

Note: Hazard information for Science of Synthesis

Hazard information and risk assessments for chemicals

Information on the hazardous properties of chemicals is a prerequisite before embarking on any manipulations with chemicals. Hazard information on chemicals is also required for compiling risk assessments for a laboratory environment. Hazard and risk are not interchangeable terms. Hazard is the set of inherent properties of a chemical substance that makes it capable of causing adverse effects in man or in the environment when a particular degree of exposure occurs. Risk is the prediction or actual frequency of occurrence of an adverse effect of a chemical substance from a given exposure to humans or the environment. In other words, risk is a function of the **physical, reactive or toxic properties** of a chemical and the **exposure** to that substance. Risk assessment therefore requires knowledge of both the hazard of a chemical and the purpose for which it is being used. Risk assessments of hazardous substances used in the workplace are part of the regulatory framework for enacting national health and safety legislation.

Hazard information and *Science of Synthesis*

The experimental procedures documented in *Science of Synthesis* are intended for use only by persons with previous training in experimental organic chemistry, awareness of the hazardous properties of chemicals, and access to hazard information. It is understood that experimental chemistry based on the chemistry documented in *Science of Synthesis* is conducted at the risk of those conducting the experiments and their respective supervisors. It is assumed that all laboratory procedures will be conducted within legislative frameworks governing the storage, manipulation, disposal and environmental impact of chemicals and biological agents in the respective country where the procedure is being conducted. Thieme Chemistry and its Editors do not warrant or guarantee the safety of individuals using procedures published in *Science of Synthesis* and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the published procedures within the content of *Science of Synthesis*.

Chemical-specific *Caution Statements* are appended to many of the procedures in *Science of Synthesis* highlighting substances and operations that present particular hazards. The absence of a chemical-specific *Caution Statement* does not imply that there are no significant hazards associated with the chemicals involved in a procedure. A lack of hazard information does not mean that the consequences of handling a chemical may be ignored. Any chemical has the capacity for harm if it is carelessly used, and, for many newly synthesized materials, their hazardous properties may not yet be apparent or may not have been cited in the literature. The toxicity of some very reactive chemicals may not have been evaluated because of ethical considerations.

Hazardous properties of chemicals

Chemicals are associated with two types of hazard: hazards that are a direct result of the physical or reactive properties of a chemical; and hazards posed by the effect of a chemical on biological systems. Flammability and the stability of a chemical in air or towards water may be included in the first group, while the carcinogenic potential of a chemical or its effect on the reproductive system are health hazards due to the biological properties of a chemical.

Identifying hazardous chemicals

Particular groups of hazardous chemicals may be identified from their physical, reactive, and biological properties. Some examples of groups of chemicals which pose physical, reactive and health hazards are listed below:

Physical and reactive chemical hazards

- Flammability
- Explosive and shock-sensitive properties
- Stability in air or in contact with water (pyrophoric and water-reactive compounds)
- Incompatibility with commonly-available chemicals and reagents
- Potential for peroxidation
- Oxidizing/reducing properties
- Storage properties

Health effects of chemicals

- The physical form of chemical substance, which can influence its absorption properties and target organ toxicity (e.g. electrostatic powders; gases/vapours/aerosols; lipophilic solvents)
- Known human carcinogens and probable human carcinogens according to the International Agency for Research on Cancer (IARC) classifications
- Known human teratogens
- Chemicals known to have an effect on human reproduction
- Chemicals that are irritants to the skin, eyes and respiratory system (data from human exposure or animal tests)
- Chemicals that are corrosive to the skin, eyes and respiratory system (data from human exposure or animal tests)
- Skin sensitizers
- Chemicals that are highly toxic as a result of some specific pharmacological mechanism (e.g. cyanide; the potent neurotoxin tetrodotoxin)
- Continual low-level exposure to organic solvents

Some chemicals which present physical, reactive, and health hazards are identified in four appendices at the end of this *Note*:

