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OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: The Carcinogen Assessment Group's Type I Risk Assessment for Maleic Anhydride

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As requested in your May 18, 1978 memorandum, The Carcinogen Assessment Group has finished the Type I risk assessments for Maleic Anhydride. We are transmitting this report to you.

Attachment

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THE CARCINOGEN ASSESSMENT GROUP'S

PRELIMINARY RISK ASSESSMENT

ON

MALEIC ANHYDRIDE

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Maleic anhydride: 

Evidence for carcinogenicity

The data base for evaluating the carcinogenicity of maleic anhydride is almost non-existent. One inadequate study treated 3 Wister-derived rats for 61 weeks with maleic anhydride and 4 untreated rats of the same type. In one treated rat, 2 fibrosarcomas occurred at the site of injection compared to no tumors in the untreated rats.

Three studies showed that maleic anhydride had anti-carcinogenic activity in mice against skin tumors induced by polycyclic aromatic hydrocarbons, against a primary tumor system Lewis lung cells inoculated into mice and against Friend leukemia virus.

Maleic anhydride should be tested for carcinogenicity using short term mutagenesis, cell transformation and animal bioassay tests.

Unit risk assessment: No adequate test of carcinogenicity has been done.

II. Introduction

Maleic anhydride dust or vapor is an acute skin, eye, and respiratory tract irritant. The U.S. occupational standard for exposure is 1 mg/m^3 (0.25 ppm) based on its high irritant property. Inhalation can cause pulmonary edema and inflammatory changes in kidneys and other organs. These changes are generally irreversible (Bober and Sagan, 1970). Direct contact with the skin may cause burns. Maleic anhydride is also a respiratory tract sensitizer and persons may become highly sensitized to very small concentrations. Chronic exposure in humans also caused asthma, chronic bronchitis, and dermatitis (Patterson et al., 1976).

III. In vitro Studies

No in vitro studies for mutagenicity or ability to transform cells exist. These tests should be done.

IV. Carcinogenesis Studies

A. Carcinogenicity in rats

The data base for evaluating carcinogenicity is almost non-existent. This chemical should be tested for carcinogenicity.

Only one inadequate test has been made of the carcinogenic properties of maleic anhydride. Dicken and Jones (1963) injected 1 mg maleic anhydride in arachis oil twice weekly into 3 Wistar-derived male rats for 61 weeks and arachis oil only into 4 rats of the same type. One treated rat developed 2 fibrosarcomas at the site of injection compared to no tumors in the controls. This study is judged to be of poor quality due to the small number of animals and the lack of histopathology. The difference between control and treated is not statistically significant and the meaning of a tumor at the site of injection of a highly irritating compound is unclear.

B. Anti-tumor activity in mice

Three studies have shown that maleic anhydride has an anticarcinogenic effect.

Crabtree (1944) showed that maleic anhydride painted on the skin of mice previously painted with dibenzanthracene or benzopyrene retarded the time at which skin tumors appeared. No control group treated only with maleic anhydride was included in the experiment. Groups of 25-30 hybrid mice (parental stocks not given) were painted twice weekly for 9 months with 0.1-0.3% benzopyrene or 0.2% dibenzanthracene. Maleic anhydride was painted over the same area 4 times weekly on the days between the carcinogen paintings. The concentration was 1, 2, 4, or 6% maleic anhydride. Highly significant anti-tumor activity of maleic anhydride was observed both in the time at which tumors first appeared and in the number of animals with tumors.

Klein (1965) treated B6AF$_1$ female mice with dimethylbenzanthracene, croton oil, and maleic anhydride in various combinations on the skin and measured skin tumors at least 1 mm in diameter. Each experimental group contained 40 mice. No control group treated only with maleic anhydride was included. Maleic anhydride reduced tumor incidence, delayed time of appearance to first tumor, and caused tumor regression.

Ottenbrite et al., (1977) studied the ability of maleic anhydride and its polymers to inhibit the growth of Lewis lung cells, a primary tumor system in BDF mice, and Friend leukemia virus in Balb/C mice. One million Lewis lung cells were inoculated subcutaneously in each mouse followed by daily i.p. injections of maleic anhydride for 10 days. Maleic anhydride homopolymer at 25, 50, or 75 mg/kg for 10 days inhibited the growth of Lewis lung tumor up to 78% inhibition of the primary tumor size at the highest dose but did not prolong survival time. These authors suggest that maleic anhydride is more effective against the primary tumor than against metastatic tumor cells. Maleic anhydride polymers of 6 different molecular weight ranges from >100,000 to <1000 inhibited splenomegaly in Friend leukemia virus-treated mice. The molecular weight fraction most effective against Friend leukemia virus was 10,000-30,000 mw (Goodell et al., 1978).

