Local Rule:
Cytotoxic Substances and Agents

1. Potential Health Effects of Cytotoxic Substances and Agents

Cytotoxic substances and agents used in a University setting either in research or teaching, are mainly known or novel drugs or agents which are primarily used, but not limited to their uses as anti-cancer therapy because of their toxicity to cells. These drugs have been associated with human cancers at high therapeutic levels of exposure and are carcinogenic and teratogenic in many animal species.

Exposure to certain cytotoxic substances and agents is associated with adverse health effects. Acute symptoms have been reported in individuals who were occupationally exposed to certain cytotoxic substances and agents. These include hair loss, abdominal pain, nasal sores, contact dermatitis, allergic reactions, skin injury, and eye injury.

Adverse reproductive outcomes have also been identified in individuals working with cytotoxic substances including miscarriage, spontaneous abortions, foetal abnormalities, infertility, and longer time to conception, preterm labour, preterm births, and learning disabilities in offspring of females exposed during pregnancy. Cytotoxic substances and agents are chemical products and, as such, all work precautions inherent to procedures performed in a chemical laboratory are also applicable in the handling of these substances.

1.1. Legal Duty

The University aims to reduce and control risks from substances hazardous to health by fulfilling the requirements of the Control of Substances Hazardous to Health Regulations 2002 (as amended) (COSHH).

In accordance with COSHH, the University is committed to preventing or reducing workers' exposure to hazardous substances by identifying where hazardous substances are used by:-

- identifying where cytotoxic substances and agents are being used;
- carrying out COSHH assessments (which will be retained for 40 years if health surveillance is in place or in particular circumstances);
- providing control measures to reduce harm to health and ensuring they are used;
- keeping all control measures in good working order;
- planning for emergencies;
- providing information, instruction and training for employees and others; and
- providing monitoring and health surveillance in appropriate cases.

Those involved in working with substances hazardous to health will be required to attend either the COSHH Awareness or the COSHH Assessors course, depending on the extent of their involvement.

Further information on COSHH can be found by reading the University's Local Rule Control of Substances Hazardous to Health.

2. Key Definitions

2.1. General Terms

Cytotoxic
A substance agent or process that is toxic to cells

Cytotoxic Agents
Substances used in the treatment of malignant and other diseases. They are designed to destroy rapidly growing cancer cells. They have been shown to be mutagenic, carcinogenic and/or teratogenic, either in treatment doses or animal and bacterial assays
Information on other **Carcinogenic Substances** can be found by referring to the University's Local Rule on COSHH.

Mutagenic
A substance agent or process capable of causing alterations/damage to genes

Teratogenic
A substance agent or process capable of causing foetal defects, either anatomic or functional

2.2. Specific Terms

Workplace exposure limits (WEL)
The maximum concentration of an airborne substance, averaged over a reference period to which employees may be exposed by inhalation and which should not cause adverse health effects. WELs are UK occupational exposure limits and are set in order to help protect the health of workers.

Risk Control Measures
A workplace precaution to reduce the risk of exposure to a substance hazardous to health
These will include any factor that contributes to reducing the likelihood of harm occurring and/or its severity, if harm did occur.

Germ Cell Mutagenicity
A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term 'mutation' applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). The term 'mutagenic' and 'mutagen' will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.
(For general considerations see Appendix 1)

Reproductive Toxicity
Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. ***(For general considerations see Appendix 1)***

Lactation Toxicity
Substances which are absorbed by women and have been shown to interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child.

2.3. Specific Target Organ Toxicity
Specific target organ toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

Single Exposure
Specific target organ toxicity (single exposure) is defined as specific, **non lethal** target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed.

Repeated Exposure
Target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. All significant health effects that can impair function, reversible and irreversible, immediate and/or delayed are included.

3. Departmental Roles

3.1. Nominated Coordinator

Nominated coordinators will have already been appointed to coordinate the COSHH assessment process and in many cases will be the Departmental Safety Convenor (DSC) However in specialised areas departments may wish to nominate a member of staff within that specialised area to administrate the procedures involved with the co-ordination and management of cytotoxic substances and agents.

