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QUEEN'S UNIVERSITY BELFAST

GUIDELINES FOR WORK WITH CHEMICAL CARCINOGENS

1. INTRODUCTION

Cancer is the generic name for a group of diseases that affect humankind, animals and plants. In humans, almost every organ in the body can be affected. It is a disease in which some of the cells of the body have an unlimited power of disordered reproduction and show some loss of structural differentiation. This usually results in the formation of malignant tumours, which are non-encapsulated (i.e. not benign) and which are able to invade other parts of the body to form secondary tumours or metastases that are commonly responsible for death.

In the UK on average each year from 1996 to 2000 there were more than 150,000 cancer deaths, making it second only to coronary heart disease as a major cause of death. Worldwide, it has been estimated that in excess of ten million new cases of cancer are diagnosed each year. These cases are split almost equally between the developed and developing world. It has also been estimated that cancer accounts for 40% of all deaths in the age range 20-64 years (i.e. the typical working years of life).

Although this disorder remains far from well characterised, three environmental risk factors are implicated in the development of cancers : exposure to radiation, exposure to chemicals and exposure to biological agents. Also included are risk factors related to personal behaviour (in particular smoking and certain dietary factors) and to occupation. Since the time delay between first exposure to a carcinogenic agent and the onset of symptoms can vary from 5 to 40 years, it is extremely difficult to establish in retrospect the proportion of cancers attributable solely to occupational exposure. However, this proportion is likely to be small. Sir Richard Doll estimated (1992) that about 4% (up to maximum of 6%) of cancer deaths are occupationally related compared with 33-35% and 10-60% of cancer deaths related to tobacco and dietary factors respectively.

Irrespective of the "actual" proportion of cancers attributable to occupational exposure to known or putative carcinogenic agents, it is widely accepted that they are largely avoidable by the adoption of good occupational practices.

It is considered that if the practices set out in this guidance note are scrupulously adhered to, the potential risk to health from the use of carcinogenic agents in the laboratory should be reduced to a level well below that commonly and unquestioningly accepted in everyday life outside the laboratory environment.

However there is no room for complacency. Although, recent (1990-1993) retrospective studies have confirmed that the overall cancer incidence rates in laboratory workers were lower than those found in the general "age-matched" population, there was also a suggestion of elevated rates for certain types of cancer, notably lymphatic and haematopoietic cancers.

1.1 Carcinogenic Agents

Although the vast majority of recognised occupational carcinogens are chemical substances, various physical agents and some biological agents are capable of inducing cancer.

1.2 Chemical Carcinogens

This group includes reactive substances that are capable of directly binding to and mutating cellular DNA e.g. bis (chloromethyl) ether, dimethyl sulphate; inert substances which are metabolised by the body into reactive species capable of exerting a carcinogenic effect e.g. benzo [a] pyrene is metabolised into an epoxide and this functions as the active carcinogenic species; and substances

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which are not conveniently categorised by either chemical structure or mode of action e.g. polycyclic aromatic hydrocarbons, aromatic amines, aromatic nitro compounds and N-nitroso compounds.

Some inorganic compounds are also known human carcinogens. These include compounds of arsenic, beryllium, cadmium, chromium and nickel. The mechanism of action of these largely remains to be elucidated.

1.3 Physical CarcinogensThis diverse group includes ionising and non-ionising radiation, (ultraviolet, x-rays and γ-radiation) and irritants such as hard wood dust and asbestos. Whilst the damaging effects of both types of radiation can be linked to chemical modification of cellular DNA, the mode of action of other physical carcinogens is less well understood.

1.4 Biological Carcinogens

Viral Agents: The proportion of all human cancers attributable to viral agents has proved difficult to assess as the evidence is generally less conclusive than that for physical and chemical agents. However, some associations have been clearly established. For example, the Epstein-Barr virus can cause Burkitt's lymphoma in a subject whose immune system is stressed by malarial infection; a human papilloma virus, which normally causes genital warts has been implicated as the cause of cervical cancer; and hepatitis B infection has been found to induce cancer of the liver.

Oncogene: This is a gene either present in a cell or carried by a virus (usually a homologue of the cellular oncogene) capable of progressing cells through a stage in the multistage cancer process. The Advisory Committee on Genetic Modification (ACGM) defines oncogenic DNA sequences as those which induce tumours in experimental animals or which cause transformation of cells in vitro leading to an escape from normal growth control, immortalisation of cells or induce anchorage independent growth.

In this Guidance Note only laboratory work with chemical carcinogens is considered. Those intending to work with ionising or non-ionising radiation should consult Departmental local rules and seek advice from their local Radiation Protection Supervisor and the University Radiation Protection Advisor. Others intending to work with oncogenes are referred to the publication, ACGM/HSE

Guidance Note 1: Guidance on construction of recombinants containing potentially oncogenic nucleic acid sequences and should seek further guidance from their local Biological Safety Officer and the University Biological Safety Advisor.

2. RECOGNITION OF CHEMICAL CARCINOGENS

In Reg 2(1) of The Control of Substances Hazardous to Health Regs (NI) 2003 ("COSHH") a carcinogen is defined as:

(a) any substance or preparation, which when classified in accordance with the classification provided for by Reg 4 of the Chemicals (Hazard Information and Packaging) Regs (NI) 2002 ("CHiP"), would be in the category of danger, carcinogenic (category 1) or carcinogenic (category 2) whether or not the substance or preparation would be required to be classified under those Regs;

 These regulations have been replaced by the Chemicals (Hazard Information and Packaging for Supply) Regs 2009. The Approved Supply List has been discontinued. The list of harmonised classifications and labelling requirements have been incorporated into Table 3.2 of Part 3 of Annex VI of the CLP Regulation;

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(b) any substance or preparation listed in Schedule 1 and any substance or preparation arising from a process specified in that Schedule which is a substance hazardous to health.

