf and Diehl (1966) Grimmer and Gernot (1966)
Lettuce	2.8 - 12.8	Grimmer and Hildebrandt (1965) Fritz and Engst (1971)
Dried seaweed	7.4 - 31.3	Shirohori and Tsuyako (1972)
Fruits (varied)	Trace - 0.15	Sharashi et al. (1972) Ruchkovski et al. (1972)

Table 3 gives ranges for green vegetables, salads and fruits. In the commodities shown in Table 3, the values can very with the site of sampling and tend to be highest for produce grown in the vicinity of heavy traffic. Although they are not included here, coffee, tea and cooking oils have also been shown to contain traces of PAH. These tables do not suggest that, for the general population, PAH intake from smoked food would be significantly greater than it would be from salads and green vegetables which are a common item in many diets.

In Tables 2 and 3 environmental levels are only given for benzo(a)pyrene as these are commonly used to indicate PAH contamination. This compound is also the only individual PAH to appear in legislation. However it may be questionable as to whether benzo(a)pyrene is an adequate guide to health risk. The paper of Engst and Fritz (13) illustrates that there can be considerable difference in the profile of PAH for different smoked products and different methods of smoking. Table 4 taken from the IARC Monograph (12) illustrates the variation which exists in selection of PAH for analysis by a number of groups occupied in environmental studies in which are included both carcinogenic and non-carcinogenic PAH. For example, benzo(ghi)perylene, which interferes in the determination of benzo(a)pyrene in some analytical methods, is included to increase confidence in benzo(a)pyrene values. Fluoranthene, on the other hand, which is non-carcinogenic and included as a quantitatively important constituent, has recently been suggested by van Duuren (14) to be a co-carcinogen. This suggests that analysis should determine as many PAH as possible in order to have sufficient data available for evaluation at some later date. This consuel of perfection, while excellent in principle, may be regarded as unrealistic by the analyst faced with routinely screening a

large number of samples; furthermore, consideration of promoting factors could present some formidable problems for legislation.

TABLE 4. Illustrating the variation in selection of individual PAH for analysis by different groups and laboratories studying a range of environmental aspects

	UICC (1970)	IARC (1971)	WHO (1970)	Stocks et al (1961)	Waller and Commins (1967)	Borneff and Kunte (1969)	Grimmer and Hildebrandt (1967)	Howard et al (1966)
Benzo(a)pyrene	*	*	*	*	*	*	*	*
Benzo(e)pyrene		*		*	*		*	*
Benzo(k)fluoranthene		*	*			*	*	
Benzo(g,h,i)perylene	*	*	*	*	*	*	*	*
Coronene	*	*		*	*		*	
Benz(a)anthracene		*				*	*	
Dibenz(a,h)anthracene	*						*	
Dibenz(a,h)acridine	*							
Pyrene	*			*			*	
Anthranthrene				*			*	
Fluoranthene			*	*		*	*	
Perylene							*	
Benzo(b)fluoranthene			*			*		
Indeno(1,2,3-cd)pyrene			*			*		
Phenanthrene							*	
Chrysene							*	
Anthracene							*	

* indicates the PAH determined by the group

At the moment comparatively little is known about co-carcinogenesis, but the possibility that it could be of great importance is illustrated, for example, by skin painting experiments carried out by Bingham and Falk (15) who found benzo(a)pyrene to be about 1,000 times more carcinogenic when applied in a 50/50 mixture of n-dodecane and decalin. Incidentally Sice (16) had already shown that a chain length of 11 was optimum for co-carcinogenicity of aliphatic hydrocarbons and 12 for the corresponding alcohols. In vitro experiments (17) have demonstrated that indole derivatives contained in cruciferous vegetables such as cabbage may exert an anti-carcinogenic effect on benzo(a)pyrene by causing decreases in binding of its metabolites to DNA. If both co- and anti-carcinogens happen to occur among the many components in food, they might affect dramatically the minimum dose level threshold dose level necessary to cause cancer in humans.

