Guidelines on Handling Chemical Carcinogens, Teratogens and Mutagens

The latest edition of this document incorporates the requirements of CoSHH 2002 and the amendments of CoSHH 2004

1. Background, Scope and Purpose of the Code

The Control of Substances Hazardous to Health Regulations 2002 (section 7) details specific legal duties relating to the use of carcinogens, including a hierarchy of precautions which are MANDATORY.

The purpose of this document is to provide Heads of Departments and others responsible for the use of known or suspected carcinogens, teratogens and mutagens guidelines for use. These guidelines must be considered when performing CoSHH assessments for such substances and can be incorporated, where appropriate, into departmental policies and specific experimental procedures.

2. Definitions

Carcinogens are agents which cause cancer. They can be categorised according to the degree of certainty that they cause cancer:

- known carcinogens
- suspected carcinogens
- agents of undetermined carcinogenicity
- non-carcinogens

This document relates to known and suspected carcinogens, although all undetermined agents must be handled with caution.

The statutory requirements in COSHH 2002, relate specifically to those substances or preparations which would be classified as carcinogenic (category 1) or carcinogenic (category 2) under regulation 4 of the CHIP regulations and substances or preparations listed in Schedule 1 or arising from a process specified in Schedule 1 (appendix 1 of this document)

Teratogens produce abnormalities in the growing embryo or foetus

Mutagens damage the genes causing heritable abnormalities in offspring.

For the purposes of the University Guidelines, no further distinction is drawn between these three categories. The guidelines concentrate on carcinogens but the procedural requirements apply equally to teratogens and mutagens.

3. Classes of Chemical Carcinogens

The following classes of chemicals are known to contain carcinogens:

- polycyclic aromatic hydrocarbons
- aromatic amines
- N-nitroso compounds
- azo dyes
- alkylating agents
- some naturally occurring compounds

Some known carcinogens in these categories are listed in Appendix 3: the list is not comprehensive and the omission of any compound does not imply that it is free from carcinogenic activity.

If an investigator is uncertain about the carcinogen risk of any agent, the available literature must be surveyed adequately before the substance is brought on to University premises. Producers and suppliers of chemicals are often a good source of information.

4. Background Information of Carcinogenesis

Carcinogenesis is the name given to the process by which cancer develops from normal tissues and their constituent cells. Irrespective of the nature of the causative agents, the process is characterised by certain general properties which are stated here because they illustrate some of the problems encountered in the identification of a carcinogenic hazard.

Cancer is a common condition and is thought to be most often due to environmental causes rather than arising spontaneously. Important known associations with an increased risk of cancer in humans include smoking (lung cancer), sexual promiscuity (cancer of the cervix) and low-fibre diet (large bowel cancer). It is estimated that about 4% of all cancers result from occupational activities.

4. 1 Dose

Some carcinogens are extremely potent and can induce cancer at very low dose levels in a susceptible species. There is often no knowledge available about the lower threshold of dose below which cancer will not occur. The probability that cancer will result is usually proportional to the dose, except that very high doses may have more immediate toxic effects.

4.2 Duration of Exposure

Unlike radiation protection control, there is no simple way of monitoring individual exposure to chemical carcinogens. A single exposure to a carcinogen may be sufficient to induce cancer.

4.3 Latency With carcinogens

There is no immediate indication that harm has resulted from exposure, unless the agent has some other toxic effect. Long intervals elapse between exposure to carcinogens and the appearance of any resulting tumours. Intervals of two or three decades are not unusual.

4.4 Co-factors

Some carcinogenic agents are unable to produce cancer alone. Subsequent exposure to another agent is necessary to amplify or promote the initial carcinogenic injury.

4.5 Routes of Entry

Carcinogens can enter the human body by the following routes: -

- by mouth into the gut
- by inhalation into the lungs
- by skin contact

The resulting cancers do not necessarily appear at the site of entry, because carcinogens require chemical transformation in the body into their active form.