Chemical substances which currently meet that definition are listed in Appendices 1, 2 and 3 (respectively).

It should be noted that under the CHiP Regs substances may be classified carcinogenic, mutagenic or toxic to reproduction (formerly teratogenic) or combinations thereof. In addition these classifications are subdivided into 3 categories with corresponding risk phrases, (R45, R49 etc). For example, carcinogenic substances are categorised as follows.

**Category 1 (R45, may cause cancer and R49, may cause cancer by inhalation)**- substances known to be carcinogenic to humans. There is sufficient epidemiological evidence to establish a causal association between human exposure and the development of a cancer.

**Category 2 (R45 and R49)**

- substances which should be regarded as carcinogenic to humans. The classification is based on appropriate long-term animal studies and other relevant information.

**Category 3 (R40, little evidence of a carcinogenic effect)**

- substances which may be carcinogenic to humans. This category includes substances, which have been fully tested and which have failed to display sufficient carcinogenicity for a Category 2 classification, as well as substances which have not been fully investigated.

Although Category 3 carcinogenic substances and substances, which have been classified as exclusively mutagenic (Muta) or toxic to reproduction (Repr) (Appendices 4, 5 & 6) are not included in the COSHH definition of "carcinogen", work with these substances should be controlled in accordance with this guidance note.

Therefore it must be stressed that the substances in Appendices 1 - 6 do not represent a definitive list of chemical carcinogens. Of the 100,000 chemical substances registered in The European Inventory of Existing Commercial Chemical Substances (EINECS) between 1.1.71 and 18.9.81, only a small fraction have been fully tested for carcinogenicity and classified under CHiP. Similarly, "new" substances (ie those not listed in EINECS) remain to be tested and classified. To date about 3000 substances have been shown to ellicit some kind of carcinogenic effect in man or animals, of which only 1% are universally regarded as definite human carcinogens. Obviously, the list of proven chemical carcinogens will grow as results from epidemiological and other studies become available.

In addition, certain classes of substances (including medicines, drugs, pesticides, "new" substances and substances either used or synthesised in research and development) are exempt from classification under CHiP. Such substances may, however, be tested and/or classified under other schemes and legislation (Appendix 7). It is therefore vitally important to consult as many sources of toxicological information as possible (Appendix 8) in assessing the possible carcinogenicity of a given substance. Unknown substances or new substances for which there is no toxicological data should be controlled as potential carcinogens until there is sufficient evidence to the contrary.

3. ASSESSMENT OF WORK WITH CHEMICAL CARCINOGENS

Under Reg 6 of COSHH, there is a requirement to conduct a 'suitable and sufficient' assessment of the health risks posed by work with substances hazardous to health prior to commencement of that work. Advice and guidance on assessment is available from each Departmental COSHH Supervisor.

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Detailed information, instruction and training in assessment is available through the University Safety Service.

Although a project worker may conduct the assessment if deemed competent it is the duty of the project supervisor to ensure that all his/her projects involving substances hazardous to health are properly assessed. (CVCP Guidance Note: Responsibilities of Supervisors towards Postgraduate and Undergraduate Students).

In view of the insidious nature of cancer, the assessment of work with carcinogens must be rigorous.

A rigorous assessment must be fully documented and include the following details:

- duration and nature of the project

* persons at particular risk from exposure to the carcinogen

- nature and quantities of carcinogenic substances to be used

 e.g. physical state (vapour, powder, aqueous/non-aqueous solution), physicochemical properties (volatility, lipophilic/lipophobic)

- nature, degree and route of possible exposure to the carcinogen

 e.g. inhalation of gases/vapours, absorption of liquids/vapours through the skin or other mucosal surfaces, penetration of the skin, contamination of the eyes, accidental ingestion

- practicability of preventing exposure to the carcinogen by substitution with non-carcinogenic substance or by total enclosure of the process

 e.g. use of glove-box

- steps taken to achieve adequate control where prevention is not practicable

 e.g. use of a fume cupboard, good laboratory practice

- use of personal protective equipment

 e.g. laboratory coats, dust masks, gloves etc.

- precautions to be adopted in an emergency

 e.g spills, fume cupboard failure

- safe storage and eventual disposal of the carcinogen

- arrangements for monitoring exposure (below)

- arrangements for health surveillance (below)

- information, instruction, training and supervision arrangements for those involved in storage, handling or use of carcinogenic substances

- assessment review period

3.1 Monitoring Exposure

Routine exposure monitoring should not be necessary for most research projects provided that the reliability and suitability of chosen control measures are carefully considered and the control measures are properly used and maintained. Further information about monitoring may be obtained from the University Safety Service.

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3.2 Health Surveillance

Health Surveillance is appropriate for all persons working with carcinogens unless their exposure to the carcinogens is not significant. Therefore, all projects likely to entail significant exposure to carcinogenic substances should be referred to the Occupational Health Physician, Occupational Health, by the project supervisor.

