

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY (IPCS)

THE GLOBALLY HARMONIZED SYSTEM FOR THE CLASSIFICATION AND LABELLING OF CHEMICALS (GHS), FIRST-AID AND POISONS CENTRES TRAINING MATERIALS

GHS, FIRST-AID AND POSIONS CENTRES

*23-25 June 2004
Freiburg, Germany*

SUMMARY REPORT

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1. The document provides a summary report of the IPCS Workshop on the Globally Harmonized System for the Classification and Labelling of Chemicals (GHS), First Aid and Poisons Centre Training Materials.

2. The Workshop was organized on behalf of the IPCS by the Freiburg Poisons Centre, Germany, 23-25 June 2004. Seventeen experts participated in the Workshop from Poisons Centres in five WHO regions, along with experts involved in the development of the GHS and in the compilation of IPCS International Chemical Safety Cards. Annex 1 provides a list of experts who participated in the Workshop.

3. The Workshop was co-chaired by Dr Edith Clarke of the Ministry of Health, Ghana and Dr Martine Mostin of the Belgium Poisons Centre. Dr Wayne Temple, of the New Zealand National Poisons Centre, was the Rapporteur.

4. The objectives of the of the Workshop were:

- To raise awareness of the Globally Harmonized System of Classification and Labelling of Chemicals and the role that poisons centres and other emergency responders can have in the implementation of this new system.
- To discuss existing first-aid advice for chemical poisoning, to identify any chemicals for which specific first-aid should be recommended, to establish the degree of consensus for a harmonized set of first aid requirements for specific chemicals and for possible formats for this information.
- To discuss the development of a training manual for poisons centres including reviewing training materials and several draft chapters of the manual.

3. Annex 2 provides the adopted agenda for the Workshop. Sessions 1 and 2 focused on first-aid and the GHS. These sessions are reported in this summary report together with the relevant conclusions and recommendations.

4. In the associated session 3, participants discussed the development of IPCS Training Materials for strengthening the operations of poisons centres. It was recommended that a chapter on the GHS be developed for inclusion in the training manual to assist in increasing awareness of the GHS among poisons centre professionals. It is planned that a companion summary report will be written to report on session 3.

Structure of Workshop

5. In plenary session, an overview of the GHS was provided by Ms Catherine Masson of the UN Economic and Social Affairs Council and presented on her behalf by Lesley Onyon. The activities of the UNITAR/ILO GHS Capacity Building Programme

were presented by Mr Jonathan Krueger, UNITAR. An overview of activities in the Americas to provide safety training for first responders at Chemical Incidents was presented by Dr Diego Gotelli, Argentina. The Workshop discussed in detail the work of the Correspondence Group on Precautionary Statements of the Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling (UNSEGHS) and the detailed proposal to be considered by the UNEGHS in July 2004 (ST/SG/AC.10/c.4/2004/8) and a discussion paper prepared by IPCS on the availability and scope of first-aid advice for chemical poisoning ([Annex 3](#)).

Summary of Discussion

6 The Workshop recognized that all countries had made a commitment to implement the GHS by 2008 as part of their overall commitments to achieving the goals of the World Summit on Sustainable Development. It further recognised that precautionary statements are a key communication tool for implementation of the GHS enabling a link between the identified hazards of the chemical and the recommended measures that should be taken to minimise or prevent adverse effects resulting from exposures to hazardous chemicals from improper storage, handling and use.

- The Workshop supported the overall approach developed by the Correspondence Group of the UNSCEGHS on the development of precautionary statements covering prevention, response in the case of accidental spillage or exposure, storage and disposal, and the proposed way of linking these to the different hazard classes of the GHS.
- The Workshop confirmed that the proposed approach assisted in the increased understanding of the need for different types of precautions for different chemicals and their application in a clear and consistent manner.

7. The Workshop recognized that the proposed GHS precautionary statements had been developed by harmonizing statements currently in use, namely those from the IPCS International Chemical Safety Cards Compilers Guide, the American National Standards (ANZI Z129.1) and the EU system of safety phrases associated with its classification and labelling directives. A poisons centre is a specialized unit that advises on, or assists with, the prevention, diagnosis and management of poisoning. The structure and function of poisons centres varies around the world. At a minimum a poisons centre is an information service. Some poisons centres may also include a toxicology laboratory and/or a clinical treatment unit.

- The Workshop supported the proposal to include directions to call a poisons centre or doctor/physician and noted that this was consistent both with existing systems of precautionary statements and with the recognized functions of poisons centres to provide information and advice on the appropriate management of exposures to chemicals.

8. The Workshop acknowledged that there were different opinions of what constituted first-aid and agreed that the term included procedures necessary to sustain life or prevent other serious consequences but did not include the use of invasive

procedures or specialized equipment. The Workshop acknowledged that sometimes the setting in which the exposure had taken place influences the type of first-aid generally used. For example, exposures to chemicals at sea or at other places remote from a hospital setting may require more specialist procedures to be given. In other cases supplementary advice may be needed before administration of basic first-aid procedures as the condition of the exposed person, including age, the estimated extent of exposure and the length of time that had elapsed since exposure sometimes influenced the advice to be given. One example of this additional advice would be whether transfer to a hospital was needed.

9. The Workshop agreed a small number of minor modifications should be made to the existing proposal (ST/SG/AC.10/C.4/2004/8) to further increase internal consistency and to match the urgency of the response to the hazards involved. An annotated copy of the proposed document is given in Annex 4 to this record. The Workshop noted that following adoption of the agreed system of precautionary statements by the UN, existing systems including the ICSC Compilers Guide will require consequential revision.