Appendix 1: Examples of reactive, toxic and corrosive chemicals, which may be encountered in the chemical laboratory

Appendix 2: Peroxide-forming chemicals

Appendix 3: Chemical carcinogens

Appendix 4: Human teratogens

Health and safety legislation

Good laboratory and manufacturing practices are encoded in national and international health and safety legislation, and place emphasis on the key attitudes to be adopted when handling and working with chemical substances (or mixtures). Although the exact regulatory details may differ from country to country, the essential aims of national health and safety legislation relating to the handling of chemicals in laboratories

(and in the workplace in general) are the same and emphasize the importance of hazard information:

- Identify the risks of handling hazardous substances and inform employees.
- Prevent, minimize, or control exposure.
- Ensure that control measures are correctly used and maintained, and that personal protection equipment is available.
- Monitor exposure in the workplace and comply with national occupational exposure limits.
- Provide information, training and instruction of the risks involved.
- Keep records of risk assessments, records of the maintenance and testing of engineering controls, and occupational health records.

In the UK, laboratory managers and supervisors (and employers, in the wider sense, in general) have a legal obligation under the Control of Substances Hazardous to Health (COSHH) Regulations 2002 to assess the risks to health from hazardous substances used in or created by workplace activities. Also, in the UK, the Classification, Labelling and Packaging Regulation (CLP Regulation) requires manufacturers and suppliers of chemicals to provide end-users [laboratory managers and personnel] with material safety data sheets (MSDS) about the physical and health hazards of chemicals by labelling their products with relevant hazard information. Where appropriate, labels for laboratory chemicals and reagents should incorporate:

- A pictogram(s) depicting the hazard (chosen from a set of nine pictograms – Figure 1).
- A hazard statement(s) summarizing the nature and degree of hazard of a substance.
- A precautionary statement(s) with information on minimizing or preventing the physical, health or environmental effects of a substance, and including first aid measures.

The UK CLP Regulation incorporates the **United Nations Globally Harmonized System of Classification and Labelling of Chemicals** (UN-GHS), in which *inter alia* the pictograms shown in Figure 1 are adopted. Other European Union (EU) countries have enacted equivalent legislation.

Chemicals produced in the research laboratory are exempted from the obligations of the CLP Regulation, provided they are not placed on the market and they are used under controlled conditions in accordance with workplace and environmental legislation. However, if substances used in research and development are physically made available or supplied to another establishment, for example by sending samples from a university to another research institute or by importing such samples, then the CLP Regulation will apply. The CLP Regulation replaced the Chemicals (Hazard Information and Packaging for Supply) (CHIP) Regulations in the UK in 2015. Under the EU's **REACH** legislation, which complements the CLP Regulation, suppliers of substances or mixtures meeting the criteria for classification as hazardous according to CLP have to compile and supply end-users with Safety Data Sheets (SDS) for use, for example, in **COSHH Assessments**. [REACH (Registration, Evaluation, Authorisation and restriction of CHemicals)].

In the **United States of America**, management of laboratory health and safety requires the preparation and implementation of a chemical hygiene plan (CHP) that complies with the Occupational Health and Safety Administration (OSHA) laboratory standard, 29 CFR 1910.1450. Full details of this standard may be found on the OSHA website:

https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=10107; accessed 19 February 2018.

European Union Directives, which protect workers from exposure to chemical (and biological) agents, may be located (with updates/amendments) on the European Agency for Safety and Health at Work website: <https://osha.europa.eu/en/legislation/directives/exposure-to-chemical-agents-and-chemical-safety/>; accessed 19 February 2018.