3.3 Prohibited Substances

Finally, it should be noted that work with the following chemical carcinogens is prohibited under Reg 4 of COSHH: 2-naphthylamine, benzidine, 4-aminodiphenyl, 4-nitrodiphenyl, their salts and substances containing the above compounds in a total concentration exceeding 0.1%. Only the Health and Safety Executive may grant exemptions to these prohibitions.

4. PREVENTION AND/OR CONTROL OF EXPOSURE TO CHEMICAL CARCINOGENSUnder Regulation 7(5) of COSHH, if it is not reasonably practicable to prevent exposure to carcinogens by using alternative substances or processes, then adequate control of exposure to the carcinogen must be achieved by application of all of the following measures:

- totally enclose the process and handling systems unless this is not reasonably practicable

 e.g. use a glove-box

- minimise generation of, or suppress and contain, spills, leaks, dusts and vapours from carcinogens by partially enclosing the process and handling systems and using local exhuast ventilation

 e.g. work in a fume cupboard. Minimise aerosol production by avoiding, if possible, use of blenders, sonicators, vigorous mixing or shaking. Avoid grinding operations which generate dust. Use spill trays. Fit cold traps to vacuum lines.

 In addition, minimise the risk of exposure to carcinogens (via absorption through the skin, accidental ingestion and accidental injection) by wearing the appropriate personal protective equipment, by prohibiting mouth pipetting, by avoiding the use of sharps and by covering all cuts and abrasions.

- limit the quantities of carcinogens used

 e.g. consider reaction scales. Keep stocks accurately but to a minimum

- minimise the number of persons who may be exposed to carcinogens

 e.g. restrict access to the laboratory to authorised personnel only

- prohibit eating, drinking, smoking and the use of cosmetics in areas that may be contaminated with carcinogens. Exclude personal items (coats, bags, radios etc.) which would be difficult to decontaminate.

- provide and maintain adequate hygiene measures, both general and personal

- designate those areas and installations which may be contaminated by carcinogens, and use suitable and sufficient warning signs

- store, handle and dispose of carcinogens safely. Carcinogens should be stored in tightly sealed and appropriately labelled containers. They should be segregated from other substances when not in use and should be stored securely in appropriately labelled refrigerators, cupboards or rooms. Safe disposal of carcinogens should be arranged with the University Safety Service.

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The application and use of the above control measures in work with carcinogens should be incorporated into a written protocol, or local rules which contain standard operating procedures and give details of good laboratory safe working practices. Written protocols should be presented to the appropriate School Safety Committee for approval prior to commencement of the work.

5. MANAGEMENT OF WORK WITH CARCINOGENS

It is the supervisor's responsibility to ensure that his/her research workers receive adequate information, instruction and training. Workers should be aware of the risks to health involved in the work and the importance of using all the requisite control measures correctly.

It is also the supervisor's responsibility to ensure that the workers are following agreed procedures and written protocols or working to agreed local rules.

Workers must not deviate from documented procedures or stray beyond the limits of the project without the supervisor's knowledge or consent.

6. REFERENCES

Approved Code of Practice : Control of substances hazardous to health, 5th Edition, HSE

Hazardous Substances : Carcinogens Guide, Croner

Occupational Carcinogens : Croner's Health and Safety Special Report 1994

EH40/0X Workplace Exposure Limits 200X, HSE

COSHH: Guidance for universities, polytechnics and colleges of further and higher education: Education Services Advisory Committee, HSC

Laboratory Work with Chemical Carcinogens and Oncogenes, Specialist Inspector Reports No. 41, HSE

Health and Safety Responsibilities of Supervisors towards Postgraduate and Undergraduate Students CVCP

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**APPENDIX 1 CATEGORY 1 CARCINOGENS**

**Category 1 Carcinogens: R45 May cause cancer**

4-aminobiphenyl and its salts

arsenic acid and its salts

arsenic pentoxide

arsenic trioxide

asbestos

benzene (+ Muta Cat 2)

benzidine and its acetate, dihydrochloride, sulphate salts

bis (chloromethyl) ether i.e. BCME

1,3 – butadiene

butane containing > 0.1% butadiene, isobutane containing > 0.1% butadiene

chloromethyl methyl ether (usually contaminated with BCME)

erionite

lead hydrogen arsenate (+Repr. Cat 1 +Repr Cat 3)2-naphthylamine and its acetate and hydrochloride salts

petroleum gases and substances (unrefined or mildly refined base oil)triethylarsenate

vinyl chloridezinc chromates, including zinc potassium chromate

**Category 1 Carcinogens: R49 May cause cancer by inhalation**

chromium trioxide (+ Muta Cat 2, + Repr Cat 3)

dinickel trioxide

nickel dioxide

nickel monoxide

nickel subsulphide

nickel sulphide

\*Additional classifications: Repr - Toxic to Reproduction

 Muta - Mutagenic

 Cat - Category number 1,2 or 3

**APPENDIX 2 CATEGORY 2 CARCINOGENS**

**Category 2 Carcinogens : R45 May cause cancer**

acrylamide (+ Muta Cat 2, Repr Cat 3)

acrylonitrile

4-aminoazobenzene

2-amino-5-azotoluene

4-amino-3-fluorophenol

p-aminophenylether and its salts (+ Muta Cat 2, + Repr Cat 3)

ammonium dichromate (+ Muta Cat 2, + Repr Cat 2)

aziridine (+ Muta Cat 2)

azobenzene (+ Muta Cat 3)