5. Prohibitions Relating to Certain Substances

The use of the following substances is banned under the *Control of Substances Hazardous to Health Regulations 2002*: -

- 2-naphthylamine
- benzidine
- 4-aminodiphenyl
- 4-nitrodiphenyl

The ban includes their salts and any other preparation containing more that 0.1% of them. The use of benzene is also prohibited for most purposes. Although its use in research and analysis is permitted under law, it is the University policy to ban its use unless specific permission for a given procedure has been obtained from Safety Services. (Note that the use other substances is also prohibited by law but not generally for reasons of carcinogenicity)

6. Requirements of the CoSHH Regulations

In order to comply with the CoSHH Regulations you must:-

- Step 1 - Assess the Risk
- Step 2 - Decide what precautions are needed, bearing in mind the specific requirements for carcinogens
- Step 3 - Prevent (preferably) or control exposure adequately
- Step 4 - Ensure that control measures are working adequately and have appropriate maintenance
- Step 5 - Monitor exposure, if necessary
- Step 6 - Carry out health surveillance, if necessary
- Step 7 - Prepare plans & procedures to deal with emergencies (accidents and incidents) and ensure the necessary equipment etc is available
- Step 8 - ensure that all workers and others who could be in the area receive appropriate information, training and supervision

There is a helpful leaflet on the HSE web-site, entitled "*COSHH: A brief guide to the Regulations*" which can be found at http://www.hse.gov.uk/pubns/indg136.pdf

7. Assessment of Procedures

There is a requirement under CoSHH to assess any procedure involving a hazardous substance before the commencement of work. This is particularly vital with carcinogens since there is unlikely to be any early warning of adverse effects. An approved University of Sheffield CoSHH form should be used as a guide.

The results of the assessment should include, or take account of, the following as a minimum: -

- the nature, hazard and extent of potential exposure
- any workers who may be particularly at risk, including the possible risk to pregnant women
- whether substitution by a less hazardous substance is reasonably practicable
- the control measures to be applied
- operating procedures to ensure minimum exposure
- procedures for maintenance and emergencies
- use of personal protective equipment
- monitoring procedures (if appropriate)
- health surveillance (if appropriate)
- arrangements for information and training
- The assessment should be reviewed if there is any indication that control measures are not working efficiently and routinely on an annual basis

8. Recording of Procedures

All work involving known or suspected carcinogens must be pursued according to written departmental procedures. Specific procedures for each operation will be drawn up in the light of the assessments.

9. Use of Alternative Substances

Investigators should find out whether suitable, safer alternatives exist before using a reagent which is a known or suspected carcinogen. Obviously if the experiment involves carcinogenesis, then there can be no alternative but to use the material. Safer alternatives may exist if the agent is being used for other laboratory purposes.

In chemical synthesis, due consideration should be given to the possible carcinogenic properties of starting materials, intermediates, reaction products and by-products. Unfamiliar techniques should be practiced using a non-carcinogen before commencing work with the carcinogen(s) and with due regard for Home Office regulations in the case of animal work.

10. Approval for the Work

The Head of Department or person with designated authority must approve all new and existing procedures involving known or suspected carcinogens. They must be satisfied that the use of the agent is essential, that the proposed scale of the work is justified, that adequate facilities exist for use, storage and disposal, and that the investigator in charge of the project is competent to work with the agent. A written record of the project summary, the

known or suspected carcinogen, the quantity used, handling and disposal procedure, and the name(s) of the user must be kept in the departmental records for 40 years. If the department ceases to exist, the record must be deposited in a suitable archive.

11. Use of Carcinogens for Teaching Purposes

The use of carcinogens, particularly those regulated by law, for teaching purposes should be avoided. If it is considered that their use in a teaching procedure is unavoidable, the need and conditions of use must be reviewed annually by the Head of Department. In any case, all the legally required safety precautions must be followed.

12. Notification and Records

Heads of Department or responsible staff designated by them must be notified before any known or suspected carcinogen is brought into the department. Heads of Department or responsible staff designated by them must keep written records of the acquisition and use of any known or suspected carcinogens in their department.

The record must include:

- the full chemical name of the carcinogen, along with any trade names or short names by which it will be known.
- the title of the project
- quantity issued, used and disposed of
- names of approved users

The records must be kept for 40 years and must be available for inspection by the Head of Safety Services or his delegated authority at any time.

All personnel associated with the procedure must be informed in advance that a known or suspected carcinogen is being used. This includes animal workers, who must be briefed about the material and potential hazards. Due regard must also be paid to any other personnel who could be involved, such as those who may be exposed during disposal, maintenance or emergencies.

13. Storage

Heads of Department must ensure that all substances listed in Appendices 1 and 2 of this document are kept in secure, locked storage except when in immediate use. Access to the storage facility must be restricted to named, authorised staff. Carcinogens must be stored in appropriate, closed, clean and clearly labelled containers. Over-stocking must be avoided.

Cupboards and refrigerators containing carcinogens must be labelled with a"carcinogen" sign. Carcinogenic waste products must be clearly labelled and stored safely until disposed of in the manner designated by the written procedure.