3.2. Principle Investigator/Supervisor

The PI or supervisor should liaise with appropriate colleagues in the laboratory to identify and assess the risks to staff and students from possible exposure to cytotoxic substances and agents; where necessary, request the services of the Occupational Hygienist through Safety Services; and to communicate assessment results to local managers to enable them to implement risk control measures. Where health surveillance is required, the PI or supervisor should liaise with Occupational Health Service to establish a surveillance programme, keep records of people who have attended and where recommendations are made by Occupational Health Service to co-ordinate any action as necessary.

3.3. Employees, Students and Others

Every employee and every other person under the supervision of a department is required to co-operate with that department to enable it to comply with its statutory duties for health and safety to reduce the risk of exposure to cytotoxic material. This includes individuals using any preventive and protective measures referred to in risk assessments, in accordance with instructions and training received.

4. Assessing Risks from Exposure to Cytotoxic Substances and Agents

4.1. Identifying Hazards

Departments must identify equipment and work activities where staff and students may be exposed to cytotoxic substances and agents. This could involve generating chemical inventories, cytotoxic substances inventories which include details of the substance, purpose for which it is used, location and staff/student group who handle the substance. This is of particular benefit for tracking cytotoxic substances and agents which will be used at different locations and by different people.

If the chemical substance has been purchased from a supplier then the material will have one of the following hazard symbols or new pictograms displayed on the label (i.e. very toxic, toxic, harmful, corrosive, irritant, sensitising, carcinogenic, mutagenic or toxic to reproduction). Information will also be found on the manufacturer's material safety data sheet (MSDS) **Please note that some cytotoxic substances and agents, if purchased in the form of a medicine, may not have these symbols on the packaging. It is highly recommended that departments make a careful assessment and review of the substances they are purchasing.** ***(For Information on hazard labelling see Appendix 2)***

Another authoritative source of information is the International Agency for Cancer Research [IARC]. The IARC is part of the World Health Organisation. Over the years it has published a series of Monographs on a variety of chemicals and classes of substance and has classified them according to severity of hazard. This information can be found at
http://monographs.iarc.fr/ENG/Classification/index.php

4.2. Possible Routes of Exposure

Environmental contamination of surfaces by cytotoxic substances and agents has been identified as a major route of exposure. In the research environment surfaces including benches, fume cupboards, biological safety cabinets, compounding isolators, floors, and computer keyboards have all been found to be contaminated.

Following this type of exposure, workers have been shown to absorb these drugs systemically as evidenced by excretion of the substances in their urine. In some cases, workers who did not physically handle a specific substance have experienced incidental exposure either by inhalation or inadvertent contact with a contaminated surface.

It has been proposed that dermal contact of contaminated surfaces accounts for most worker exposure, although the production of aerosols and dried chemical residue may lead to exposure by inhalation; another possible route of exposure is hand-to-mouth after touching contaminated surfaces. Workers who do not wear appropriate personal protective equipment, such as gloves, gowns and respiratory protection are likely to come into contact with chemical-contaminated surfaces throughout the workday. In addition, chemical residues have been shown to migrate outside of areas where they are handled and found in places further afield, such as corridors or on computers, posing an exposure risk to unsuspecting workers.

4.3. Evaluating Risks

At present all cytotoxic substances and agents are evaluated using a COSHH Assessment Form. (Form S21) The advice on the MSDS can also be utilised to assist in the identification of the hazard. Where the substance is a product of a new manufacturing process or research activities and the hazards are unknown, **then the substance should be treated with the highest caution using the precautionary principle of control.**

To evaluate

- decide who might be harmed and how – which employees and others might be exposed to cytotoxic substances and agents or agents and how this might happen? For example, through surface contamination of drug vials or leakage of drugs during preparation and administration;
- particular attention should be paid to groups of workers who may be at particular risk, e.g. young workers, trainees and new and expectant mothers. Pregnant workers are especially relevant, as certain cytotoxic substances or agents may be harmful to the unborn child. If a significant health and safety risk is identified for a new or expectant mother, which goes beyond the normal level of risk found outside the workplace, then advice should be sought from the University Occupational Health Service;
- further guidance is contained in New and expectant mothers at Work: A Guide for Employers and also the University's Local Rule New and Expectant Mothers;
- consider others who could be indirectly exposed, such as cleaners, contractors and maintenance
- workers; and
- assess how likely it is that cytotoxic substances and agents could cause ill health and decide if existing precautions are adequate or whether more should be done. Exposure from all routes should be prevented or adequately controlled to protect the health of employees from any potential adverse effects.