Basic Red 9

Basic Violet 3 (> 0.1% of Michler’s ketone)

benzidine based azo dyes

benz(e) acephenanthyrlene

benzo [a] anthracene

benzo [b] fluoranthene

benzo[j] fluoranthene

benzo [k] fluoranthene

benzo [a] pyrene (+ Muta Cat 2, Repr Cat 2)

benzo [e] pyrene

benzyl chloride

2,2’-bioxirane (+ Muta Cat 2)

4,4'-bis (dimethylamino) benzophenone (+ Muta Cat 3), Michler’s keton

cadmium chloride (+ Muta Cat 2, Repr Cat 2)

cadmium oxide (+ Muta Cat 2, + Repr Cat 2)

cadmium sulphate (+ Muta Cat 2, + Repr Cat 2)

cadmium sulphide (+ Muta Cat 2, + Repr Cat 2)

cadmium fluoride (+ Muta Cat 2, Repr Cat 2)

calcium chromate

captafol

carbadox

4-chloroaniline

p-chlorobenzotrichloride (+ Repr Cat 3)

chloroprene

4-chloro-o-toluidine and its hydrochloride (+ Muta Cat 3)

chromium III chromate

chyrsene (+ Muta Cat 3)

coal tar products

p-cresidine

2,4-diaminoanisole and its sulphate (+Muta Cat 3)

4,4'-diaminodiphenylmethane (+ Muta Cat 3)

2,4-diaminotoluene

o-dianisidine, its salts, azo based dyes

diazomethane

dibenz [a,h] anthracene

1,2-dibromo-3-chloropropane (+ Muta Cat 2, Repr Cat 1)

1,2-dibromoethane

2,3 dibromo-1-propanol (+Repr Cat 3)

3,3'-dichlorobenzidine and its salts

1,4-dichlorobut-2-ene

1,3-dichloro-2-propanol

diethyl sulphate (+ Muta Cat 2)

dimethylcarbamoyl chloride

1,1-dimethylhydrazine

1,2-dimethylhydrazine

dimethylnitrosamine

dimethylsulfamoyl chloride

(ii)

APPENDIX 2 (continued)

dimethyl sulphate (+ Muta Cat 3)

2,3-dinitrotoluene (+ Muta Cat 2, Repr Cat 3)

2,4-dinitrotoluene (+ Muta Cat 2, Repr Cat 3)

2,5-dinitrotoluene (+ Muta Cat 3, Repr Cat 3)

2,6-dinitrololuene (+ Muta Cat 2, Repr Cat 3)

3,4-dinitrololuene (+ Muta Cat 3, Repr Cat 3)

3,5-dinitrololuene (+ Muta Cat 3, Repr Cat 3)

Direct Black 38 (+ Repr Cat 3)

Direct Blue 6 (+ Repr Cat 3)

Direct brown 95

Direct Red 28 (+ Repr Cat 3)

Disperse Blue 1

epichlorohydrin

2,3-epoxypropan-1-ol (+ Muta Cat 3, Repr Cat 2)

1,2 epoxy propane-3-phenoxy propane (+ Muta Cat 3)

ethylene dibromide

ethylene dichloride

ethylene oxide (+ Muta Cat 2)

furan (+ Muta Cat 3)

hexachlorobenzene

hexamethylphosphoramide (+ Muta Cat 2)

hydrazine and its salts

hydrazine bis (3-carboxy-4-hydroxybenzenesulphonate)

hydrazine trinitromethane

hydrazobenzene

6-hydroxy-1-(3-isopropoxy propyl)-4-methyl-2-oxo-5-[4-(phenylazo)phenylazo]-1,2-dihydro-3-

 pyridinecarbonitrile

(6-(4-dhyroxy-3-(2-methoxyphenylazo)-2-sulphonato-7-naphthylamino)-1,3,5-triazin-2,4-diyl)bis[(amino-1-

 methylethyl) ammonium] formate

isobutyl nitrite (+ muta Cat 3)

2-methoxyaniline (+ Muta Cat 3)

methoxy-m-phenylenediamine (+ Muta Cat 3)

methylacrylamidomethoxy acetate (containing) ≥ 0.1% acrylamide) (+ Muta Cat 2)

methylacrylamidoglycolate (containing ≥ 0.1% acrylamide (+ Muta Cat 2)

2-methylaziridine

methylazoxymethanol acetate (+ Repr Cat 2)

4-methylbenzene-sulphonate(s)-oxiranemethanol (+ Muta Cat 3)

4,4'-methylenebis (2-chloroaniline) and its salts

4,4'-methylene-di-o-toluidine

1-methyl-3-nitro-1-nitrosoguanidine

5-nitroacenophthene

2-nitroanisole

4-nitrobiphenyl

nitrofen (+ Repr Cat 2)

2-nitronaphthalene

2-nitropropane

nitrosodiethanolamine

nitrosodimethylamine

2,21-(nitrosoimino) bisethanol

nitrosodipropylamine

2-nitrotoluene (+ Muta Cat 2, Repr Cat 3)

Petroleum Distillation Products

phenylhydrazine and its chloride and sulphate salts (+ Muta Cat 3)

potassium bromate

1,3-propanesultone

(iii)

APPENDIX 2 (continued)