Threshold dose level may generally be defined as the minimum dose given chronically which does not cause a significant increase in tumours within the normal life span of the species. This is extremely difficult to establish in carcinogenicity studies. Cancer is mainly a disease which becomes manifest after middle age and this is partly responsible for a widely held view that a high proportion of cancers result from a life-time exposure to very small amounts of chamical carcinogens. The normal toxicological approach using dose response relationship which must be carried out at a sufficiently high dosage to obtain statistically valid results may be susceptible to considerable error on extrapolation to the trace level at which so many environmental carcinogens are found. Even though the dose response relationships may appear to be sensibly linear in the practical dose range, linearity cannot be assumed to hold over a diminishing magnitude of several orders. In reviewing the mathematical aspects of dose response studies which have been proposed to explain carcinogenesis, Brown (18) concludes that the mathematical models, which are based mainly on the transition of a single cell which eventually develops into a tumour, are still crude tools which cannot yet resolve the question of threshold dose. It is possible that in vitro studies such as mutagenicity testing may in time offer an alternative approach but at the moment a majority of experts appear to regard them as economic screening techniques only.

The numerous uncertain factors concerning carcinogenicity lead experts to conclude that it is impossible at the moment to propose a "safe" limit for any carcinogenic substance so that there has been no fundamental change in view since that expressed by a UICC Symposium in 1956 (19), which recommended "... that any substance shown to be carcinogenic at any dose in any species and by any route should not be authorized for use in food ..." This in principle would appear to rule against the use of smoke in any from in which PAH could be detected.

On face value, the most practical approach to the problem of threshold dose would still seem to be a combination of epidemiology and environmental analytical chemistry, but even this approach is still, however, a somewhat hit or miss process. Where a population is suspected of being exposed to a particular carcinogen the studies have proved informative, as in the case of aflatoxins where positive correlations have been demonstrated between the incidence of liver cancer in man and aflatoxin intake in the diet (20-23). In regard to smoked foods, Engst and Fritz (13) in the paper to follow point out several instances of a correlation between intestinal cancer and high consumption of smoked foods, a good example of which is the high level of PAH in the homesmoked products in Iceland where stomach cancer incidence is the highest in Europe. Similar observations have been made in Japan with regard to consumption of smoked fish (24). Although such evidence for the carcinogenicity of PAH in food may be strong we cannot afford to neglect the possibility of effects from other carcinogens such as N-nitroso compounds for which analysis may not have been carried out. This applies to a large proportion of the chemical/epidemiological evidence on PAH. In a recent study on cutting oils which had been formulated with nitrate and triethanolamine, is was shown that the concentration of nitrosamine formed could

exceed the PAH concentration by a factor in the order of 10 (6). It would be very pertinent to measure nitrosamine for other established sites for industrial PAH exposure.

The tandem epidemilogy/chemistry approach is being used for the investigation of the very high oesophageal cancer incidence in the Caspian Littoral of Iran; we have carried out extensive analyses of food and water supplies for volatile nitrosamines which are particularly of concern with respect to oesophageal cancer for their potential precursors nitrate and nitrite and also for PAH and aflatoxins. Comparative investigations were carried out in both high and low cancer incidence regions. From the results it appears unlikely that these compounds cause oesophageal cancer in this area. The most solid statistical correlation came from nutritional studies which correlated oesophageal cancer incidence with a high consumption of bread, which seems unlikely to be responsible for an extremely high cancer incidence.

The LARC is also investigating a high oesophageal cancer incidence in North West France which correlates with diseases resulting from alcoholism. Analysis in our laboratories of farm-produced apple brandies, which are widely consumed in the area, shows a few ppb of benzo(a)pyrene in all samples and slightly lower traces of volatile nitrosamines in 40-50%. Table 5 shows the levels of benzo(a)pyrene in a number of these apple brandies as well as some other alcoholic drinks. Table 6 shows the results of a more detailed analysis of a sample of apple brandy from Normany kindly undertaken for us by Dr Grimmer. If nitrosamine had not been analysed the persistent appearance of benzo(a)pyrene could be taken to suggest that PAH is the causal factor of oesophageal cancer in this area. However, the statistics at present suggest that the correlation is with total consumption of ethanol rather than of the regional beverages (25), even though animal studies do not suggest that ethanol is carcinogenic. Traces of N-nitroso compounds have also been reported in smoked foods (26-28), and the possibility that nitrous fumes in smoke may result in nitrosamine formation is discussed elsewhere in the Symposium by Dr Möhler (29).