Factors to consider include:

- the frequency and scale of contact with cytotoxic substances and agents;
- how the substance will be used within the enclosed system or LEV system;
- any relevant information available from accident records; and
- the control measures in use and their effectiveness.

5. Deciding on and Implementing Risk Control Measures

Where any working exposure level (WEL) is likely to be reached or exceeded then the department must implement measures to reduce the risk to as low a level as reasonably practicable as identified on the COSHH assessment form.

Departments must also seek ways of reducing the risk of exposure to cytotoxic substances and agents, even where levels are below the working exposure levels, by considering the following:

- whether the substance can be substituted or eliminated i.e., can the work can be done in some other way without use of the chemical e.g. substituted by a non or less hazardous substance;
- the type of hazard (solid, powder, liquid or gas handling);
- the route by which the particular substance(s) can enter the body - inhalation, ingestion or penetration of the skin, mucosal surfaces or eyes;
- level of exposure (amount and for how long);
- the method of engineered controls to mitigate the effects of exposure;
- the appropriate PPE to be worn;
- operating and maintenance instructions and procedures (where applicable); and
- emergency and spillage procedures

Administration controls should also be considered e.g.

- organising work to reduce the quantities of drugs used;
- reducing the number of employees potentially exposed and their duration of exposure, to the minimum;
- arranging for the safe handling, storage and transport of cytotoxic drugs and waste material containing or contaminated by them;
- using good hygiene practices and providing suitable welfare facilities, e.g. prohibiting eating, drinking and smoking in areas where drugs are handled and providing washing facilities; and
- training all staff who may be involved in handling cytotoxic drugs or cleaning areas likely to be contaminated, in the risks and the precautions to take.

5.1. Engineered Controls

Exposure to cytotoxic substances and agents should be controlled by total containment of the substance or process. Whilst this is unlikely to be possible in every occasion within a research environment, the use of glove boxes or isolators must be employed **if reasonably practicable,** particularly where cytotoxic substances and agents presents a dust or vapour inhalation hazard. Further information on the choice of isolators can be found by reading the HSE guide on Handling Cytotoxic drugs in Isolators in NHS laboratories.

Routine maintenance procedures for the isolator and regular changes of the isolator gloves are essential and this must be performed in a way which minimises possible contamination. Safe systems of work (or safe operating procedures) should also be established for changing exhaust HEPA filters. Practical advice on the cleaning of Isolators can be found in the accompanying toolkit.

If used in conjunction with any biological material, the use of a Class I or II ducted Microbiological Safety Cabinet (MSC) should be used. Recirculating MSC's should not be utilised because of the potential for the cytotoxic substance to be returned to the normal air supply.

Where it is not possible to totally or partially enclose a process which presents a cytotoxic dust or vapour inhalation hazard, then appropriate local exhaust ventilation (LEV) must be used as a minimum.

5.2. Appropriate Personal Protective Equipment (PPE)

Personnel handling cytotoxic substances and agents should assess the risk of exposure and decide on the required PPE

Hand and Arm protection

No glove material will provide unlimited protection from cytotoxic substances and agents. When handling cytotoxic substances and agents or their waste products, the use of disposable, single use nitrile gloves is recommended .These should be changed frequently(approximately every hour) if work is carried on continuously or whenever the gloves break. When the risk of exposure is high, double gloving is highly recommended.

Eye and face protection

Where cytotoxic drugs are being handled outside an enclosed system and there is a risk of splashing, as identified by the risk assessment, a suitable number of options are available. Dependant on the risk and the control measures implemented, these can include a face shield or visor, goggles and safety spectacles with side fitting protective shields.

Respiratory Protection

As described above ,where it is not possible to totally or partially enclose a process which presents a cytotoxic dust or vapour inhalation hazard, then appropriate local exhaust ventilation (LEV) must be used as a minimum and respiratory protective equipment (RPE) worn. The selection of the appropriate RPE and filters must be appropriate to the toxicity of the substance and its route of exposure. Surgical masks will not protect against the inhalation of fine dust or aerosols.