1,3-propiolactone

propylene oxide (+ Muta Cat 2)

safrole (+ Muta Cat 3)

strontium chromate

styrene oxide

sulfallate

N,N,N',N'-tetramethyl-4,4'-methylenedianiline

thioacetamide

4,4'thiodianiline and its salts

o-tolidine, its salts, its azo based dyes

2,4-toluenediammine

toluene-2,4-diammonium sulphate

o-toluidine

trichloroethylene (+ Muta Cat 3)

1,2,3,-trichloropropane (+ Repr Cat 2)

2,4,5-trimethylaniline and its hydrochloride

∝,∝,∝-trichlorotoluene

urethane (INN)

vinyl bromide

**Category 2 Carcinogens : R49 May cause cancer by inhalation**

beryllium

beryllium compounds except aluminium beryllium silicate

beryllium oxide

cadmium oxide (+ Muta Cat 3, Repr Cat 3)

chromic oxychloride

chromium (VI) compounds except barium chromate

cobalt dichloride

cobalt sulphate

potassium chromate (+ Muta Cat 2)

potassium dichromate (+ Muta Cat 2, Repr Cat 2)

refractory ceramic fibres

sodium chromate (+ Muta Cat 2, Repr Cat 2)

sodium dichromate and its dihydrate (+ Muta Cat 2, Repr Cat 2)

**APPENDIX 3 COSHH Schedule 1**

**Other substances and processes to which the definition of “carcinogen” relates.**

Aflatoxins

Arsenic

Auramine manufacture

Calcining, sintering or smelting of nickel copper matte or acid leaching or electrorefining of roasted

 matte

Coal soots, coal tar, pitch and coal tar fumes

Hard wood dusts

Isopropyl alcohol manufacture (strong acid process)

Leather dust (shoe manufacture)

Magenta manufacture

Mustard gas (β, β’ - dichlorodiethyl sulphide)

Rubber fume and dust during processing

Used engine oils

Polychlorodibenzodioxins:

 2,3,7,8 – TCDD\*

 1,2,3,7,8 – PeCDD

 1,2,3,4,7,8 – HxCDD

 1,2,3,6,7,8 – HxCDD

 1,2,3,7,8,9 – HxCDD

 1,2,3,4,6,7,8 – HpCDD

Polychlorodibenzofurans:

 2,3,7,8 – TCDF

 2,3,4,7,8 – PeCDF

 1,2,3,7,8 – PeCDF

 1,2,3,4,7,8 – HxCDF

 1,2,3,7,8,9 – HxCDF

 2,3,4,6,7,8 – HxCDF

 1,2,3,4,6,7,8 – HpCDF

 1,2,3,4,7,8,9 – HpCDF

*\*Where T=tetra, Pe=penta, Hx=hexa, Hp=hepta & O=octa*

**APPENDIX 4 CATEGORY 3 CARCINOGENS**

# Category 3 Carcinogens: R40 Limited evidence of a carcinogenic effect

acetaldehyde

acetamide

alachlor

aldrin

allyl chloride (+ Muta Cat 3)

allyl 2,3-epoxypropylether (+ Muta Cat 3, Repr Cat 3)

allyl glycidyl ether (+ Muta Cat 3, Repr Cat 3

4-aminotoluene

amitrole

aniline and its salts

antimony trioxide

ANTU

atrazine (+ Repr Cat 3)

auramine and its salts

Basic Violet 3

benzal chloride

benzyl chloride

benzyl violet 4B

biphenyl-2-amine

bromoethane

1-bromo-3,4,5-trifluorobenzene

2-butanone oxime

butyl 2,3-epoxypropylether

cadmium sulphide

camphechlor

captan

carbaryl

carbon tetrachloride

chlordane

chlordecone

chlordimeform and hydrochloride

chloroalkanes C10 – C13

chloroacetaldehyde

chloroethane

chloroform

1-chloro-4-nitrobenzene

chlorotoluron (+Repr Cat 3)

chlozolinate

daminozide

DDT

di-allate

2,2-dibromo-2-nitroethanol

1,4-dichlorobenzene

(+/-)2-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl) propyl-1,1,2,2-tetrafluoroethylether

dichloroacetylene

dichloromethane

dieldrin

diethylcarbamoyl chloride

dihydroxybenzene

4-(4-(1,3-dihydroxyprop-2-yl) phenylamino)-1,8-dihydroxy-5-nitroanthraquinone

N,N-dimethylaniline

2,6-dimethylaniline

N,N-dimethylanilinium tetrakis (pentafluorophenyl) borate

3,5-dinitro-2,6-dimethyl-4t butylacetophenone (Musk ketone)

1,4-dioxane

(ii)

APPENDIX 4 (continued)

Disperse Yellow 3

diuron

epoxiconazole (+ Repr Cat 3)

1,2 epoxybutane

5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole

flusilazole (+ Repr Cat 2)

folpet

formaldehyde

2-furaldehyde

furmecyclox

heptachlor and its epoxide

hexachlorocyclohexane

hydroquinone (+ Muta Cat 3)

iprodione

isoproturon

kresoxim-methyl

lead acetate (+ Repr Cat 1, Repr Cat 3)

lead chromate (+ Repr Cat 1, Repr Cat 3)

lead chromate molybdate sulphate red (+ Repr Cat 1, Repr Cat 3)

linuron (+ Repr Cat 2, Cat 3)

methyl chloride

methyl iodide

4,4’-methylenebis (2-ethylaniline)

mineral wool

Mirex (+ Repr Cat 3)