Another aspect of nitrosamine formation which needs further investigation is the catalytic effect of certain phenolic compounds on this reaction which may be relevant to possible <u>in vivo</u> formation of nitrosamines (30). In current investigations we find that while phenol itself can promote the formation of nitrosodiethylamine, p-nitrosophenol, which is readily formed by nitrosation of phenol under acid conditions, appears to be about 20 times more effective than phenol itself. We therefore propose to extend our investigation to the actual phenols which occur in smoke and to their nitroso derivatives. Fitko et al (31, 32), in papers to follow, examine the toxic and pathological effects of smoke extract flavour. The results do not suggest a particular toxic hazard. However the duration of the experiments (20 and 90 days) would be short to evaluate the carcinogenicity which normally requires a minimum of six months. From this point of view we can expect to see these studies extended.

Now that facts relating to the risks from smoked foods have been very broadly reviewed the approaches to legislation can be considered. To be effective,

TABLE 5. Benzo(a)pyrene in some alcoholic beverages

Sample type	Benzo(a)pyrene * (ug/kg)	Fluoranthene * (ug/kg)
Apple brandy (Brittany) " eau-de-vie de famille" 15 samples	5 - 10	5 - 15
Apple brandy (U.S.A.) (single source, separate batches) 11 samples	N.D. ≠	1 - 5
Moonshine Rum (Puerto Rico)	N.D.	1 - 5
Moonshine Rum " "	"	"
Rum " "	"	"
Liqueur (Jamaica)	"	"
Alcohol wine "	"	"
Bread wine "	"	"
Pimento liqueur "	"	"
Rice wine "	"	"
Commercial rum "	"	"
Rum (Singapore)	"	"
Wine (Iran)	Trace	"
Wine "	N.D.	"
Vodka "	"	"

* Determined by a single TLC method

≠ N.D. indicates Not Detected

TABLE 6. Results of analysis on a sample of apple brandy from Normandy*

PAH	Content ug/kg
Fluoranthene	27.3
Pyrene	19.0
Benzo(a)fluorene	1.71
Benzo(b/c)fluorene	0.99
Benzo(c)phenanthrene	2.18
Benzo(ghi)fluoranthene	1.04
Benzo(a)anthracene	4.57
Chrysene	5.30
Benzofluoranthenes (b/k/j)	3.50
Benzo(e)pyrene	1.95
Benzo(a)pyrene	1.79
Perylene	0.57
Dibenz(a,j)anthracene	0.26
Indeno(1,2,3-cd)pyrene	0.65
Benzo(ghi)perylene	0.75
and several unknown PAH	

* Method: Grimmer et al. J. AOAC 58 725-733 (1975)

TABLE 7. Legislative status on the presence of carcinogens in different areas of the environment IARC Internal Technical Report 74/001

What is the present legislative status of the presence of carcinogens in the field of:	Italy	UK	USA	Federal Republic of Germany	France	Japan	Netherlands	Canada
(1) Food additives	1	1	2,3	1(3)	2	1	1	3
(2) Food contaminants	1	1	1	1(3)	2*	1	3	3
(3) Drugs	1	1	1	2(3)	2	1	2	1
(4) Cosmetics	0	0*	1	1(3)	2	1	3	1
(5) Surgical implants	0	0*	1	1	1	1	1	1
(6) Drinking water	0	1	1,3	1(3)	1	1	0*	1
(7) Effluent water	0	1	1	1 3	1	1	0*	1
(8) Ambient air	1					1		
- home		0	1	1	1	0	0*	0
- community	1	1	1	1(3)	1	1	0*	1
- working place	1	1	3	3	3	3	1	3
(9) Effluent air	1	1	1	1	1	1	0*	3
(10) Soil	0	1	1	1	1	1	0*	0
(11) Household materials	1	0*	1	1(3)	1	1	1	1
(12) Alcoholic drinks	0	0*	1	1	1	1	0*	1
(13) Tobacco smoke	0	0	3	1	1	0	0*	1
(14) Occupational environment other than air:								
- general	1			1	2	1	1	3
- specific	3			3	3	3	1	3
- acceptable levels	0			0			3	1
(15) Specific chemicals (See table 8)	*	**	1	3*	**	0	3	0