In **Japan**, the Japan International Center for Occupational Safety and Health has published ‘Guidelines for the Necessary Measures to Prevent Health Impairments to Workers Due to Chemical Substances, Etc. (2000)’ (available at: <https://www.jniosh.go.jp/icpro/jicosh-old/english/guideline/chemical.htm>; accessed 19 February 2018). These guidelines include a ‘Chemical Substances Management Plan’, and mirror the European and USA approach to handling chemicals in the workplace. A special issue of *Journal of Environment and Safety*, 2016, issue 2, Proceedings of the 2nd Asian Conference on Safety and Education in Laboratory, December 1-2, 2015 (available from J-STAGE) provides a contemporary overview of the management of chemicals in Japanese research laboratories.

In **China**, laboratory safety and the manipulation of chemicals are covered by the ‘Regulations on Safe Management of Hazardous Chemicals in China – Decree 591’ (<http://www.cirs-reach.com/news-and-articles/regulations-on-safe-management-of-hazardous-chemicals-in-china-decree-591.html>); accessed 19 February 2018), which broadly reflects the European and USA legislative approach.

Further reading

Reactive hazards

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Laboratory safety

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Safe Storage of Laboratory Chemicals, 2nd ed., ed. D. A. Pipitone, Wiley, New York, 1991.

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Electronic sources for hazard information

The web is a comprehensive resource for hazard information and for advice on safe practices in the chemical laboratory. Many UK and USA university chemistry departments have posted their safety policies and guidance for laboratory workers on the web and added links to other health and safety websites. Websites of the following organisations are also useful sources of hazard information:

Organization	Internet address and description of content
Agency for Toxic Substances and Disease Registry	http://www.atsdr.cdc.gov/ ; accessed 19 February 2018
American Conference of Governmental Industrial Hygienists	www.acgih.org ; accessed 19 February 2018 Sources of information on TLVs, biological exposure indices, chemicals under study and revisions to TLVs
Health and Safety Executive (HSE)	http://www.hse.gov.uk/ ; accessed 19 February 2018

HSE COSHH homepage	http://www.hse.gov.uk/coshh/index.htm ; accessed 19 February 2018
The CLP Regulation	http://www.hse.gov.uk/chemical-classification/legal/clp-regulation.htm ; accessed 19 February 2018
International Agency for Research on Cancer Agents Classified by the <i>IARC Monographs</i> , Volumes 1–120	www.iarc.fr/ ; accessed 19 February 2018 http://monographs.iarc.fr/ENG/Classification/ ; accessed 19 February 2018
International Programme on Chemical Safety (WHO) with links to: Environmental Health Criteria	http://www.inchem.org/ ; accessed 19 February 2018 http://www.who.int/ipcs/publications/ehc/en/ ; accessed 19 February 2018 Environmental Health Criteria (EHC) documents provide international, critical reviews on the effects of chemicals or combinations of chemicals and physical and biological agents on human health and the environment
National Institute for Occupational Health and Safety (NIOSH)	www.cdc.gov/niosh/ ; accessed 19 February 2018 Research studies, health hazard evaluations, extensive links to occupational safety and health resources on the Internet
NIOSH Pocket Guide to Chemical Hazards	http://www.cdc.gov/niosh/npg/ ; accessed 19 February 2018 Also gives a link to The Registry of Toxic Effects of Chemical Substances (RTECS) database
NIOSH Workplace Safety and Health Topics – Chemicals	https://www.cdc.gov/niosh/topics/chemical.html ; accessed 19 February 2018
NIOSH Workplace Safety and Health Topics – Solvents	A bibliography of the health effects of organic solvents and related topics http://www.cdc.gov/niosh/topics/organsolv/ ; accessed 19 February 2018.
National Library of Medicine	www.nlm.nih.gov/ ; accessed 19 February 2018
Databases include PubMed and TOXNET	http://www.ncbi.nlm.nih.gov/pubmed/ and http://toxnet.nlm.nih.gov/ . Both accessed 19 February 2018
National Toxicology Program	https://ntp.niehs.nih.gov/ accessed 19 February 2018 Extensive information on chemicals, reactivity, long-term and short-term effects