Molinate

monuron and monuron – TCA

morpholine-4-carbamoyl chloride

Musk xylene (5t butyl-2,4,6-trinitro-m-xylene)

naphthalene

1,5 naphthalene diamine

N-2-naphthylaniline

1-(1-naphthylmethyl) quinolinium chloride (+ Muta Cat 3)

nickel

nickel carbonate

nickel dihydroxide

nickel sulphate

nickel tetracarbonyl (+ Repr Cat 2)

nitrobenzene (+ Repr Cat 3)

5-nitro-o-toluidine and its hydrochloride

pentachloroethane

pentachlorophenol and its alkali salts

o-phenylenediamine and its hydrochloride

N-phenyl-2-naphthylamine

Pigment Red 104 (+ Repr Cat 1, Repr Cat 3)

Pigment Yellow 34 (+ Repr Cat 1, Repr Cat 3)

Propargite

propazine

propyzamide

pymetrazine

resorcinol diglycidylether (+ Muta Cat 3)

(2RS,3RS) -3-(2-chlorophenyl)-2-(4-fluorophenyl)-[(1H-1,2,4-triazol-1-yl)methyl]oxirane

simazine

sodium pentachlorophenate and potassium salts

solvent yellow 14 (+ Muta Cat 3)

tetrachloroethylene

(iii)

APPENDIX 4 (continued)

tetrachloroisophthalonitrile

thiourea (+ Repr Cat 3)

TDI

p-toluidine and chloride and sulphate salts

tributyl phosphate

2,3,4-trichlorobut-1-ene

1,1,2-trichloroethane

trichloroethylene

3,5,5-trimethylcyclohex-2-enone

2,4,6-trichlorophenol

triphenyl tin and its acetate and hydroxide (+ Repr Cat 3)

tris (2-chloroethyl) phosphate

vinclozolin (+ Repr Cat 2)

vinylidene chloride

1-vinyl-2-pyrrolidone

**APPENDIX 5 MUTAGENIC SUBSTANCES**

# Category 1: Substances known to be mutagenic to humans

R46 *May cause heritable genetic damage.*

 None

**Category 2: Substances which should be regarded as if they are mutagenic to humans.**

R46 *May cause heritable genetic damage.*

 benomyl (+ Repr Cat 2)

 carbendazim (+ Repr Cat 2)

 TGIC-triglycidyl isocyanurate

 1,3,5-tris-[(2S and 2R)-2,3-epoxypropyl]-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione

# Category 3: Substances which cause concern for humans owing to possible mutagenic

 **effects.**

R68 *Possible risk of irreversible effects.*

allyl epoxypropylphenol mixtures

2-aminophenol

4-aminophenol

1,3-bis (vinylsulphonylacetamido) propane

bromomethane

2 butenal

(3-chlorophenyl)-(4-methoxy-3-nitrophenyl) methanone

cresylglycidyl ether

crotonaldehyde

cycloheximide (+ Repr Cat 2)

2,3-dichloropropene

5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidine)-3-fluoro-2-hydroxymethyltetrahydrofuran

DNOC

2,3-epoxypropyl-o-tolyl ether

4-ethoxyaniline

41-ethoxy-2-benzimidazoleanilide

1-ethyl-1-methylmorpholium bromide

1-ethyl-1-methylpyrrolidinium bromide

Fenthion

Glyoxal

hexahydrocyclopenta[c]pyrolle-1-(1H)-ammonium N-ethoxy carbonyl-N-(p-tolylsulphonyl) azanide

(4-hydrazinophenyl)-N-methylmethanesulphonamide hydrochloride

2-(isocyanatosulphonylmethyl) benzoic acid methyl ester

2-methyl-m-phenylenediamine

monocrotophos

4-nitrosophenol

phenol

m-phenylenediamine and its hydrochloride

phosphamidon

pyrogallol

N,N,N1,N1-tetraglycidyl-4,41diamino-3,31-diethyldiphenylmethane

(+/-) tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate(+ Repr Cat 2,

 Repr Cat 3)

2,21-((3,31,5,51-tetramethyl-(1,11-biphenyl)-4,41-diyl)-bis(oxymethylene))-bis-oxirane

thiophanate-methyl

m- and p-tolyloxy methyl oxirane

trifluoroiodomethane

trisodium bis (7-acetamido-2-(4-nitro-2-oxidophenylazo)-3-sulphonato-1-naphthalato) chromate

(ii)

APPENDIX 5 (Continued)

vanadium pentoxide (+ Repr Cat 3)

9-vinylcarbazole

**APPENDIX 6 SUBSTANCES TOXIC TO REPRODUCTION**

# Category 1: Substances known to impair fertility in humans.

 **Substances known to cause developmental toxicity in humans.**

R60 *May impair fertility and may cause harm to the unborn child.*

2-bromopropane

tri lead bis (orthophosphate) (+ Repr Cat 3)

R61 *May cause harm to the unborn child.*

carbon monoxide

4-hydroxy-3-(3-oxo-1-phenylbutyl)-2-benzopyrone

lead alkyls (+ Repr Cat 3)

lead azide (+ Repr Cat 3)

lead di (acetate) (+ Repr Cat 3)

lead hexafluorosilicate (+ Repr Cat 3)

lead methanesulphonate

lead styphnate (+ Repr Cat 3)

lead 2,4,6-trinitroresorcinoxide (+ Repr Cat 3)