Code: 0 = no legislation at all;
1 = carcinogens not specifically mentioned, included as hazardous substances;
2 = carcinogens mentioned as a group;
3 = carcinogens listed individually in one or more sectors.
* and ** are explained in Table 8

legislation must be realistic. The facts undoubtedly point to a potential health hazard from carcinogenic PAH in smoked food whilst the nitrosamine aspects are insufficiently detailed to fit into the epidemiological background, therefore legislative action in some form is required to control the PAH content. As these compounds are ubiquitous in the environment and as we cannot define safe backround limits, the problem is to find a compromise between the philosophy of zero tolerance and the reality of a cost/benefit ratio, because food flavouring and preservation by smoking are just as much an accepted part of our environment as the automobile with its exhaust fumes, plastics with vinyl chloride residues and cigarette smoking. Looking at the levels of PAH to which we are unavoidably exposed, by consumption of our green vegetables for example, should we regard normal levels of PAH in smoked food as an avoidable additional burden or as an integral part of some undefined background level? This problem must of course be decided by each national health authority in terms of its own cost/benefit ratio. In practice a nation faced with an acute problem of malaria is less likely to be concerned with the weak carcinogenic properties of DDT than with control of the mosquito unless a more suitable alternative to DDT is available.

In 1973 the IARC Advisory Committee on Environmental Carcinogens met to consider some general questions relating to control of environmental carcinogens. Included was a general overview of legal action taken in a number of countries. Tables 7 and 8 summarise the results of these enquiries (33). Although Table 7 does not refer to all the national legislations reviewed, it is broadly representative. It illustrates that as a general rule national legislation does not single out chemical carcinogens for special mention. In Table 7 the question of PAH in foods is dealt with under the general heading of hazardous substances as food contaminants. Typical of this type of legislation is the United Kingdom Food and Drugs Act which "... prohibits the use in food of substances injurious to health ..." Similar phraseology appears in the legislation of a number of countries. In principle, this approach can facilitate the problems of control on the basis of cooperation between government and industry. It is still, however, indecisive and therefore open to argument. That decisions can be made on maximum allowable levels is evident from Table 8 where definite limits were set for aflatoxins which are established carcinogens if fact decisions on aflatoxin limits have now been taken by a number of countries. A risk, however, in setting maximum allowable concentrations is that they may become confused with safe limits.

During the course of this year enquiries have been made concerning current national legislation with regard to smoke and smoked foods. Although at present only fifteen replies have been received from the thirty countries contacted, they do suggest that, while the legislation in many countries has not changed, some health authorities have the matter of PAH under review. In the German Federal Republic, the regulations have recently been changed to introduce a limit to the levels of benzo(a)pyrene in meat and cheese of 1 ug/kg. In Austria benzo(a)pyrene in smoked food is also limited to 1 ug/kg. In Australia an AOAC Official Method for analysis of PAH in smoked flavours was recommended for adoption in 1975.

TABLE 8. Footnotes to Table 7

Italy	*	Aflatoxin in food - upper limit of 20 ppb at present
United Kingdom	**	Regulations control the important, sale and use (sith certain exceptions) of p-naphtylamine, benzidine, 4-amino-diphenyl and 4-nitrodiphenyl in factories and certain other places
	*	No specific legislation, although some control is exerted by general regulations or voluntary controls and codes of practice.
Federal Republic of Germany	*	DDT-law
	( )	Figures in brackets: new federal legislation in preparation
France	**	Aflatoxins in food. Upper limit of 20 ppb at present
	*	Benzene in industrial solvents: not more than 1% in volume
	**	Carcinogenic polycyclic aromatic hydrocarbons and aromatic amines in food dyes as impurities. At present no detectable amounts by the most sensitive analytical methods (now under revision in the case of PAH taking into account the high sensitivity of available analytical methods).
	*	Except for some specific chemicals
Netherlands	*	Aflatoxins There are general measures that apply to these substances and enable them to be regulated.
Canada		Includes federal and/or provincial legislation