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*Abstracted version.

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THE IARC PROGRAMME ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN

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In a recent paper (Murray and Axtell 1974)[1] cancer mortality data in the USA were reviewed with the purpose of assessing the loss to society caused by cancer. For this reason, the years of life lost and the work years lost due to cancer mortality for cancer occurring at different ages and at different sites were evaluated. The authors came to two main, and rather obvious, conclusions: (1) that cancer occurring at an early age represents a greater loss in terms of work years lost than cancer occurring at a late age, even if at a much greater frequency; cancer of the prostate in males, for instance, ranks second in frequency and yet lower than twelfth as a cause for work years lost. (It is perhaps pertinent to remember that occupational cancer is not a disease of old age: the average age at diagnosis of people with haemangiosarcoma of the liver due to vinyl chloride is 47 years and that of the 33 cases for which complete information is available, five were diagnosed before 39, and 12 between 40 and 44, years of age.) (2) that in view of the limited success obtained up to now with improved diagnostic systems and therapy, the greatest potential for cancer control lies in preventive measures.

Even if one looks at the cancer problem with an eye on costs and benefits, it appears that the most promising and rewarding approach is

that of primary prevention, which means firstly the avoidance of exposure to carcinogenic agents. In addition, it does not appear that periodic health examinations give any guarantee of a longer and healthier life (Siegel 1966)[2]. Accordingly, an intensified health surveyance of people at high cancer risks, as for instance people exposed to high levels of vinyl chloride, does not guarantee a better survival or an improved outcome of the disease.

It has been stated repeatedly that a large number of cancers can be attributed to environmental factors in proportions which can vary from 75% (WHO 1964)[3] to 80% (Haddow 1967, Boyland 1969)[4,5] to 90% (Higginson 1968)[6]. One can dispute these percentages and reduce them to much lower and more acceptable proportions, but the fact remains that a certain proportion of human cancers are certainly due to environmental factors. Of these factors, some have been identified and their carcinogenic effect on man has been proved, many more have been identified as possibly hazardous to man, but the actual proof of their carcinogenicity relies only on experimental evidence, and for an even larger number, the available data are insufficient to build up any kind of evaluation.

When the IARC was first faced with the request to provide useful information on environmental carcinogens, our first reaction was to prepare two lists of chemical carcinogens, one for chemicals carcinogenic to man and the other for chemicals carcinogenic in experimental animals. This project was soon discarded because (1) a list was considered too rigid to take into account the multiple aspects required for a proper evaluation, and (2) because it would have been relatively easy to prepare lists of chemicals for which results were clear and unquestionable, but it would

have been impossible to include in any given list chemicals for which the quantity and/or quality of the available data varied considerably. There was also the implicit danger that all chemicals not included in the "black list" of carcinogens could be automatically assumed safe.

For these reasons, the IARC, following the advice of an *ad hoc* working group, initiated the programme on the evaluation of the carcinogenic risk of chemicals to man, which is centered on the preparation of monographs on individual chemicals. Each monograph comprises several sections in which data are summarized on: chemical and physical characteristics; production, use, occurrence and analytical methods; biological data relevant to the evaluation of the carcinogenic risk of the chemical to man, covering all available data on carcinogenicity studies, data on the metabolism of the chemical in experimental animals and man, the carcinogenicity of the metabolites, if tested, essential data on acute toxicity and, since last year, data on mutagenicity; and observations in man covering epidemiological studies and case reports. The last section of the monograph is a brief comment on the ensemble of the experimental and human data with, whenever possible, an evaluation of the data in terms of a possible risk to man.

Up to now, eight volumes[7-14], each containing several monographs, have been published. The first volume, which appeared in 1972, contained monographs on 19 chemicals pertaining to different chemical groups. Once the feasibility of the monographs was agreed, each volume contained data on chemicals pertaining to one or two chemical groups, plus a non-related substance when its evaluation appeared particularly urgent. This was the case, for instance, with vinyl chloride, which was added to the session called in June 1974, when anti-thyroid substances and nitrofurans were evaluated.