Warfarin

**Category 2: Substances which should be regarded as if they impair fertility in humans.**

 **Substances which are regarded as if they cause developmental toxicity.**

R60 *May impair fertility and may cause harm to the unborn child.*

2,2-bis(41-hydroxyphenyl)-4-methylpentane

bis (2-methoxyethyl) ether

di –(2-ethylhexyl) phthalate

di-n-pentylphthalate

3-ethyl-2-methyl-2-(3-methybutyl)-1,3-oxazolidine

2-ethoxyethanol

methoxyacetic acid

2-methoxyethanol

2-ethoxyethyl acetate

fluazifop-butyl(ISO)

formamide

2-methoxyethyl acetate

N-methylacetamide

n-pentyl-isopentyl phthalate

n-propyl bromide (+ Repr Cat 3)

R61 *May cause harm to the unborn child.*

azafenden (+ Repr Cat 3)

benzene butyl phthalate (+ Repr Cat 3)

1,2-benzenedicarboxyli acids and dipentyl esters

binapacryl

bis (2-methoxyethyl) phthalate (+ Repr Cat 3)

dibutyl phthalate (+ Repr Cat 3)

N,N-dimethylacetamide

dimethylformamide

dinocap

dinoseb, and its salts and esters (+ Repr Cat 3)

dinoterb, and its salts and esters

diphenyl ether, octabromo derivative

2-ethylhexyl 3,5-bis(1,1-dimethyl)-4-hydroxyphenyl methylthioacetate

ethylene thiourea

(ii)

APPENDIX 6 (continued)

etacelasil

flumioxazin

2-[2-hydroxy-3-(2-chlorophenyl) carbamoyl-1-naphthylazo]-7-[2-hydroxy-3-(3-chlorophenyl)carbamoyl-1-

naphthylazo] fluorene-9-one

2-methoxypropanol

2-methoxypropyl acetate

N-methylformamide

tetrahydrothiopyran-3-carboxaldehyde

tridemporph

triethylene glycol dimethyl ether

**Category 3: Substances which cause concern for human fertility.**

 **Substances which cause concern for humans owing to possible developmental**

 **toxic effects.**

R62 *Possible risk of impaired fertility.*

N-[2-(3 acetyl-5-nitrothiophen-2-ylazo)-5-diethylaminophenol] acetamide

benzyl 2,4-dibromobutanoate

bis(eta 5-cyclopentadienyl)-bis(2,6-difluoro-3[pyrrol-1-yl]-phenyl)titanium

bisphenol A

R-5-bromo-3-(1-methyl-2-pyrrolidmylmethyl)-1H-indole

2-(4-tbutylphenyl) ethanol

butylmethyl ketone

2-(4-tert-butylphenyl) ethanol

chinomethionat

2-chloroacetamide

chloro 1,3-dihydro-2H-indol-2-one

chlorotoluran

1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

N,N1-dihexadecyl-N,N1-bis(2-hydroxylethyl) propanediamide

(S)-2,3-dihydro-1H-indole-2-carboxylic acid

1,3-diphenylguanidine

(ethylmethylsilylene) di [(4-methylpentan-2-one)oxime]

n-hexane

hexan-2-one

2-(2-hydroxy-3,5-dinitroanilino) ethanol

nonylphenol

octamethylcyclotetrasiloxane

(R) –a-phenylethylammonium(-)-(1R,2S)-(1,2-epoxypropyl) phosphonate monohydrate

5,6,12,13-tetrachloroanthra (2,1,9-def: 6,5,10-d1e1f1) diisoquinoline-1,3,8,10(2H,9H)-tetrone

trans-4-cyclohexyl-L-proline monohydrochloride

trans-4-phenyl-L-proline

valinamide

R63 *Possible risk of harm to the unborn child.*

amitrole

bromoxynil and its octanoate

1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl) pentan-3-ol

cyproconazole

diethylene glycol monomethyl ether

2-ethylhexanoic acid

(iii)

APPENDIX 6 (continued)

fenpropimorph

fluazifop-P-butyl(ISO)

ioxynil and its octanoate

isoxaflutole

malachite green and its oxalate

methylisocyanate

myclobutanil

oxadiargyl

propylenethiourea

toluene

1,2,4-triazole

1,2,5-trioxan

R62 and R63 *(as above)*

carbon disulphide

fenarimol

5-(3-butyryl-2,4,6-trimethylphenyl)-2-[1-(ethoxyimino) propyl]-3-hydroxycyclohex-2-en-1-one

**APPENDIX 7 IARC CLASSIFIED CARCINOGENS\***

**Group 1: Carcinogenic to humans. Groups 2A: Probably carcinogenic to humans.**

adriamycin

aristolochic acid

azacitidine

azathioprine

bischloroethyl nitrosourea

chlorambucil

chloramphenicol

chlornaphazine

1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)

chlorozotocin

cisplatin

cyclophosphamide

cyclosporin

dibenzo[a,l] pyrene

N-ethyl-N-nitrosourea

etoposide

gallium arsenide

glycidol

indium phosphide

IQ(2-amino-3-methylimidazo[4,5-f]quinoline

melphalan

methoxypsoralen

methoxysalen

methyl-CCNU

methyl methanesulphonate

N-methyl-N-nitrosourea

mustard gas

myleran

nitrogen mustard

N-nitrosodiethylamine

phenacetin

procarbazine hydrochloride

tamoxifen

teniposide

tetrachloroethylene

thiopeta

treosulphan

tris(2,3-dibromopropyl)phosphate

vinyl fluoride

**Group 2B: Possibly carcinogenic to humans.**

A-α-C(2-amino-9H-pyrido[2,3-b]indole

AF-2

amino-α-carboline

2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole

amsacrine

o-anisidine

antimony trioxide

aramite

azaserine

benzofuran

benzo[c]phenanthrene

2,2-bis(bromoethyl)propane-1,3-diol

*\*International Agency for Research on Cancer. Only substances not previously listed are included.*