14. Control of Exposure

If the use of a carcinogen is deemed to be essential, then adequate control of exposure must be ensured. All the following control measures are legally required: -

14.1 The process and handling systems must be totally enclosed unless this is not reasonably practicable.

14.2 Plant, processes and systems of work which minimise the generation of, or suppress leaks of, fumes and vapours of carcinogens must be employed. Procedures must be in place to contain spillages.

14.3 The quantity of carcinogen in the workplace must be limited.

14.4 The number of persons who might be exposed to a carcinogen must be kept to a minimum. Non-essential personnel should be excluded. This will apply as much in an emergency situation as during routine work.

14.5 Eating, drinking and smoking in areas that may be contaminated by carcinogens must be prohibited. Similarly, the use of snuff, the application of cosmetics and finger-mouth contact is inappropriate in such areas.

14.6 Hygiene measures including adequate washing facilities must be provided. All users should wash their hands in luke-warm (rather than hot) water before leaving the laboratory or work area.

14.7 Walls and surfaces must be cleaned regularly.

14.8 Suitable and sufficient warning signed must be displayed in those areas and installations which may be contaminated by carcinogens.

14.9 Carcinogens must be stored in a secure place and in suitable, closed and clearly labeled containers

14.10 Protective Clothing

a) If the above measures do not provide adequate control, the use of suitable personal protective equipment shall, in addition to the above measures, be obligatory.

b) It is however University policy that regardless of whether control measures are deemed to be adequate, a laboratory coat and suitable impervious gloves together with safety spectacles must be worn whenever carcinogens are in use.

c) Protective clothing must not be worn outside the area designated for handling carcinogens. In shared areas due precautions must be taken in handling telephones, pens and other equipment which could be used by other people

d) The possibility of exposure to carcinogens by inhalation should normally be controlled by engineering means. It would be regarded as very exceptional for a worker to require the use of personal respiratory protective equipment. If the use of a cartridge mask is required then the user must hold a current training voucher.

15. High Risk Operations

This list is NOT to be regarded as definitive and may be extended in the light of individual experience or knowledge.

- Any process which can produce aerosols, vapours or dusts of carcinogenic substances
- Synthesis of carcinogens using for example distillation, crystallisation, filtration, electrophoresis or chromatography
- Storage and manipulation of carcinogenic gases, volatile carcinogens and

compounds that decompose spontaneously evolving a carcinogen
- Weighing of carcinogens and the preparation of solutions containing them
- Recovery of carcinogens from TLC plates and other separation procedures
- Changing of traps and exhaust filters
- Husbandry of animals treated with carcinogens

Careful thought must be given to preventing exposure during these operations. Since they all involve standard techniques, it is easy to forget their risk potential. However, concern over the long-term hazards of carcinogens must not be allowed to divert attention from the precautions essential for protecting against most immediate hazards such as acute toxicity, fire etc.

16. Disposal of Carcinogens

The procedure for the safe disposal of carcinogens and materials contaminated by them must be determined before the agent is taken into the department. Known or suspected carcinogens must be disposed of safely: this is normally by incineration or by disposal to a specialist contractor. These agents must not be washed down the drains or placed in the general waste bins. Waste litter from the cages of animals exposed to known or suspected carcinogens must be disposed of in sealed containers according to University waste procedures. Safety Services may be able to advise on the procedure for specific agents and on disposal by specialist contractors.

It should be noted that the disposal of toxic waste is a costly exercise and appropriate budgetary arrangements must be made during the planning stages of the procedure.

Decontamination methods used for experimental residues and glassware should ensure complete chemical conversion into non-carcinogenic substances. Only named persons who have been specifically instructed in the appropriate safe procedures should be employed to wash-up contaminated glassware.

17. Monitoring of the Workplace

Because exposure to carcinogens can result in serious health effects, consideration should be given to monitoring procedures. This should take two forms:

a) A regular check at pre-determined intervals that procedures are being followed and are effective.

b) Where there is possibility that containment may not be effective and a suitable environmental monitoring procedure should be instigated.

Environmental monitoring is mandatory, by law, in the case of any procedure using vinyl chloride monomer.

Records of monitoring should be made available to those involved in the procedure and should be kept for at least 40 years.

18. Health Advice and Surveillance

Health surveillance is appropriate in the case of all carcinogenic substances unless exposure is not significant. It is required by law in the case of persons using:

- vinyl chloride
- 1-naphthylamine and its salts
- orthotoluidine and its salts
- dianisidine and its salts
- dichlobenzidine and its salts

Females who are pregnant must not handle suspected carcinogens: the risk of teratogenic effects is greatest in the early stage of pregnancy. Female staff who work with known or suspected carcinogens and who are contemplating pregnancy should seek medical advice from the Occupational Health Unit or their own General Practitioner.