The chemicals for which a monograph is prepared are selected according to two main criteria: (1) that there is evidence of human exposure, and (2) that some experimental evidence of carcinogenicity and/or some evidence or a strong suspicion of a human hazard exists. The extent of the possible human exposure is assessed in many instances with some approximation on the basis of the data on the use and production of a chemical. This information has been obtained mainly through the collaboration of the Stanford Research Institute, operating under an agreement with the NCI.

The data are also intended to be of some help to epidemiologists, as they may indicate where a study could be initiated. The NCI supports this programme financially and has helped the Agency considerably by providing surveys of available pertinent literature. It is worth noting that it has been our policy to only include for consideration work which has been published or accepted for publication, and to disregard unpublished results and personal communications. After having assembled reprints on studies related to the chemicals selected for the preparation of a monograph, a draft monograph is prepared, either by an external consultant or by IARC staff. These drafts are then circulated among IARC staff and a group of expert consultants for comments. An *ad hoc* working group of experts is then convened in Lyon and the monographs are finalized after a careful and painstaking checking of all data.

The first eight volumes cover a total of 196 chemicals. Of these, 17 (about 9%) were found to be associated with the induction of tumours in man (Table I). These 17 chemicals are listed in Table II. Aflatoxin is included in this list, but it must be noted that only a strong suspicion,

and not absolute evidence, of its role on the induction of liver cancer in man exists. The carcinogenicity for man of the majority of these chemicals was established as a result of studies conducted on people who were occupationally exposed to them. In fact, with the exception of aflatoxin, on which, as mentioned before, some doubts still exist and for which exposure is dietary, and of chlornaphazine and stilboestrol, for which exposure is medicinal, exposure to all others is occupational (Table II). If we compare the effect of these human carcinogens on experimental animals, we find that nearly all are carcinogenic in one or more animal species, the exceptions being arsenic, haematite and possibly benzene. If we then compare target organs in man and experimental animals (Table III), we can see that often, but certainly not always, target organs coincide. This is certainly not a new observation, but it is perhaps worth stressing, as it may have some relevance in assessing the value of studies on chemicals for which human data are not available.

That exposure levels are mostly unknown means several things:

(1) that nobody really queried exposure of workers to compounds which, in most cases, before being found carcinogenic, were known to produce acute and subacute toxic effects;

(2) that there was no real interest in finding out the exposure levels which produced a high incidence of cancer, as they would have shown a fantastically high difference between the present levels or the accepted levels and the levels to which workers had been exposed for a long time. The example of vinyl chloride (VC), for instance, is quite demonstrative: at present, several companies are fighting for the acceptance of a level which lies between 25 and 10 ppm, while a few companies are orientated

towards accepting levels between 1 and 5 ppm. Although there is no evidence whatsoever that even 1 ppm would be without adverse effects, it is worth remembering that workers were exposed only recently to 2,000-3,000 ppm. At these levels of exposure, it is well known that a number of lesions and diseases were caused, but with the present upgrading of cancer as the disease *par excellence*, other sometimes very serious diseases are forgotten;

(3) that the recent interest to establish the actual levels causing cancer in exposed workers, could be rather suspicious. Somebody would surely be interested in demonstrating that cancer occurs only at very high levels of exposure and that low levels are "safe".

For 94 of the 196 chemicals, there is unquestionable evidence of carcinogenicity in experimental animals. For 89 of them, human exposure has been confirmed (Table IV) and again in the majority of cases, it is occupational (Table V). For 41 chemicals, a limited carcinogenic activity has been found in experimental animals. For most of these chemicals, human exposure has been confirmed and, as before, in a large proportion it is occupational (Table VI). For 26 chemicals, the available data were insufficient to reach any conclusion on their possible carcinogenicity in experimental animals, while for 18 the available data did not reveal a carcinogenic effect.

In general, there were more experimental than epidemiological or case reports (Table VII). This can in part be explained by the higher cost and longer duration of human than animal studies, but it also reflects the greater emphasis which for quite a long time was put on experimental rather than on human studies.

