Information on Chemical Carcinogens

1. Introduction

Chemical carcinogens are agents that are capable of inducing cancer in humans or animals. Most of the many hundreds of chemical carcinogens known have been recognised as such as a result of tests in rats or mice. A relatively small number are occupational carcinogens, having been found to cause cancer in persons exposed to them in the workplace. Sometimes occupational cancer has arisen from materials where the actual causative agent remains unknown. Some chemicals used as drugs are also known to have caused human cancer.

Many lists of human carcinogens have been published, and differ widely according to the strength of the evidence that is accepted. It should not be assumed that carcinogens recognised only experimentally are necessarily less hazardous than accepted occupational carcinogens that happen to have been encountered in industrial processes, often under working conditions now regarded as extremely poor.

Chemical carcinogenesis is a prolonged process with many stages, mostly very imperfectly understood, and a variety of other factors are known which potentiate or inhibit the development of cancer. Occupational cancer has commonly taken 20 or more years from first exposure to become apparent, and this time-lag contributes to the difficulties experienced in linking cause and effect. Nevertheless, identification of carcinogenic factors, coupled with changes in industrial practices and various legislative measures, have resulted in the virtual elimination of some former occupational cancers. Examples are cancer of the scrotum in chimney sweeps, cotton-spinners and tar workers, and bladder cancer in rubber workers. Asbestos dust, on the other hand, will present health problems for many years, though hopefully on a much smaller scale than when exposure to the most hazardous forms was very much greater.

Occupational causes of cancer have been much simpler to identify when there has been a greatly increased risk of workers developing a particular form of cancer, or when the cancer caused has been one that is very uncommon in the general population. For example, past conditions in those parts of the chemical industry using certain aromatic amines led to a 30-fold increased risk of workers developing bladder cancer. Mesothelioma of the pleura and peritoneum, and haemangiosarcoma of the liver, are normally very rare forms of cancer but have arisen in workers exposed to asbestos dust and vinyl chloride respectively. The limitations of epidemiology are such, however, that it is very difficult to identify a cause of cancer where the cancer is one already common in the general population (especially lung cancer), and where the proportional increase in risk is not very large.

Because of the long time-lag in chemical carcinogenesis, it is particularly important to avoid exposure of young persons to potential carcinogenic agents. Special care is also needed to avoid exposure to carcinogens and other harmful chemicals of women who are pregnant, or may become pregnant. This is because the foetus is at high risk from harmful chemicals ingested by the mother.

This document is particularly concerned with the many different types of chemical carcinogens, their potency as carcinogens, the wide differences in their biological effects, and other factors

influencing their risks of actually causing cancer. However, concern over possible carcinogenic risks must not deflect attention from the very many much shorter-term risks from chemicals. Apart from fire and explosion hazards, there are the many forms of toxic action that can rapidly cause death or serious injury. Chemicals must always be handled responsibly, not only with due regard for known hazards but also, especially in research, for the unexpected. A recent tragic example of this was the rapid development of irreversible brain damage from a relatively simple pyridine derivative (MPTP) formed during illicit drug synthesis.

2. Types of Chemical Carcinogen

Many, but not all, known chemical carcinogens fall into some fairly well-defined chemical classes, such as polycyclic aromatic hydrocarbons (PAHs), aromatic animes and nitro compounds, alkylating agents and N-nitroso amines and amides. The N-nitroso compounds do not include any accepted occupational carcinogens, but are outstanding in that most of the several hundred tested are potent experimental carcinogens. In the inorganic field, human cancers have been caused by occupational exposure to largely uncertain compounds of nickel, chromium and arsenic, and especially to asbestos dust.

3. Carcinogenic potency

The basic principle of toxicology, that it is the dose that makes the poison, was laid down over 400 years ago. Substances regarded as entirely innocuous will still be harmful in very large amounts, while highly toxic substances will not be harmful in sufficiently small amounts. Carcinogens are unusual in toxicology terms in that the effects of exposure are cumulative.