IARC Internal Technical Report 74/001

The indirect control of PAH in smoked foods by control of the smoke additive is a commonly used approach. For example, in Finland, benzo(a)pyrene in smoked additives is restricted to 30 ug/kg with the application rate limited to 0.5 g/kg of smoke concentrate of foodstuffs, although the legislation does not contain limits for benzo(a)pyrene in smoked foods. Australian regulations state that "...smoke flavours shall be free from any polycyclic aromatic hydrocarbons ..." Polish food legislation requires toxicological evaluation of smoke or smoke substitutes before approval for use. Restrictions also frequenty refer to the source of materials used to produce the smoke. For example, the Republic of South Africa standard specifications for smoke require that the wood employed for production of smoke should be free from resin, paint, timber preservatives or other added substances. Reports that smoked food could become contaminated by arsenic from preserved wood (34) illustrates the risk of contamination from materials other than PAH.

CONCLUSION

As a means of controlling PAH in smoked food, the papers of Engst and Fritz

(13) and those of Fitko and col. (31, 32) among others, demonstrate that regulation of the smoke additive is one practical approach to the problem. Whether it is entirely adequate in view of the possibility that nitrosamines may be subsequently formed in the food itself is a matter which requires further investigation. We have also to consider the suitability of benzo(a)-pyrene alone as a measure of contamination. It does, however, offer a decision point. Understandably toxicologists generally are reticent on the subject of safe levels where chemical carcinogens are concerned; neverthelles, in the Soviet Union dose response studies have been used to define a Maximum Allowable Concentration (MAC) for benzo(a)pyrene in ambient industrial environments (35). Finally I quote from the Nineteenth Report of the FAO/WHO Experts Committee on Food Additives (1975) which on the question of smoke condensates and liquid smoke states that "... The establishments of specifications that include a method for detecting the presence of carcinogenic polycyclic aromatic hydrocarbons is required..." As an analytical chemist I believe adequate and reliable methods of analysis for polycyclic aromatic hydrocarbons are available; it remains to come to some decision as to which PAH we analyse and the levels we are prepared to tolerate in our food.

REFERECNES

1. S.A. Henry, Cancer of the scrotum in relation to occupation, London, New York, Toronto, Oxford University Press (1946).
2. H.T. Butlin, Three lectures on cancer of the scrotum in chimney sweeps and others. III Tar and paraffin cancer. Brit. med. J. 1, 368 (1892).
3. P. Bogovski, Occupational skin tumours due to fuel processing products. Leningrad, Medgiz (1960).
4. S. Kennaway and N.M. Kennaway, A further study of the incidence of cancer of the lung and larynx. Brit. J. Cancer 1, 260 (1947).
5. S. Kuroda and K. Kawabata, "Uber die gewerbliche entstehung des Lungenkrebses bei generatorgasarbeitern. Z. Krebsforsch. 45, 36 (1936).
6. R. Doll, M.P. Vessey, R.W.R. Beasley, A.R. Buckley, E.C. Fear, R.E.W. Fisher, E.J. Gammon, W. Gunn, G.O. Hughes, K. Lee and B. Norman-Smith, Mortality of dasworkers - final report of a prospective study. Brit. J. Industr. Med. 29, 394 (1972).
7. J.A.H. Waterhouse, Cutting oils and cancer. Ann. occup. Hyg. 14, 161 (1971).
8. C. Thony and J. Thony, Enquête épidémiologique sur le cancer des huiles de coupe. In Proceedings of the 16 th Congress of the Permanent Commission and International Association on Occupational Health, Tokyo, Japan Industrial Safety Association, p. 655 (1969).
9. J.W. Llloyd, Long-term mortality study of steel-workers. V. Respiratory cancer in coke plant workers. J. occup. Med. 13, 53 (1971).
10. E.L. Kennaway, Experiments on cancer-producing substances. Brit.med. J. ii, 1 (1925).
11. E.L. Kennaway and I. Hieger, Carcinogenic substances and their fluorescence spectra. Brit. med. J. i, 1044 (1930).