The case of recognized chemical carcinogens is (or at least should be) clear, as everybody agrees that human exposure to carcinogens must be avoided, although disagreement exists on how, to what extent and how quickly this should be done. A different and major problem is the evaluation of the possible carcinogenic effect of a chemical to man in the absence of epidemiological studies or case reports. Of the 196 chemicals considered in the IARC Monographs, there are 124 for which such a problem exists. For 15 of these (4,4'-methylene bis (2-chloroaniline) (MOCA), BHC, dieldrin, DDT, chlorobenzilate, amitrole, PCBs, CCl_4, hydrazine, 1,1-dimethylhydrazine, ethylene thiourea, *o*-dianisidine, beryllium, lead salts, β-propiolactone) the world production figure is above 500 thousand kilograms a year. Present regulations recommend a zero tolerance in food for chemicals for which experimental evidence of carcinogenicity exists. In so far as food additives are concerned, therefore, an extrapolation for public health purposes is carried out systematically with a procedure which obviously implies that experimental evidence of carcinogenicity is sufficient *per se* to suggest carcinogenicity in man (Tomatis *et al.* 1973)[15]. However, this cautious procedure, with which most people agree, has not been applied to other situations, and certainly not to chemicals present in and around factories.

In the literature there is an evident preoccupation of warning scientists about unduly extrapolating from experimental data to man and emphasis is, of course, put on the fallacy of interpreting toxicity data obtained in experimental animals as automatically indicating a danger for man. Very little emphasis, if any, if put on the mistakes made in the opposite direction, that is, mistakes made when results obtained in animals were not taken as indicative of a possible danger to man.

There is no evidence that a chemical which is carcinogenic to experimental animals will not in any circumstances produce tumours in man (Saffiotti 1973)[16]. Neither is there any scientific criteria on which to base the usual argument that as it is impossible to extrapolate from experimental data to man, experimental evidence of carcinogenicity has no value in attempting an assessment of a possible human risk. The fact is that an obvious declaration of impotence has been used for different purposes. There are data which indicate that experimental results can be taken as indicators of a possible human hazard and that measures should be taken to warrant an immediate control of the state of health of people who are or who have been exposed, and to adopt immediate steps to reduce or possibly eliminate exposures until the results are carefully assessed. There is really no justification to wait for the proof that a chemical causes cancer in man before measures to avoid exposure are taken (Doll 1967)[17].

The example of bis(chloromethyl)ether and vinyl chloride well illustrate this statement[18](Table VIII). In fact, experimental evidence of carcinogenicity of the former compound existed in 1968 and was confirmed in 1969, but it was only in 1973, after a retrospective epidemiological study showed an excess of lung cancer in workers exposed to bis(chloromethyl)ether that measures to reduce exposure in the working environment were adopted. Similarly, for vinyl chloride, experimental evidence of carcinogenicity existed already in 1970 and was long preceded by the evidence of toxic effects of the same type in man and experimental animals. It was only in 1974, however, that measures for drastically reducing its acceptable concentration were adopted and only after a report on the occurrence of angiosarcoma of the liver among workers exposed to vinyl chloride.

- not so for VCM
- if action taken in 1970 as 1974 would expect little difference in results to date.
- would expect some effect in about 1980-1985.

In these two cases, a more cautious attitude would have resulted in a successful prevention.

One of the discrepancies of the present situation is that on the one hand we accept that certain population groups are exposed to relatively high risks and that certain preventive measures are in some instances adopted once the risk is detected on the basis of the epidemiological evidence of an unusually high incidence of cancer. On the other hand, there are objections against the use in carcinogenicity testing of experimental models which will maximize the possible carcinogenic effect of a chemical under test (and in particular the use of high dose levels) as if this were an improper procedure which would never reflect the human situation and would give misleading results. It is difficult to accept these objections because in most instances when a chemical has been found to be closely related to cancer in man this was because the incidence was so high that it could be easily detected. The working environment, therefore, maximized the hazard to such a macroscopic effect that epidemiologists or alert physicians could not help but detect it. The hazard, however, is not necessarily limited to the workers involved in a particular manufacturing process: they are at the forefront of the risk, but this may expand far beyond the borders of the factories. The risk may be relatively low or at least low enough that normal epidemiological methods are unable to detect it, even if the incidence of cancer related to a given chemical could be numerically important as a large proportion of the population may be exposed. The observations of a few cases of angiosarcoma of the liver in persons with no occupational exposure to VC, but who had lived for many years in the proximity of factories utilizing polyvinyl chloride, and the