Specific information can be found by reading the University's Local Rule on PPE.

5.3. Recording the Significant Findings

The significant findings of the risk assessment process must be recorded and include the following:

- the tasks assessed;
- the risk of exposure to cytotoxic substances and agents and who could be affected;
- the likelihood of the working exposure level being exceeded;
- the control measures already in place to manage the risk;
- the relevant information, instruction and training to be provided to staff and students;
- the scheme of health surveillance in use or planned as identified by Occupational Health; and
- the action plan of additional controls to reduce the risk.

The risk assessment will need to be reviewed if there is any reason to suspect that the original assessment is no longer valid or there has been a significant change in the work to which the assessment relates.

6. Arranging Health Surveillance

Health surveillance is only appropriate where:

- exposure to a hazardous substance is such that an identifiable disease or adverse health effect may be related to exposure;
- there is a reasonable likelihood that the disease or effect may occur under the particular conditions of the work undertaken; and
- there are valid techniques for detecting indications of the disease or effect; and the technique of investigation is of low risk to the employee.

Health Surveillance is not a substitute for effective control measures however there will be a few circumstances where the risk assessment process has identified that particular staff and students are likely to be regularly exposed to cytotoxic substances and agents, at or above the working exposure levels and engineered controls cannot be employed, or if there is a risk to staff e.g. females of child bearing age or immune-compromised individuals then health surveillance must be organised through the University Occupational Health Service.

When a programme of health surveillance is completed, the Occupational Health Service will provide the department with an anonymised general report of the results advising whether there are any health issues emerging. Departments must use this information to determine if the current risk control measures are effective or if further action is required. In any case the assessment should be reviewed annually.

6.1. Health Records

Those working with substances with workplace exposures limits (WEL) which are listed in the HSE publication EH40 Workplace Exposure Limits and who are deemed susceptible, or have prior knowledge of sensitisation to that substance, **will be required** to have their health information recorded on a health record form which will be completed by the Occupational Health Service for substances such as:

- respiratory sensitisers;
- skin sensitisers; and
- COSHH Schedule 6 Carcinogens

In addition the Occupational Health Service will report to the departments on each person's fitness to continue to work with these substances. Both report and record should be kept by the department for 40 years, however, only the Occupational Health Service will retain records which contain personal medical information.

It is therefore important that the COSHH assessment clearly identifies the staff at risk as this will be used to select which members of staff require health surveillance. (See University's Local Rule on Occupation Health.

Record of Personal Work Activity

In practice, the criteria for health surveillance above are unlikely to be met for handling cytotoxic drugs. However, it is recommended by the HSE that employers keep a record of work activity on all staff students and others potentially exposed to these compounds. The record should contain at least the following: surname, forenames, gender, date of birth, permanent address, and postcode, National Insurance Number, date of present employment started and a historical record of pharmaceutical products and work in this employment involving exposure to cytotoxic substances and agents should also be completed. This form can also incorporate susceptibility or potential exposure to other substances such as:

- nanomaterials or medicines of unknown toxicity; and
- non COSHH Schedule 6 Carcinogens.

The University Record of Personal Work Activity Form S31 can be found on the Safety Services website. An electronic version, accessed via Pegasus is currently under development. The record should be kept by the department and although at the moment there is no statutory timeframe, it is suggested that this record be also kept for 40 years.

6.2. Occupational Hygiene Monitoring

Safety Services currently manage the Occupational Hygiene monitoring programme.

Workplace exposure monitoring should be requested:

- where there is uncertainty about the levels of airborne contaminants generated by work activity using cytotoxic substances and agents;
- when failure or deterioration of control measures could result in a serious health effect;
- as an additional check on the effectiveness of control measures;
- when measurement is required to ensure an workplace exposure limit or in-house working standard is not exceeded; and
- when any change occurs in the conditions affecting employees' exposure which could mean that adequate control of exposure is no longer being maintained.

Departments should contact Safety Services if Occupational Hygiene Monitoring is required.