(ii)

APPENDIX 7 (continued)

bleomycins

bromodichloromethane

butylated hydroxyanisole

β-butyrolactone

caffeic acid

carbon black

catechol

chlorendic acid

3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone

1-chloro-2-methylpropene

chlorophenoxy herbicides

4-chloro-o-phenylenediamine

chloroprene

chlorothalonil

CI Acid Red 114

CI Direct Blue 15

Citrus Red No 2

cobalt and its compounds

p-cresidine

dacarbazine

dantron

daunomycin

NN’-diacetylbenzidine

2,4-diaminoanisole

4,4’-diaminodiphenyl ether

dibenz [a,h] acridine

dibenz [a,j] acridine

7H-dibenzo [c,g] carbazole

dibenzo [a,e] pyrene

dibenzo [a,h] pyrene

dibenzo [a,i] pyrene

dichloroacetic acid

1,2-dichloroethane

2,3-dibromopropan-1-ol

p-dichlorobenzene

3,3’-dichloro-4,4’-diaminodiphenyl ether

1,3-dichloropropene

Dichlorvos

diepoxybutane

1,2-diethylhydrazine

diglycidyl resorcinol ether

dihydrosafrole

diisopropyl sulphate

4-dimethylaminoazobenzene

trans-2-[(dimethylamino) methylimino]-5-[2-(5-nitro-2-furyl)-vinyl]-1,3,4-oxadiazole

3,7-dinitrofluoranthene

3,9-dinitrofluoranthene

1,6-dinitropyrene

1,8-dinitropyrene

ethyl acrylate

ethylbenzene

ethyl methanesulphonate

2-(2-formylhydrazino)-4-(5-nitro-2-furyl)thiazole

fumonisin B1

furothiazole

Glu-P-1

(iii)

APPENDIX 7 (continued)

Glu-P-2

glycidaldehyde

griseofulvin

HC Blue No 1

hexachloroethane

1-hydroxyanthraquinone

indeno[1,2,3-cd]pyrene

iron-dextran complex

isoprene

lasiocarpine

MeA-α-C

medroxyprogesterone acetate

MeIQ

MeIQx

5-methylchrysene

methy mercury cpds

2-methyl-1-nitroanthraquinone

N-methyl-N-nitrosourethane

methylthiouracil

metronidazole

mitomycin C

mitoxantrone

monocrotaline

5-(morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone

nafenopin

naphthalene

nifuradene

niridazole

nitrilotriacetic acid

6-nitrochyrsene

2-nitrofluorene

1-[C5-nitrofurfurylidene)]-2-imidazolidinone

N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide

nitromethane

nitrogen mustard N-oxide

1-nitropyrene

4-nitropyrene

N-nitrosodi-n-butylamine

3-(N-nitrosomethylamino) propionitrile

4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

N-nitrosomethylethylamine

N-nitrosomethylvinylamine

N-nitrosomorpholine

N’-nitrosonornicotine

N-nitrosopiperidine

N-nitrosopyrrolidone

N-nitrososarcosine

ochratoxin A

oil orange SS

oxazepam

palygorskite

panfuran S

phenazopyridine hydrochloride

phenobarbital

phenolphthalein

phenoxybenzamine hydrochloride

(iv)

APPENDIX 7 (continued)

phenyl glycidyl ether

phenytoin

PhIP

polychloropenols and their sodium salts

Ponceau MX

Ponceau 3R

progestins

propylthiouracil

riddelline

sodium-o-phenylphenate

sterigmatocystin

streptozotocin

styrene

tetrafluoroethylene

tetranitromethane

4,4’-thiodianiline

thiouracil

titanium dioxide

TDI

trichlormethine

Trp-P-1

Trp-P-2

Trypan blue

uracil mustard

vanadium pentoxide

vinyl acetate

4-vinylcyclohexene

4-vinylcyclohexene diepoxide

zalcitabine

zidovudine

APPENDIX 8

# Toxicity Data: Sources of Information

Databases:

 Registry of Toxic Effects of Chemical Substances (NIOSH)

 Chemical Safety Newsbase (RSC)

 Occupational Safety and Health (NIOSH)

 Toxline (National Library of Medicine)

 Medline (National Library of Medicine)

 Sigma-Aldrich-Fluka, Material Safety Data Sheets on CD-Rom

Bibliography:

 Sigma-Aldrich Library of Chemical Safety Data, Vols I and II

 Handbook of Identified Carcinogens and Noncarcinogens, vols I and II, Soderman,

 CRC Press

Dangerous Properties of Industrial Materials, Vols I, II and III, Von Nostrand, Reinhold

The Merck Index, Merck and Co Inc

Registry of Toxic Effects of Chemical Substances, Vols I and II, NIOSH

Dictionary of Substances and their Effects (DOSE) Vols 1-7, Richardson and Gargoli, RSC

Biochem Coc, Special Publication No 5 “Safety in Biological Laboratories”

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