12. International Agency for Research on Cancer, IARC Monographs on the evaluation of carcinogenic risk of the chemical to man Vol 3 Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds (1973).
13. R. Engst and W. Fritz, Contribution of the food-hygienic toxicological evaluation on the occurrence of carcinogenic hydrocarbons in smoked products. IUPAC/IUFOST International Joint Symposium on Advances in Smoking of Food, Warsaw (1976).
14. B. van Duuren, New Scientist, 63, 907 (1974).
15. E. Bingham and H.L. Falk, Environmental carcinogens. The modifying effect of co-carcinogens on the threshold response. Arch. environ. Hlth. 19, 779 (1969).
16. J. Sice, Tumour-promoting activity of n-alkanes and 1-alkanols, Toxicol. Appl. Pharmacol. 9, 70 (1966).
17. L.W. Wattenberg, Effects of dietary constituents on the metabolism of chemical carcinogens. Cancer Res. 35, 3326 (1975).
18. C.C. Brown, Biometry Branch, National Cancer Institute USA in press , (1976).
19. Symposium on potential cancer hazards from chemical additives and contaminants to foodstuffs, Rome 1956. Unio Internationalis Contra Cancrum Acta XIII, No. 2 (1957).
20. M.E. Alpert, M.S.R. Hutt, G.N. Wogan and C.S. Davidson, Association between aflatoxin content of food and hepatoma frequency in Uganda. Cancer Philad. 28, 253 (1971).
21. R.C. Shank, N. Bhamarpravati, J.E. Gordon and G.N. Wogan, Dietary aflatoxins and human liver cancer. IV. Incidence of primary liver cancer in two municipal populations in Thailand. Food Cosmet. Toxicol. 10, 171 (1972).
22. F.G. Peers and C.A. Linsell, Dietary aflatoxin and liver cancer: a population based study in Kenya. Brit. J. Cancer. 27, 473 (1973).
23. S.J. van Rensburg, J.J. van der Watt, I.F.H. Purchase, L. Pereira Coutinho and R. Markham, Primary liver cancer rate and aflatoxin intake in a high cancer area, S. Afr. Med. J. 48, 2508 (1974).
24. Y. Masuda, K. Mori and M. Kuratsune, Polycyclic Aromatic Hydrocarbons in common Japanese Foods. I. Broiled fish, roasted barley, shoyu and caramel. GANN 57, 133 (1966).
25. A. Tuyns, Private communication, IARC
26. T. Panakaks, J.R. Iyengar and N.P. Sen, Nitrate, nitrate and dimethylnitrosamine in cured meat products. J. AOAC 56, 62 (1973).
27. T. Panalaks, J.R. Iyengar, B.R. Donaldson, W.F. Miles and N.P. Sen, Further survey of cured meat products for volatile nitrosamines, J. Assoc. Offic. Anal. Chemists 57, 806
28. T. Fazio, R.H. White and J.W. Howard, Analysis of nitrite and/or nitrate--processed meats for N-nitrosodimethylamine, J. Assoc. Offic. Anal. Chemists 54, 1157 (1971).
29. K. Möhler, Formation of NO and reaction with meat in smoke chambers directly heated with gas. IUPAC/IUFOST International Joint Symposium on Advances in Smoking of Food. Warsaw (1976).
30. E.A. Walker, B. Pignatelli and M. Castegnaro, Effects of gallic acid on

nitrosamine formation. Nature 258, 176 (1975).

31. R. Fitko, J. Grabarski, H. Krzymowska, K. Markiewicz and T. Szuperski, The acute toxicity of smoke extract flavour /PDW/. IUPAC/IUFOST International Joint Symposium on Advances in Smoking of Food. Warsaw (1976).
32. R. Fitko, K. Markiewicz, T. Szuperski and H. Krzymowska, The zootechnical indexes and pathological changes in animals after smoke extract flavour PDW application in subacute toxicity test. IUPAC/IUFOST Joint International Symposium on Advances in Smoking of Food. Warsaw (1976).
33. Meeting of the IARC Advisory Committee. Lyon 15-16 Oct. 1973. IARC Internal Technical Report 74/001
34. C.C. Watson, Contamination of fish by arsenic in smoke from preserved wood. N.Z. J. Sci. 1, 369 (1958).
35. Methods used in the USSR for establishing biologically safe levels of toxic substances. Papers presented at a WHO meeting held in Moscow, 12-19 December 1972. WHO Geneva (1975).