7. Providing Information, Instruction, Training and Supervision

7.1 Information

Where staff and students are exposed to cytotoxic substances and agents then departments must inform them about:

- the risks to health from exposure to cytotoxic substances and agents;
- how the risks can be reduced; and
- arrangements for health surveillance where this is deemed necessary;

7.2. Instruction and Training

Staff and students must be provided with relevant instruction and training on how to work with and handle cytotoxic substances and agents safely. Information on training for COSHH Awareness Training and also COSHH Assessors Training is available from the Safety Services website.

7.3. Supervision

Where there is a risk of exposure to cytotoxic substances and agents and possible ill health, departments must provide adequate supervision to monitor that risk control measures required to eliminate or reduce the risk are being implemented and remain effective.

8. Waste

Cytotoxic and cytostatic substances possessing hazardous characteristics can either be disposed of as Clinical waste or Hazardous waste, both of which are managed by Estates Services, (depending on their use and co- material).

Cytotoxic waste is designated as Special Waste under the EU Directive, regulated by the Special Waste Regulations (Scotland) Act 2004, regulated by the Scottish Environment Protection Agency (SEPA) http://www.legislation.gov.uk/ssi/2004/112/contents/made and follows the Guidance Safe Management of Healthcare Waste (PDF, 3698K)

Special waste should be segregated and suitable approved coloured containers clearly labelled and solely for the use of cytotoxic waste, should be available. Suitable approved coloured sharps containers should be used for the safe disposal of needles etc. Waste should not be allowed to accumulate

9. Further Information and Guidance

9.1 HSE Source

Publications free to download from the Health and Safety Executive website
http://www.hse.gov.uk/

Safe handling of Cytotoxic Drugs - HSE Information Sheet MISC7615

Biological Monitoring in the Workplace: A guide to its practical application to chemical exposure

The Control of Substances Hazardous to Health: The Control of Substances Hazardous to Health Regulations 2002. Approved Code of Practice and Guidance L5 (Fifth Edition) HSE Books 2005
Free pdf download available 

Health Surveillance at Work HSG61 (Second Edition) HSE Books 1999 ISBN 0 7176 1705 X

Latex and You Leaflet INDG320 HSE Books 2000 (single copy free or priced packs of 10 ISBN 0 7176 1777 7)

New and expectant mothers at work: A guide for employers HSG122 (Second edition) HSE Books 2002ISBN 0 7176 2583 4

Management of Health and Safety at Work: Management of Health and Safety at Work Regulations1999. Approved Code of Practice and Guidance

Personal Protective Equipment at Work: The Personal Protective Equipment at Work Regulations 2002

The Selection, Use and Maintenance of Respiratory Protective Equipment: A practical guide HSG53

Selecting Protective Gloves for work with Chemicals: Guidance for Employers and Health and Safety Specialists

9.2 Other sources

The Health and Safety at Work etc. Act 1974 Ch37: The Stationery Office 1974 ISBN 0 10 543774 3

Special Waste Regulations 1996 SI 1996/972 The Stationery Office 1996 ISBN 0 11 054565 6 as amended by Special Waste (Amendment) Regulations1996 SI 1996/2019 ISBN 0 11 062894 2

Allwood M, Stanley A and Wright P (editors): The Cytotoxics Handbook
Ratcliffe Medical Press 2002ISBN 1 85775 504 9

International Agency for Research on Cancer Some antineoplastic and immunosuppressive agents: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans Volume 26 IARC 1981 ISBN 92 832 1226 6

International Agency for Research on Cancer Overall evaluation of carcinogenicity an updating of IARC monographs Volumes 1-42: IARC monographs on the evaluation of carcinogenic risks to humans Supplement7 IARC 1988 ISBN 92 832 1411 0

International Agency for Research on Cancer Pharmaceutical drugs: IARC monographs on the evaluation of carcinogenic risks to humans Volume 50 IARC 1991 ISBN 92 832 1250 9

International Agency for Research on Cancer Some antiviral and antineoplastic drugs and other pharmaceutical agents: IARC monographs on the evaluation of carcinogenic risks to humans Volume 76 IARC 2000 ISBN 92 832 1276 2