Chemical carcinogens similarly vary very greatly in potency. Recently much work has been done to express carcinogenic potency quantitatively as the daily dose that will result in cancer in 50% of test animals in long-term experiments (18 or 24 months, most of the life-span of a rat or mouse). Based on past tests judged sufficiently trustworthy, these show that carcinogenic potencies range over some 6-7 orders of magnitude, from aflatoxin B_1, carcinogenic for rats at only 1 μg per kg body-weight per day, to compounds with barely detectable activity at 1 g per kg per day. Many of the most important carcinogens fall around the middle of this range. There is no clear dividing line between very weak carcinogens and completely inactive substances.

Obviously, carcinogenic potency is an important factor to be considered in assessing to what extent a chemical reported carcinogenic is likely to be hazardous to health. It is not, however, the only factor. Since a chemical has to enter the body in order to elicit carcinogenic or other toxic effects, account also has to be taken of volatility or dustiness, which may lead to the substance being inhaled, and of course to the scale of its use. Some chemicals are much more readily absorbed through the skin than others.

4. Mechanisms of carcinogenic action

The basic biological action of a chemical leading to cancer is thought to be an attack on DNA, the basic genetic material of the cell, to produce a change that is not repaired by the body's DNA-repair mechanisms, and which is then passed from cell to cell during division. Such heritable changes are known as 'mutations'. Alkylating agents interact directly with DNA and other macromolecules, but most carcinogens (PAHs, aromatic amines, etc.) do not do so until they have

undergone one or more metabolic changes to yield an 'ultimate carcinogen'.

Many chemicals other than known carcinogens have long been known to induce mutations in living materials, i.e., are 'mutagens'. Recognition of the importance of metabolism of carcinogens to active agents suggested a close relationship between mutagens and carcinogens, and is the basis of many short-term tests (particularly the Ames bacterial test) being used as indicator of chemicals that may also be carcinogenic. Substances active in such tests are termed 'genotoxic'.

Some substances found to be carcinogenic, however, do not show genotoxic activity, and these are referred to as 'epigenetic' or 'non-genotoxic'. This ill-defined class includes tumour promoters, co-carcinogens, some hormones and immune-suppressants, which in various ways magnify or accelerate carcinogenicity by other agents, including viruses. For non-genotoxic carcinogens there may well be a threshold dose level below which there is no risk of any carcinogenic action. For genotoxic carcinogens, on the other hand, dose-response relationships have failed to show the existence of a threshold level though, as with toxic agents, there must be some level below which risks become negligible.

The value of a battery of short-term tests is increasingly seen as revealing mechanisms of biological action, rather than as simply indicating possibilities of carcinogenicity. Information on metabolic processes is also important, particularly with regard to differences in metabolism between experimental animals and man. Better understanding of this type indicates that some weakly carcinogenic agents of industrial importance are very unlikely to pose any significant risks of carcinogenesis in practice.

5. Carcinogenic chemicals

As already indicated, there are very great differences between chemical carcinogens in their carcinogenic potency, mechanisms of action and other factors influencing the extent to which they may pose a carcinogenic risk. In the lists which follow, indications of possible risks are given, based on the system of 1 to 3 stars as used at the University of Birmingham in its earlier information and rules for chemical carcinogen use (1980). As then, the gradings are necessarily very subjective and based on current knowledge, but **do** attempt to allow for factors such as volatility or persistence in the body as well as carcinogenic potency. It cannot allow, of course, for the scale and frequency of any intended use.

The letter H is used to show a RECOGNISED human carcinogen, usually occupational but also including some anti-cancer drugs. Chemicals without an H, particularly many N-nitroso compounds, may well pose greater carcinogenic risks in practice than many accepted human carcinogens. It is again emphasised that, even for many undoubted carcinogens, the principal risks of exposure often derive from their much shorter-term toxic actions.