Natural Environment Research Council (NERC) Procedures, Guidance and Forms	A series of advice and guidance notes for laboratory workers, including: laboratory design; health and safety committee constitution; risk assessment and risk management; working with hazardous chemicals in the laboratory; safe storage of laboratory chemicals; maintenance and use of fume cupboards. Emphasis on UK health and safety regulation. Available as downloadable pdfs from the NERC website http://www.nerc.ac.uk/about/policy/safety/procedures/ ; accessed 19 February 2018
Occupational Safety and Health Administration (OSHA) Laboratory Safety Guidance, 2011	Guidance for working with chemicals and other hazardous agents in the laboratory with citations to the relevant US health and safety legislation. Available as a downloadable pdf from the OSHA website https://www.osha.gov/Publications/laboratory/OSHA3404laboratory-safety-guidance.pdf ; accessed 19 February 2018
United Nations Economic Commission for Europe (UNECE)	The nine GHS pictograms and related hazard and precautionary statements are listed in the UNECE's <i>Globally Harmonized System of Classification and Labelling of Chemicals</i> https://www.unece.org/info/media/stories/use-chemicals.html ; accessed 19 February 2018

Appendix 1

Examples of reactive, toxic and corrosive chemicals, which may be encountered in the chemical laboratory

Pyrophoric liquids

Compounds that may spontaneously ignite upon exposure to oxygen, moisture, or both:

- neat trialkylaluminums (e.g. Me₃Al) or alkylaluminums in solution
- *tert*-butyllithium, *sec*-butyllithium and other alkyl- and aryllithium reagents
- diisobutylaluminum hydride (DIBAL-H)
- Grignard reagents (alkyl- or arylmagnesium halides)
- borane•THF
- diethylzinc
- other substances of comparable properties

Pyrophoric solids

Compounds that may spontaneously ignite upon exposure to oxygen, moisture, or both:

- alkali metals (Na, K, Rb, Cs)
- high purity, powdered metal hydrides (e.g. NaH, KH, LiAlH₄)
- Raney nickel, palladium on carbon, and other spent catalysts that have been exposed to hydrogen
- Barium manganate
- other substances of comparable properties

Highly corrosive compounds

- acid chlorides
- halogens (F₂, Cl₂, Br₂)
- hydrofluoric acid
- nitric acid
- perchloric acid
- phenol
- piranha solution (H₂SO₄ + H₂O₂)
- strong organic acids (e.g. methanesulfonic acid)
- other substances of comparable properties

Highly toxic solids, liquids, and gases

- acrylamide
- alkyltins
- benzyl halides
- carbon tetrachloride
- dimethylcadmium
- dimethylmercury
- dimethylsulfate
- ethidium bromide
- formaldehyde
- hexamethylphosphoramide
- mercury salts
- methyl fluorosulfonate (Magic Methyl)
- methyl and trimethylsilyl triflate
- nickel carbonyl
- osmium tetroxide
- trimethylsilyl cyanide
- trimethylsilyl diazomethane
- tetramethylammonium hydroxide
- other substances of comparable properties

Gases that possess toxic, pyrophoric, corrosive, and/or flammable characteristics

- carbon monoxide
- chlorine
- hydrogen cyanide
- phosphine
- germane
- diborane
- silane
- alkyl phosphines
- alkyl halides
- other substances of comparable properties

Potentially Explosive Substances

Substances that undergo a chemical reaction that releases a large amount of heat and a rapidly expanding volume of gas.

- acetylenes
- azides
- diazonium salts and diazo compounds (e.g. diazomethane)
- nitrogen triiodide
- organic peroxides
- oxygen (liquid)
- ozone
- ozonides
- perchlorate salts, perchloric acid
- peroxyacids
- poly-nitro compounds (e.g. picric acid)
- triacetone triperoxide (TATP)
- other substances of comparable properties

Other explosive hazards

- Dess-Martin Periodinane precursor compound (IBX)
- liquid O₂ from N₂-cooled vacuum traps
- nitric acid + organic substances