MARC. (Management and Awareness of the Risks of Cytotoxics) Guidelines available on the website: www.marcguidelines.com

Parsons M Guidelines for the safe use of cytotoxic chemotherapy in the clinical environment Scottish Executive Health Department 2001 ISBN 1 84268 987 8

Goodman I (editor) Clinical practical guidelines: The Administration of Cytotoxic Chemotherapy: Recommendations RCN 1998 ISBN 1 873853 81 5

Goodman I (editor) Clinical practical guidelines: The Administration of Cytotoxic Chemotherapy: Technical Report RCN 1998 ISBN 1 873853 80 7

The Stationery Office (formerly HMSO) publications are available from The Publications Centre, PO Box 276, London SW8 5DT Tel: 0870 600 5522Fax: 0870 600 5533 Website: www.tso.co.uk (They are also available from bookshops).

The following summarises how departments can effectively implement this Local Rule and integrate it into its management systems. These processes will be monitored as part of Safety Services' Audit Programme, and where departments are able to demonstrate fulfilment of key actions, this is likely to provide strong evidence of good practice.

		Key Management Actions
1.	**Departmental Roles**	• Ensure that a responsible person is appointed to co-ordinate the COSHH assessment process and that the duties are defined. • Ensure that appropriate management, administrative and technical arrangements are in place to effectively control risks from exposure to cytotoxic substances and agents, through the COSHH assessment process and these are regularly reviewed.
2.	**Identifying Hazards**	• Ensure that work activities and agents which may present a risk of exposure to cytotoxic substances and agents are identified. • Ensure that novel compounds and waste substances are included as part of the process.
3.	**Evaluating Risks**	• Ensure information about the hazards of cytotoxic substances and agents is gathered. • Ensure that individuals complete a record of personal work activity where required. • Ensure that the results of the occupational hygiene monitoring are considered to evaluate which work activities and people will be exposed to cytotoxic substances and agents risks that could damage their health.
4.	**Implementing Risk Control Measures**	• Ensure that on receipt of the specific exposure to cytotoxic substances and agents reports, any recommendations made regarding controlling exposure are implemented. • Ensure that the range of risk control measures available and implement those measures that will reduce exposure to cytotoxic substances and agents are considered. • Ensure effective emergency procedures and contingency plans are implemented. • Ensure that recommendations and action points as a result of Occupational Hygiene Monitoring are implemented and communicated to staff.
5.	**Maintaining Risk Control measures**	• Ensure implemented risk control measures are maintained. • Ensure all local exhaust ventilation (LEV) systems are maintained by a competent person within the statutory requirement of 14 months and that records are kept.
6.	**Recording the Significant Findings**	• Ensure records of COSHH assessments and significant findings for exposure to cytotoxic substances and agents are kept. • Ensure that the assessment(s) are reviewed annually unless other changes occur before this period.
7.	**Arranging Health Surveillance**	Where the risk assessment identifies the need for health surveillance, ensure that a member of staff has been appointed to liaise with the Occupational Health Service to implement a health surveillance programme • Consider the anonymised general report from the Occupational Health Service to determine if the current controls are effective and ensure that the reports are kept. • Monitor that the relevant staff and students have attended for health surveillance.

8.	**Arranging Occupational Hygiene Monitoring**	Where there is uncertainty about the levels of airborne cytotoxic substances and agents generated by work activity or the consequences of exposure are significant. • Ensure that Occupational Hygiene Monitoring has been requested if concerns have been raised by the Occupational Health Service that controls are not effective. • Ensure that on-going monitoring is requested when significant changes in procedures are adopted.
9.	**Hazardous Waste**	• Ensure that nominated members of staff are appointed as Clinical and Hazardous waste co-ordinators. • Ensure that all Clinical and Hazardous waste is being treated and disposed of as per University policy.
10.	**Providing Information, Instruction, Training and Supervision**	Where staff and students are exposed to the risk of exposure to cytotoxic substances and agents. • Ensure assessors have received University COSHH assessors training course. • Ensure appropriate levels of supervision determined by the level of competence and knowledge of those involved. • Ensure those working with cytotoxic substances and agents attend the University's COSHH awareness course. • Ensure relevant information, instruction, training and supervision about the health risks is provided. • Ensure a record of the training provided, staff attending and any information issued is retained.