19. Accidents

A record must be kept of all accidents involving known or suspected carcinogens, even if there is no apparent injury. Each accident must be reported to Safety Services following the usual procedure. Records must be kept for 40 years.

Contact with skin, eyes or any body surface must be followed by liberal washing with cold water (not using soap) and medical advice sought on subsequent steps.

20. Information, Instruction and Training

Appropriate instruction, information and training must be given, by law, to all users of carcinogens. Because the manifestations of exposure may be delayed for several decades it is vital that such instruction and training is to a very high standard. Everyone using carcinogenic materials should be fully aware of the risks, the correct procedures for the use of such materials and the action to take in an emergency.

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Appendix One

Substances and Processes Defined in Schedule 1 of COSHH 2004 to which the definition "carcinogen" relates: -

Aflatoxins

Arsenic

Calcining, sintering or smelting of nickel copper matte or acid leaching or electro-refining of roasted matte

Coal soots, coal tar, pitch and coal tar fumes

Hard wood dusts

Isopropyl alcohol manufacture (strong acid process)

Leather dust in boot or shoe manufacture

Magenta manufacture

Mustard gas (B,B'Dichlorodiethyl sulphate)

Rubber manufacture

Used engine oils

Note that any substance defined as "carcinogen - category 1" and "carcinogen category 2" under the Chemicals (Hazard Information and Packaging) Regulations 1993 also attract the legal provisions under the Control of Substances Hazardous to Health Regulations 2002.

Appendix Two

A. Examples of Known or Suspected Carcinogens

This list gives only a few examples. It is not comprehensive and the omission of any agent from this list does not deem it to be free of carcinogenic activity.

As a guide to the hazard, the following designations are used:

*** = High carcinogenic hazard
** = Significant carcinogenic hazard
* = Carcinogenicity established, but little hazard if careful
(no mark) Carcinogenicity weak or possible
H = Known to have caused cancer in humans

1. Aromatic Amines

Benzidine (4,4'diaminobiphenyl), 2-naphthylamine and 4-aminobiphenyl are established causes of bladder cancer in industrial workers. They were banned from British industry by the Carcinogenic Substances Regulations 1967 (now superseded by CoSHH). Some related 2- and 3- ring aromatic amines are also carcinogenic, and some were controlled by the Regulations. 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-toluidine and 3-amino-9-ethylcarbazole are carcinogenic. The carcinogenicity of 1-naphthylamine appears to be entirely due to contamination with 2-naphthylamine.

H***	• 2-naphthylamineH 1-naphthylamine • 4-aminobiphenyl • Benzidine
***	• 2-aminofluorene • 2-acetamidofluorene
**	• o-toluidine • 3,3'-dichlorobenzidine • 4-aminostilbene • 3-amino-9-ethylcarbazole
*	• 3,3'-dimethoxybenzidine (o-dianisidine)4,4'-methylene dianiline • 4,4'-methylenebis (2-chloroaniline) • Quinoline • Diphenylamine (if contaminated with 4- aminobiphenyl)
No mark	• aniline (main risk from toxicity) • ethidium bromide (carcinogenicity unknown, but is a potent mutagen)

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 derivative of polycyclic aromatic hydrocarbons

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 yellow or Methyl yellow) • o-aminoazotoluene chrysoidines (2,4-diaminoazobenzenes methyl - derivatives are more mutagenic and may be more carcinogenic)
?H	• Auramine (some bladder cancer cases in manufacturing workers) • Magenta (some bladder cancer cases in manufacturing workers but no evidence that the dye itself is carcinogenic)

4. Alkylating Agents

These interact directly (ie 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 for the treatment of cancer. 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 it forms precursors methylnitrosourea,

N-methyl-N'-nitroso-N-nitro-guanidine (MNNG) and especially methylnitrosourethane are potent carcinogens, though methylnitroso-p-toluenesulphonamide is not.

The methylating agent fluorosulphate ("magic methyl") has been reported to cause rapid death after a relatively small laboratory spillage; in such cases possible carcinogenic risks are hardly relevant.