→ according to CDC / EPA } no known deaths.

clustering of cases of mesothelioma in areas close to asbestos factories (Greenberg and Davies 1974)[19], illustrate well this eventuality. -

That preventive measures are successful in decreasing cancer risks is proven, and of course not only in occupationally-exposed people. The removal or at least drastic reduction of occupational exposures to hazardous chemicals may be obtained in the majority of cases by an improvement in manufacturing procedures. These improvements do not represent in general too severe a blow to the economy of a factory, but just a marginal loss of profit. An example of the success which can be obtained in this way is the disappearance of the excess of nasal sinus and lung cancer in nickel workers in the UK and Norway, who began their work after an industrial process had undergone major changes in order to eliminate exposure of workers to dust and fumes (Doll *et al.* 1970, Pedersen *et al.* 1973)[20,21].

Another side of the same problem is the possibility of preventing or reducing the incidence of cancer in people who have already been exposed. Does prevention help in such a condition? According to Doll[22], "the effect of stopping exposure to a carcinogen after a prolonged period of exposure is likely to vary with the nature of the carcinogen". It also depends, for a given carcinogen, on the different target organs, as was the case of the persistence of the risk of developing nasal cancer and the decreasing risk of developing lung cancer up to 40 years after cessation of exposure to nickel carbonyl (Doll 1970)[20]. In a non-occupational situation, the high risk of lung cancer in heavy cigarette smokers decreased if exposure to cigarette smoke was discontinued but still remained higher than in people who had never smoked[22].

Once a chemical is marketed and produced in large amounts, the claim is often made that its withdrawl would be an economic disaster for-all, and that the reshaping of the manufacturing processes in order to protect workers from exposure would increase the cost of production to impossible levels. Of course, people who use these two arguments forget about the profit already made with the chemical. One can therefore explain why certain industries look at long-term toxicity tests as procedures "to satisfy whims rather than provide data for safety evaluation" (Gehring *et al.* 1973)[23]. Another argument is that all present health regulations are taken at the expense of the manufacturers and that this expense finally reverberates on the consumer (Gehring *et al.* 1973)[23]. It is therefore obvious that the manufacturers take it for granted that if the manufacturing process became more costly to satisfy the elementary protection of the workers and the general population, the product would have to be sold at a higher price.

SUMMARY

The International Agency for Research on Cancer has initiated a programme to evaluate the carcinogenic risk of chemicals to man. This programme is centered on the production of monographs on individual chemicals, consisting of data on use and production, carcinogenicity in experimental animals, epidemiological studies and case reports, and other biological data such as metabolism and mutagenicity, and ending with a balanced evaluation of all the data made by an international group of experts. Chemicals to be surveyed for the preparation of monographs have so far been selected among those for which some evidence or suspicion of carcinogenicity in experimental animals and/or man exists and for which human exposure is known to occur. Of the 196 compounds already evaluated, 17 have been found to be associated with cancer in man. Ninety-four compounds were definitely carcinogenic in experimental animals and 41 were shown to have a limited carcinogenic effect in experimental animals. A number of the chemicals found carcinogenic in experimental animals are produced in very large quantities. The type of exposure to the 17 chemicals found carcinogenic to man was occupational for 14, medicinal for two and dietary for one.