***	High carcinogenic hazard
**	Significant carcinogenic hazard
*	Carcinogenicity established, but little hazard with reasonable care
No mark	Carcinogenicity weak or possible
H	Known to have caused cancer in humans

5.1 Aromatic amines

2- (or α-) Naphthylamine, 4-aminobiphenyl and benzidine (4,4'-diaminobiphenyl) are established causes of bladder cancer in industrial workers. Some related 2- and 3-ring aromatic amines are

also carcinogenic. Some activity has been detected in some single-ring amines.

Benzidine has had many uses in analytical chemistry and safer alternatives should be used. 3,3' ,5,5'-Tetramethylbenzidine and 3,3' ,4,4'-tetra-aminobiphenyl (diaminobenzidine) are free of significant activity, but o-tolidine and 3-amino- 9-ethylcarbazole are carcinogenic. The carcinogenicity of 1-naphthylamine appears to be entirely due to contamination with 2-naphthylamine.

H***	2-naphthylamine
H	1-naphthylamine
H***	4-aminobiphenyl
H***	benzidine
**	o-tolidine
**	3,3'-dichlorobenzidine
*	3,3'-dimethoxybenzidine (o-dianisidine)
	4,4'-methylenedianiline
*	4,4'-methylenebis (2-chloroaniline)
***	2-aminofluorene
***	2-acetamidofluorene
**	4-aminostilbene
**	3-amino-9-ethylcarbazole
*	quinoline
*	diphenylamine (if contaminated with 4-aminobiphenyl)
	aniline (main risks from toxicity)
	ethidium bromide (carcinogenicity unknown, but is a potent mutagen)

5.2 Aromatic nitro compounds

Those corresponding to carcinogenic aromatic amines should be assumed to be carcinogenic.

***	4-nitrobiphenyl
***	4,4'-dinitrobiphenyl
**	2-nitronaphthalene
**	2-nitrofluorene
**	many substituted 2-nitrofurans
**	4-nitroquinoline 1-oxide and related compounds
*	nitro derivatives of polycyclic aromatic hydrocarbons

5.3 Dyes

A number of azo and other dyes are carcinogenic for experimental animals. Methyl or methoxy groups can markedly increase activity. Many commercial dyes are of very low purity.

*	4-dimethylaminoazobenzene (butter or methyl yellow) (diethyl homologue is inactive)
*	o-aminoazotoluene
	chrysoidines (2,4-diaminoazobenzenes; methyl derivates more mutagenic and possibly more carcinogenic)
?H	auramine (some bladder cancer cases in manufacturing workers; this and weak activity of commercial dye possibly due to Michler's ketone)
	magenta (some bladder cancer cases in manufacturing workers, but no evidence that dye itself is carcinogenic)

5.4 Alkylating agents

These interact directly (i.e. without prior metabolism) with biological materials and commonly have irritant, toxic, mutagenic and carcinogenic actions. They include chemicals of major industrial importance, and also various drugs used in cancer treatment. Mustard gas and bis(chloromethyl) ether (BCME) have caused occupational lung cancer, while human cancer has also occurred in some patients treated with alkylating agent drugs. Any reactive alkylating

agent should be assumed to be potentially carcinogenic in addition to its other hazards.

BCME may arise unintentionally from interaction of formaldehyde with hydrogen chloride. Amounts formed in air appear to be generally very small, but high levels have been detected from Friedel-Craft mixtures containing formaldehyde, and commercial chloralkylation may have led to some lung cancer cases.

Methylation with diazomethane is known to be hazardous. Also its precursors methylnitrosourea, N-methyl-N'-nitroso-N-nitro-guanidine (MNNG) and especially methylnitrosourethane are potent carcinogens (see Section 6), though methyl-nitroso-o-toluenesulphonamide is not. The methylating agent methyl fluorosulphonate ('magic methyl') has been reported to cause rapid death after a relatively small laboratory spillage; for such substances possible carcinogenic risks are hardly relevant.