Appendix 1 - *General considerations and the classification criteria for substances*

Germ Cell Mutagenicity

The more general terms 'genotoxic' and 'genotoxicity' apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

Classification criteria for substances This hazard classification based on the categories below is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ cells in vivo are also considered in classifying substances and mixtures within this hazard class.

Hazard categories for germ cell mutagens

Categories Criteria
CATEGORY 1: Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans.

Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans

Category 1B*:* The classification in Category 1B is based on:

- positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or
- positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells, in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or
- positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.

CATEGORY 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans

Category 2 is based on:
- positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:somatic cell mutagenicity tests in vivo, in mammals; or other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.

Note: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

Appendix 1 (Contd.) - ***General considerations and the classification criteria for substances***

Reproductive toxicity
The definitions presented below are adapted from those agreed as working definitions in IPCS/EHC Document No 225, Principles for Evaluating Health Risks to Reproduction Associated with Exposure to Chemicals. For classification purposes, the known induction of genetically based heritable effects in the offspring is addressed in Germ Cell Mutagenicity (section 2.1), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

Hazard categories for reproductive toxicity
For the purpose of classification for reproductive toxicity, substances are allocated to one of two categories. Within each category, effects on sexual function and fertility, and on development, are considered separately.
In addition, effects on lactation are allocated to a separate hazard category.

In this classification system, reproductive toxicity is subdivided under two main headings:

(a) adverse effects on sexual function and fertility;
(b) adverse effects on development of the offspring.

Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, substances with these effects, or mixtures containing them, shall be classified as reproductive toxicants.

Categories Criteria

CATEGORY 1: Known or presumed human reproductive toxicant

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

Category 1A: Known human reproductive toxicant
The classification of a substance in Category 1A is largely based on evidence from humans.

Category 1B: Presumed human reproductive toxicant
The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on Reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

CATEGORY 2; Suspected human reproductive toxicant
Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.

Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Lactation Toxicity
Substances which fall under the definition of being Lactation toxic shall be classified and labelled to indicate this property hazardous to breastfed babies.

Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation.

Specific target organ toxicity - Single exposure
Classification identifies the substance or mixture as being a specific target organ toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

These adverse health effects produced by a single exposure include:

- consistent and identifiable toxic effects in humans, or, in experimental animals;
- toxicologically significant changes which have affected the function or morphology of a tissue/organ; or
- have produced serious changes to the biochemistry or haematology of the organism, and these changes are relevant for human health.

Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.

Categories for specific target organ toxicity - Single exposure

Categories Criteria

Category 1: Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure

Substances are classified in Category 1 for specific target organ toxicity (single exposure) on the basis of:

(a) reliable and good quality evidence from human cases or epidemiological studies; or
(b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations.

Category 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure

Substances are classified in Category 2 for specific target organ toxicity (single exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations.

Category 3: Transient target organ effects
This category only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function.

Appendix 1 (Contd.) - *General considerations and the classification criteria for substances*

Specific target organ toxicity - Repeated exposure
Classification for target organ toxicity (repeated exposure) identifies the substance as being a specific target organ toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

These adverse health effects include:

- consistent and identifiable toxic effects in humans, or, in experimental animals;
- toxicologically significant changes which have affected the function or morphology of a tissue/organ; or
- have produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health.

Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.

Categories for specific target organ toxicity - Repeated exposure

Categories Criteria

Category 1: Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure.

Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of:

(a) reliable and good quality evidence from human cases or epidemiological studies; or
(b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations.

Category 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure.

Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations.

In exceptional cases human evidence can also be used to place a substance in Category 2

Appendix 2 - Labelling and Hazard Statements.

Reproductive toxicity

Classification	Category 1A or Category 1B	Category2	Additional category for effects on or via lactation
GHS Pictograms			No pictogram
Signal Word	Danger	Warning	No signal word
Reproductive toxicity (Hazard Statement)	H360: May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H362: May cause harm to breast-fed children.
Germ Cell Mutagenicity (Hazard Statement)	H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H341: Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	
Carcinogenicity (Hazard Statement)	H350: May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H351: Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	