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Table I

NUMBER OF CHEMICALS EVALUATED	196
NUMBER OF CHEMICALS CARCINOGENIC TO MAN	17

TABLE II

CHEMICALS FOR WHICH CARCINOGENICITY TO MAN OR A STRONG SUSPICION OF CARCINOGENICITY TO MAN HAS BEEN FOUND

CHEMICAL	*TYPE OF EXPOSURE*	*TARGET ORGAN(S)*	*ROUTE OF EXPOSURE*	*EXPOSURE LEVEL*
AFLATOXIN?	Dietary	LIVER	Oral	5-15 µg/kg bw/day
4-AMINOBIPHENYL	Occupational	BLADDER	Inhalation, oral	Unknown
ARSENIC COMPOUNDS	Occupational, medicinal	SKIN, ?LUNG	Oral, inhalation	Unknown
ASBESTOS (CROCIDOLITE, AMOSITE & CHRYSOTILE)	Occupational	LUNG & PLEURAL CAVITY GASTROINTESTINAL TRACT	Inhalation, oral	Unknown
AURAMINE	Occupational	BLADDER	Oral, inhalation, skin	Unknown
BENZENE	Occupational	BONE MARROW	Inhalation, skin	Unknown
BENZIDINE	Occupational	BLADDER	Inhalation, oral, skin	Unknown
BIS(CHLOROMETHYL)ETHER	Occupational	LUNG	Inhalation	Unknown
CADMIUM OXIDE & SULPHATE	Occupational	PROSTATE, LUNG	Inhalation, oral	Unknown
CHROMIUM (CHROMATE PRODUCING INDUSTRIES)	Occupational	LUNG	Inhalation	Unknown
HAEMATITE (MINING)	Occupational	LUNG	Inhalation	Unknown
2-NAPHTHYLAMINE	Occupational	BLADDER	Inhalation, oral	Unknown
NICKEL (NICKEL REFINING)	Occupational	NASAL CAVITY, LUNG	Inhalation	Unknown
N,N-BIS(2-CHLOROETHYL)2-NAPHTHYLAMINE	Medicinal	BLADDER	Oral	4-350 g (total dose)
SOOT and TARS	Occupational Environmental	LUNG SKIN (SCROTUM)	Inhalation Skin contact	? 320 µg BaP/hr Unknown
STILBOESTROL	Medicinal	VAGINA, UTERUS	Oral	1.5-150 mg/day
VINYL CHLORIDE	Occupational	LIVER, BRAIN, LUNG	Inhalation, skin	50-3000 ppm

TABLE III

CHEMICAL CARCINOGENS IN MAN AND THEIR EFFECTS ON EXPERIMENTAL ANIMALS

CHEMICAL	*SPECIES*	*TARGET ORGAN(S)*	*TARGET ORGAN(S) MAN*
AFLATOXIN	Rat, trout, duck	LIVER, STOMACH, INTESTINE, KIDNEY	?LIVER
	Rat, mouse	LOCAL, LIVER, LUNG, TRACHEA	
4-AMINOBIPHENYL	Mouse, rabbit, dog	BLADDER	BLADDER
	Newborn mouse, rat	LIVER, MAMMARY GLAND, INTESTINE	
ARSENIC	Mouse, rat, dog	Negative	SKIN, LUNG, LIVER
ASBESTOS	Mouse, rat	LUNG, PLEURA, PERITONEUM	LUNG, PLEURA, INTESTINE
AURAMINE	Mouse, rat	LUNG, LOCAL, INTESTINE	BLADDER
BENZENE	Mouse	?LEUKAEMIA	BONE MARROW
BENZIDINE	Mouse, rat, hamster	LIVER	BLADDER
	Dog	BLADDER	
BIS(CHLOROMETHYL)ETHER	Mouse, rat	SKIN, LOCAL, LUNG	LUNG
CADMIUM OXIDE & SULPHATE	Rat	LOCAL, TESTIS	PROSTATE, LUNG
CHROMIUM COMPOUNDS	Mouse, rat	LUNG, LOCAL	LUNG
HAEMATITE	Guinea pig, mouse, hamster	Negative	LUNG
2-NAPHTHYLAMINE	Mouse	LIVER, LUNG	BLADDER
	Rat, rabbit	No effect	
	Hamster, dog, monkey	BLADDER	
NICKEL COMPOUNDS	Mouse, rat	LOCAL	NASAL CAVITY, LUNG
N,N-BIS(2-CHLOROETHYL)2-NAPHTHYLAMINE	Mouse	LUNG	BLADDER
	Rat	LOCAL	
SOOT and TARS	Mouse, rat	SKIN, LOCAL, LUNG, STOMACH*	SKIN (SCROTUM), LUNG
STILBOESTROL	Mouse	MAMMARY GLAND, LYMPHORETICULAR TISSUE, TESTIS, VAGINA	VAGINA, UTERUS
	Rat	HYPOPHYSIS, MAMMARY GLAND, ?URINARY BLADDER	
	Hamster	KIDNEY	
	Squirrel, monkey	UTERINE SEROSA	
VINYL CHLORIDE	Mouse, rat, hamster	LUNG, LIVER, KIDNEY, ZYMBAL GLAND	LIVER, LUNG, BRAIN