H***	bis(2-chloroethyl) sulphide (mustard gas)
H***	bis(chloromethyl) ether (BCME)
***	chloromethyl methyl ether (normally contains some BCME)
H***	various nitrogen mustard derivatives
**	alkyl methanesulphonates
**	dimethyl sulphate
***	methyl fluorosulphonate (very high toxicity - see above)
***	diazomethane and certain precursors (see above)
**	dimethylcarbam(o)yl chloride
*	triethylene phosphoramide (TEPA)
*	triethylene thiophosphoramide (thio TEPA)
**	tris(2,3-dibromopropyl) phosophate (former clothing flameproofer)
**	2,3-dibromo-1-chloropropane (has caused sterility in males)
**	2,3-dibromopropan-1-ol
	bromomethane (methyl bromide)
	iodomethane (methyl iodide)
?H*	benzotrichloride
**	β-propiolactone
*	propane sultone
?H	some aziridines (ethyleneimines)
?H*	ethylene oxide
	other epoxides where ring is unstable

5.5 Other organic halides, etc

Compounds with a very stable carbon-halogen bond may still be metabolished to a carcinogenic species, including vinyl chloride which led to liver blood-vessel cancer in heavily-exposed workers. Various polyhalogenated chemicals are of considerable concern because of their persistence in the environment and the body, toxic effects and association with highly toxic polychlorinated dibenzodioxins and dibenzofurans; relatively little is known about the carcinogenic risk. For halogenated solvents, see section F.

H*	chloroethene (vinyl chloride)
*	chloroprene
H**	cyclophosphamide
	polychlorinated biphenyls (PCBs)
	polybrominated biphenyls (PBBs)
	some polychlorinated pesticides

5.6 N-Nitroso compounds and hydrazines

A very high proportion of nitrosamines (RR'N.NO) tested are potent experimental carcinogens, with a very wide range of body organs being affected. The initial discovery resulted from the occurrence of severe liver poisoning from the use of N-nitrosodimethylamine as a solvent by laboratory workers. Risks from many are increased by their volatile nature.

Related carcinogens include alkylnitrosamides (e.g. methylnitrosourea), 1,2-dialkylhydrazines, diazoalkanes, and guanidines such as the strong mutagen MNNG. Involvement of some N-nitroso compounds in some human cancers is strongly suspected but not firmly established.

***	N-nitrosodimethylamine (dimethylnitrosamine)
***	N-nitrosodiethylamine (diethylnitrosamine)
**	most other compounds RR N.NO, with some exceptions (N-nitrosodiphenylamine, and those with a tert-butyl group)
*	N-nitrosodiethanolamine (found in engineering oils bases on ethanolamines with nitrite inhibitor)
**	N-nitrosopiperidine
**	N-nitrosopiperazine
**	N-nitrosomorpholine
*	N-alkyl-N-nitrosoureas, $H_2N.CO.N(NO)R$, also N-nitroso di- and tri-alkylureas
***	N-alkyl-N-nitrosourethanes (powerful local carcinogens)
**	N-alkyl-N'-nitro-N-nitrosoguanidines (e.g. MNNG)
**	1,2-dialkylhydrazines, RNH.NHR'
*	procarbazine (drug; substituted 1,2-dimethylhydrazine)
**	azoalkanes, R.N-N.R'
**	azoxyalkanes, R.NO-N.R;
*	methylazoxymethanol
*	1-phenyl-3,3-dimethyltriazene and analogues

5.7 Polycyclic aromatic hydrocarbons and heterocycles

Many such compounds containing 4 to 6 aromatic rings are potent carcinogens, their risks being increased by their likely persistence in the body. Benzo(a)pyrene is among the complex mixtures of such compounds formed during incomplete combustion of organic matter, held responsible for occupational scrotal and skin cancer in workers in contact with soots, tars and mineral oils. Their role in other forms of human cancer is uncertain, but they may well be one of the factors in lung cancer caused by smoking.

Use of the pure compounds outside cancer research is (or should be) very limited, but they require particular care in handling owing to their potency and likely persistence within the body.

***	benzo(a)pyrene
***	7,12-dimethylbenz(a)anthracene
***	3-methylcholanthrene
***	dibenz(a,h)anthracene
H*	cutting oils, lubricants, tars, soots etc., when contaminated with agents of this type.