H***	• Bis(2-chloroethyl) sulphide (mustard gas) • Bis(chloromethyl) ether (BCME) • Various nitrogen mustard derivatives
***	• Chloromethyl methyl ether (normally contains some BCME) • Methyl fluorosulphate (very high toxicity)

****	• Alkyl methanesulphonates • Dimethyl sulphate • Dimethylcarbam(o)yl chloride • Tris(2,3-dibromopropyl)phosphate (former clothing flameproofer) • 2,3-dibromo-1-chloropropane (has caused sterility) • 2,3-dibromopropan-1-ol • Beta-propiolactone
***	• Triethylene phosphoramide (TEPA) • Triethylene thiophosphoramide (thioTEPE) • Propane sultrone • Ethylene oxide
?H*	• Benzotrichloride • Some aziridines (ethyleneamines)
No mark	• Bromomethane (methyl bromide) • Iodomethane (methyl iodide) • Other epoxides where the ring is unstable

5. Other organic halides etc

Compounds with a very stable carbon-halogen bond may still be metabolised 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 effectsand association with highly toxic polychlorinated dibenzodioxins and dibenzofurans; relatively little is known about the carcinogenic risk. For halogenated solvents see section B.

H**	• Cyclophosphamidepolychlorinated biphenyls (PCBs) • Polybrominated biphenyls (PBBs) • Some polychlorinated pesticides
H*	• Chloroethene (vinyl chloride)
***	• Chloroprene

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 of many are increased by their volatile nature. Related carcinogens include alkylnitrosamides (eg 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) • N-alkyl-N-nitrosourethanes (powerful local carcinogens)
****	• Most other compounds RR'N.NO with some exceptions (N-nitrosodiphenylamine and those with a tert-butyl group)

	• N-nitrosopiperidine • N-nitrosopiperazine • N-nitrosomorpholine • N-alkyl-N'-nitro-N-nitrosoguanidines (eg MNNG) • 1,2-dialkylhydrazines, RNH.NHR' • Azoalkanes, R.N-N.R' • Azoxyalkanes, R.NO-N.R'
*	• N-nitrosodiethanolamine (found in engineering oils based on ethanolamines with nitrite inhibitor) • N-alkyl-N-nitrosoureas, H2N.CO.N(NO)R, also N- nitroso di- and tri-alkylureas • Procarbazine (drug - substituted 1,2- dimethylhydrazine) • Methylazomethanol • 1-phenyl-3,3-dimethyltriazene and analogues

7. Polycyclic aromatic hydrocarbons and heterocycles

Many such compounds containing 4 and 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 and is 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 are (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 • Dibenz(a,h)anthracene • 3-methylcholanthrene
**	• Certain benzacridines and similar heterocyclic compounds
H*	• Cutting oils, lubricants, tars, soots, when contaminated with agents of this type

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 hazard if handled as the 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 wood working 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 Aspergillus)
**	• Phorbol esters (potent tumour-promoting and co-carcinogenic constituents)
*	• Sterigmatocystin (from Aspergillus)

	• Griseofulvin (from Penicillin) • Streptozotocin (from a Streptpmyces) • Cycastin (from Cycads) • Bracken fern
H*	• Dusts from certain hardwoods

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***	**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 control)
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) **Chromium** (human and experimental lung carcinogen; apparently Cr(VI) compounds only) **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 use)

B. Toxicity and Carcinogenicity of Some Solvents and Other Compounds

Many solvents are used in particularly large quantities, and the volatility of many contributed to the possibilities of extensive exposure. They vary very greatly in their toxicity, some show carcinogenicity in animals, and benzene is an accepted occupational carcinogen for man.

H Benzene**	Toxicity high, bone-marrow poison, can cause severe 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.
?H* Acrylonitrile	Highly toxic for nervous system, with effects similar to cyanide. Some suspicions of possible occupational carcinogenesis.
**** Hexamethyl phosphoramide (hexametapol)**	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 to man also.
**** 1,2-Dibromoethane**	Toxicity high and is a potent experimental carcinogen,

(ethylene dibromide)	leading to increasing restrictions on its commercial use.
*** Acrylamide**	Toxicity high, including by skin contact. Accepted neurotoxin, with evidence accumulating that it may cause testicular damage and general effects. A weak experimental carcinogen.
*** Ethyl carbamate (urethane)**	Experimental carcinogen, but most tests required the presence of a tumour promoter also.
Dichloromethane (methylene chloride)	Some evidence for weak carcinogenicity of borderline significance only.
Trichloromethane (chloroform)	Toxicity high; has given slight evidence for experimental carcinogenicity.
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.
Tetrachloroethylene (perchloroethylene)	Evidence for weak carcinogenicity of borderline significance.
1,2 Dichloroethane (ethylene dichloride)	Has caused many cases of acute poisoning. Some evidence for experimental carcinogenicity.
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)	Carcogenicity tests have been negative.
isoPropanol	Former "strong acid" process of manufacture caused cases of nasal sinus cancer in workers. No evidence that the solvent itself is carcinogenic.
1,4-Dioxane	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.
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.