*Produced by some polycyclic hydrocarbons tested separately

Table IV

NUMBER OF CHEMICALS CARCINOGENIC

IN EXPERIMENTAL ANIMALS ONLY

94

HUMAN EXPOSURE KNOWN FOR	89
OCCUPATIONAL EXPOSURE KNOWN FOR	78*
MEDICINAL EXPOSURE KNOWN FOR	16
GENERAL ENVIRONMENTAL EXPOSURE KNOWN FOR	49*

*including 15 polycyclic aromatic hydrocarbons present in soot, tar and exhaust fumes

Table V

CHEMICALS CARCINOGENIC IN EXPERIMENTAL ANIMALS ONLY

	Compound	EXPOSURE			
		Unknown	Occupational	Medicinal	General Environmental
1	Acetamide		+		
2	2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole		+	+	
3	Amitrole		+		+
4	Aramite[R]		+		+?
5	Benz(c)acridine *		+		+
6	Benz(a)anthracene *		+		+
7	Benzo(b)fluoranthrene *		+		+
8	Benzo(j)fluoranthene *		+		+
9	Benzo(a)pyrene *		+		+
10	Benzo(e)pyrene *		+		+
11	Beryl ore		+		
12	Beryllium		+		
13	Beryllium oxide		+		
14	Beryllium phosphate		+		
15	Beryllium sulphate		+		
16	BHC (technical grades)		+		+
17	Calcium chromate		+		
18	Carbon tetrachloride		+		+
19	Chlorobenzilate		+		+?
20	Chrysene *		+		+
21	Cycasin				+
22	DDD		+	+	+
23	DDE		+		+
24	DDT		+		+
25	Diazomethane		+		

* present in soot and tars

	Compound	EXPOSURE			
		Unknown	Occupational	Medicinal	General Environmental
26	Dibenz(a,h)acridine *		+		+
27	Dibenz(a,j)acridine *		+		+
28	Dibenz(a,h)anthracene *		+		+
29	7H-Dibenzo(c,g)carbazole *				+
30	Dibenzo(a,e)pyrene *				+
31	Dibenzo(a,h)pyrene *				+
32	Dibenzo(a,i)pyrene *				+
33	3,3'-Dichlorobenzidine		+		
34	Dieldrin		+		+
35	1,2-Diethylhydrazine		+		
36	Diethyl sulphate		+		
37	Dihydrosafrole		+		+
38	3,3'-Dimethoxybenzidine (o-Dianisidine)		+		
39	trans-2[(Dimethylamino) methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole	+			
40	3,3'-Dimethylbenzidine (o-Tolidine)		+		
41	1,1-Dimethylhydrazine		+		
42	1,2-Dimethylhydrazine		+?		
43	Dimethyl sulphate		+		
44	Ethinyloestradiol		+	+	
45	Ethyl methanesulphonate	+			
46	2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole	+?			
47	Hydrazine		+		
48	Indeno(1,2,3-cd)pyrene *		+		+

* present in soot and tars

	Compound	EXPOSURE Unknown	Occupational	Medicinal	General Environmental
49	Isonicotinic acid hydrazide		+	+	
50	Isosafrole		+		+
51	Lead acetate		+		+
52	Lead phosphate		+		
53	Lead subacetate		+		
54	Lindane		+		+
55	Mestranol		+	+	
56	Methylazoxymethanol acetate				+
57	4,4'-Methylene bis (2-chloroaniline)		+		
58	4,4'-Methylene bis (2-methylaniline)		+		
59	Methyl methanesulphonate			+	
60	N-Methyl-N'-nitro-N-nitrosoguanidine		+		
61	Mirex		+		+
62	5-(Morpholinomethyl)-3-[(5-nitrofurfurylidine)-amino]-2-oxazolidinone		+	+	
63	4-Nitrobiphenyl		+		
64	1[(5-Nitrofurfurylidene)-amino]-2-imidazolidinone		+	+	
65	N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide		+	+	
66	N-Nitroso-di-n-butylamine	+			
67	N-Nitrosodiethylamine				+
68	N-Nitrosodimethylamine				+
69	Nitrosoethylurea		+		
70	Nitrosomethylurea			+	