5.8 Naturally occurring carcinogens

A variety of plants and micro-organisms produce carcinogenic metabolites. Having complex structures they are not very volatile, but some are highly potent and may represent considerable hazards if handled as isolated chemicals. Aflatoxins, metabolites of a fungus contaminating foodstuffs, may have contributed to the high level of liver cancer in parts of tropical Africa. Dusts encountered in the woodworking and leather industries have caused cancer of the nasal sinuses in workers, but the agents responsible are not known.

?H**	aflatoxin B1 and less active analogues (from an Aspergillus)
*	sterigmatocystin (from an Aspergillus)
*	griseofulvin (from a Penicillium)
*	streptozotocin (methylnitrosourea glucoside; from a Streptomyces)

* cycasin (methylazoxymethanol glucoside; from Cycads)

* patulin (carcinogenic on injection but not orally)

* bracken fern (complex toxic and carcinogenic metabolites)

** phorbol esters (potent tumour-promoting and co-carcinogenic constituents)

H* dusts from certain hardwoods

5.9 Inorganic carcinogenic agents

Various processes involving mining, refining and uses of some metals, particularly nickel and chromium, have been associated with occupational cancers of the respiratory tract. Exposures to dusts and fumes have been complex, and are of uncertain relevance to work under laboratory conditions, where toxic hazards are probably much more important.

H* **nickel**
(dusts and fumes have caused lung and nasal sinus cancers in workers. Various compounds, possibly only sparingly soluble ones, are carcinogenic in animals, particularly nickel subsulphide Ni3S2 but not amorphous NiS)

H* **chromium**
(human and experimental lung carcinogen; apparently Cr(VI) compounds only)

H* **beryllium**
(human and experimental lung carcinogen)

?H **cadmium**
(dubious evidence for small increase in risk of prostate cancer)

H* **arsenic**
(inorganic compounds carcinogenic for human skin and lung in former medicinal and agricultural uses)

H*** **asbestos dust**
(major occupational health hazard, having led to cancer of lung, particularly in smokers, mesothelioma of the pleura and peritoneum, and crippling fibrous degeneration of the lung. Uses and handling subject to strict legislative controls.

6. Toxicity and carcinogenicity of some solvents and other compounds

Many solvents are used in particularly large quantities, and the volatility of many contributes to the possibilities of excessive exposure. They vary very greatly in their toxicity, some show carcinogenicity in animals, and **benzene is an accepted occupational carcinogen for humans**. Some (1,1,1-trichloroethane, tetrachloromethane) may be phased out to help control ozone layer depletion.

H** **Benzene**
This highly toxic bone-marrow poison can cause severe or fatal anaemia. Accepted cause of leukaemia from high exposure of workers in various occupations. Toluene and other alkylbenzenes are detoxified by metabolism of the alkyl group(s); they are correspondingly less toxic, with no suspicions of carcinogenic risk.

Dichloromethane (methylene chloride)
Some evidence for weak carcinogenicity of borderline significance only.

Trichloromethane (chloroform)
Toxicity high; has given slight evidence for experimental carcinogenicity.

?H* **Tetrachloromethane (carbon tetrachloride)**
Toxicity high. Experimental liver carcinogen, suspected in having caused liver cancer in a few heavily exposed workers.

Bromomethane (methyl bromide)
Fumigant use has caused toxic effects and some deaths. Some experimental evidence for carcinogenic action.

Trichloroethylene
Readily breaks down to more toxic agents in absence of an inhibitor. Very weak experimental carcinogen, by mechanisms not applicable to humans.

Tetrachloroethylene (perchloroethylene)
Evidence for weak carcinogenicity of borderline significance only.

1,2-Dichloroethane (ethylene dichloride)
Has caused many cases of acute poisoning. Some evidence for experimental carcinogenicity.

** **1,2-Dibromoethane (ethylene dibromide)**
Toxicity high, and is a potent experimental carcinogen, leading to increasing restrictions on its commercial use.

1,1,1-Trichloroethane (methyl chloroform)
No evidence for any carcinogenicity, but has caused fatalities through high industrial exposure and solvent abuse.