Stench chemicals and lachrymators

- butyric acid
- valeric acid
- selenium compounds
- tellurium compounds
- thiols (e.g. ethane thiol, hydrogen sulfide, bis(trimethylsilyl) sulfide)
- isonitriles
- alkyl phosphines
- alkyl halides
- other substances of comparable properties

Appendix 2

Peroxide-forming chemicals

Peroxides are sensitive to shock, sparks, or other accidental ignition. Ethers such as tetrahydrofuran, ethyl ether, diisopropyl ether, especially when purified (i.e. not containing stabilizers, or inhibitors of autooxidation), may form high concentrations of peroxides within a short period of time when exposed to the air. Diisopropyl ether forms a crystalline bis-peroxide that explodes with deadly force. Also note that exposure of peroxidizable solvents to peroxides or other oxidants, especially in the air, can generate hazardous levels of peroxides. All substances with weak carbon-hydrogen bonds should be considered as potentially peroxidizable and, therefore, hazardous.

Compounds known to autoxidize to form peroxides

These compounds can readily form peroxides when exposed to atmospheric oxygen and light:

- aldehydes
- ethers, especially cyclic ethers and those containing primary and secondary alkyl groups
- compounds containing benzylic hydrogens
- compounds containing allylic hydrogens (C=C–CH), including most alkenes, vinyl, and vinylidene compounds
- compounds containing a tertiary C–H group (e.g. decalin; 2,5-dimethylhexane)

Appendices 1 and 2 are reproduced with permission from text in the Harvard Department of Chemistry and Chemical Biology Laboratory Safety Manual, revised 2012.

Appendix 3

Chemical carcinogens

Lists of IARC Evaluations of Carcinogenicity

The International Agency for Research on Cancer (IARC) classifies the carcinogenicity of chemical substances and chemical mixtures according to one of five categories:

Group 1 – The agent (mixture) is carcinogenic to humans.

The exposure circumstance entails exposures that are carcinogenic to humans.

Group 2A – The agent (mixture) is probably carcinogenic to humans.

The exposure circumstance entails exposures that are probably carcinogenic to humans.

Group 2B – The agent (mixture) is possibly carcinogenic to humans.

The exposure circumstance entails exposures that are possibly carcinogenic to humans.

Group 3 – The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.

Group 4 – The agent (mixture) is probably not carcinogenic to humans

IARC Overall evaluations of carcinogenicity to humans

Agents Classified by the IARC Monographs, Volumes 1–120 are listed on the website:

<http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf>; 19 February 2018

The US National Toxicology Program and other North American agencies carry out similar surveys and classifications of human and probable human carcinogens, and these are listed on the American Cancer Society website: <https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-carcinogens.html>; 19 February 2018

Appendix 4

Known human teratogens

From: Shepard, T.H., *Catalog of Teratogenic Agents*, 13th ed., The Johns Hopkins University Press, Baltimore, 2010.

Drugs and environmental chemicals

aminopterin and methylaminopterin	iodides and goiter
androgenic hormones	lithium
busulfan	mercury (organic)
captopril (renal failure)	methimazole and scalp defects
chlorobiphenyls	methylene blue via intraamniotic injection
cocaine	misoprostol
coumarin anticoagulants	penicillamine
cyclophosphamide	13- <i>cis</i> -retinoic acid (isotretinoin and accutane)
diethylstilbestrol	tetracyclines
diphenylhydantoin and trimethadione	thalidomide
enalapril (renal failure)	toluene abuse
etretinate	trimethadione
fluconazole, high dose	valproic acid

Possible human teratogens

carbamazepine	vitamin A (large doses)
colchicine	lead
disulfiram	primidone
ergotamine	quinine (very large doses)
streptomycin	
zinc deficiency	

Figure 1: UN-GHS and UK CLP Regulation Hazard Pictograms



Oxidising



Flammable



Explosive



Acute toxicity



Corrosive



Gas under pressure



Serious health hazard



Hazardous to the environment



Health hazard