1,2-Dichlorobenzene (o-dichlorobenzene)
Carcinogenicity tests have been negative.

isoPropanol
Former 'strong-acid' process of manufacture caused cases of nasal sinus cancer in workers. No evidence that solvent itself is carcinogenic.

1,4-Dioxane
High exposures have caused deaths in workers. High dosage to rats and mice in drinking water were carcinogenic, but there is no human evidence for carcinogenicity.

Dimethylformamide
Heavy occupational exposure has given rise to suspicions of testicular damage and cancer.

Dimethyl sulphoxide (DMSO)
No reason to suspect carcinogenicity, but may facilitate entry of more harmful substances into the body.

*** **Hexamethylphosphoramide (hexametapol) (HMPA)**
Inhalation at extremely low levels has induced nasal cancer in rats. The mechanism of this may not be directly relevant to man, but pending further knowledge it must be assumed to be a significant carcinogenic hazard for man also.

Formaldehyde and formalin
Highly irritant and toxic. Inhalation at levels causing significant tissue damage causes cancer in nasal sinuses of rats. To date no reliable evidence that extensive occupational exposure has caused human cancer.

Glutaraldehyde
Highly irritant and toxic. No evidence to date for carcinogenicity.

* **Butadiene**
Clearly carcinogenic for rats and mice inhaling high levels of the gas. No evidence that large-scale industrial use has been carcinogenic for humans.

* **Acrylamide**
Toxicity high, including by skin contact. Accepted neurotoxin, with evidence accumulating that it may cause testicular damage and genetic effects. A weak experimental carcinogen.

?H* **Acrylonitrile**
High toxicity for nervous system, with effects similar to cyanide. Some suspicions of possible occupational carcinogenesis.

* **Ethyl carbamate (urethane)**
Experimental carcinogen, but most tests required presence of a tumour promoter also.

7. Epidemiological Surveys of chemists

Two studies of the mortality of chemists (USA, 1969; Sweden, 1976) indicated that some causes of death were less common in chemists than in the general population, but that there was an increased risk of death from lymphoma (cancer of the lymphoid system). In Britain the Royal Society of Chemistry studied mortality data from 1965-1989 and the results showed overall low mortality rate but with an excess mortality from lymphatic and haematopoietic cancers, in particular leukaemias.

Development of lymphoma, probably a virally-induced form of cancer, can be an unfortunate consequence of treating transplant patients with drugs to suppress their immune system. It seems possible that heavy exposure to some as yet unidentified chemicals in the workplace might similarly have an immunosuppressive action, which could then trigger development of lymphoma in some people. While this at present is speculative, it emphasises the desirability of avoiding excessive exposure to chemicals in general, not simply those already recognised as having toxic or carcinogenic actions.

8. Causes of cancer

The proportion of cancers resulting from occupational carcinogenesis has been controversial, but has generally been put at around 5% of the total incidence. Such estimates reflect working conditions of some two decades earlier. With greater knowledge and improvements in working conditions in countries such as Britain, the proportion of cancer attributable to working conditions will hopefully be less and decreasing with time.

Smoking (and other ways of using tobacco) are now held responsible for one third of all cancer deaths in Britain and the USA, largely but not entirely those from lung cancer. A high, but much more uncertain, proportion of cancers is attributed to various unsatisfactory aspects of diet. Much heart disease, as well as other diseases characteristic of the 'western' way of life, are also attributed in large measure to smoking or dietary factors.

Many serious diseases, once accepted as inevitable, are thus now regarded as having definite causes and as being capable of prevention. For a detailed study of the causes of cancer (in the USA but very relevant to Britain also), the now classic analysis is by the British epidemiologists R Doll and R Peto ('*The Causes of Cancer: quantitative estimates of avoidable risks of cancer in the United States today*' Oxford University Press, 1981). At the more popular level, P Goodwin's '*Can you Avoid Cancer?*' (British Broadcasting Corporation, 1984) can be strongly recommended.

The following brief bibliography may also be useful:

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