Key recommended changes to Annex 3 ST/SG/AC.10/C.4/2004/8

10. Of the changes recommended by the Workshop to the proposed precautionary statements (ST/SG/AC.10/C.4/2004/8) the following are considered the most important.

11. The Workshop noted that advice to induce vomiting was included in the proposals as a first-aid measure but that the means of doing so was not specified. Vomiting can be induced in various ways many of which can place the exposed person at greater risk than the ingested poison e.g. administration of salt water. Commonly labels and safety data sheets recommend syrup of ipecacuanha.

- The Workshop did not agree that the induction of vomiting should be included in the proposals.
 - The deletion of the recommended use of induction of vomiting is consistent with position statements of key professional groups such as the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) and the American Academy of Clinical Toxicology (AACT). *J Tox Clin Tox* (Vol. 42, No. 2, pp. 133–143, 2004).
 - Furthermore experience with the treatment of chemical poisoning over the last decade has shown that there was no evidence of clinical benefit to justify the routine use of syrup of ipecacuanha This is consistent with the deletion of syrup of ipecacuanha from both the WHO List of Essential Medicines the WHO Model Formulary (April 2003).
 - A supplementary note regarding the deletion of recommendations to induce vomiting may be useful supplementary advice for manufacturers and suppliers.
- The Workshop noted that existing precautionary statements advise use of activated charcoal as a first-aid measure and this has been shown to be

effective. The Workshop agreed with the proposed precautionary statements that it should not be specifically included but be one of the additional measures supported based on the further advice from a poisons centre or doctor/physician.

- The Workshop agreed that the use of oxygen as a means of resuscitation should be undertaken by trained personnel and for chemicals which are known to interfere with oxygen uptake and metabolism in the body. This is consistent with the IPCS Compilers Guide for ICSC.

12. After examining a number of international, regional and national contemporary sources of first aid advice for chemicals poisoning it was found that a small number of chemicals were commonly listed as having specific first-aid directions. On closer examination, while this was supported it was found that the existing references were not harmonized and that they included first-aid measures over and above the those in general use.

13. It was noted that there was further reference within the precautionary statements to further reference information of various types. The Workshop noted that the purposes was to highlight additional first-aid in certain circumstances and that further information could be found on the safety data sheet or other reference sources.

14. The Workshop acknowledged and supported the primary role of manufacturers and suppliers in both classifying the hazardous chemicals they produce and ensuring the correct labelling. However, the Workshop had reservations about this primary responsibility automatically extending to providing specialised first-aid or medical treatment advice. In view of this and the substantial variation found even among existing authoritative sources, the Workshop agreed that publication of a globally consensus view would be a useful supplementary reference to the GHS to prevent unnecessary risks, ineffective treatment

- The Workshop agreed that harmonized special first-aid advice should be available for a limited number of chemicals such as cyanide, hydrofluoric acid, organophosphorus and carbamate pesticides and paraquat and this should be referred to from within the GHS.
- The Workshop recommended that IPCS should work in partnership with relevant professional bodies such as EAPCCT, AACT, Asia-Pacific Association of Medical Toxicologists (APAMT) to achieve a consensus on the chemicals to be included on the above list and to harmonise and update the specialist first-aid advice that should be given. If agreed by the UNSCEGHS this action should not delay adoption of the current proposals.

Other issues relating to implementation of the GHS

15. Given the discussions of the GHS, the existing role of poisons centres and the proposals to include them as key reference points in the implementation of the proposed precautionary statements the Workshop concluded that further specific consideration

was needed to address the role of poisons centres in implementing the GHS. Four actions were identified:

- At a national level, among governments and bodies responsible for poisons centres so that they can consider the role that poisons centres will play as part of the GHS, and how these centres should be supported in this activity.
- At the professional level awareness and understanding of the GHS should be increased among professionals working in poisons centres so that they can understand and the basis for, and implications of, the hazard classification information provided.
- Appropriate information about chemicals should be provided by manufacturers and suppliers of hazardous chemicals to poisons centres so that these centres can more effectively provide specific advice on the management of chemical exposures and at the same time collect information about unexpected signs and symptoms being reported from specific chemicals in use.

16. The Workshop requested that further advice be obtained on an appropriate mechanism or forum for addressing the above general issues to ensure effective implementation of the proposals for precautionary statements.

17. The Workshop agreed that a summary of its discussions and suggested changes to the proposed precautionary statements being considered by the UN would be forwarded by the IPCS for the next meeting of the UNSCEGHS for its July 2004 meeting. The timetable envisaged for adoption of the proposed precautionary documents is December 2004 so it was foreseen that there would be an opportunity for further fine tuning in the meantime.

CLOSURE

18. The Co-chairs of the Workshop thanked participants for their active participation and the local organisers for their efficient organization and welcome to Freiburg.

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CLASSIFICATION AND LABELLING OF CHEMICALS (GHS), FIRST-AID
AND POISONS CENTRES TRAINING MATERIALS**

Freiburg, Germany

23-25 June 2004

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**WORLD HEALTH ORGANIZATION
INTERNATIONAL LABOUR ORGANIZATION
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**IPCS WORKSHOP - THE GLOBALLY HARMONIZED SYSTEM FOR THE
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DRAFT AGENDA

*To be held at Leifman House, Guest House of University, Goethestr , 33-35, Freiburg,
Germany*

23 - 25 June 2004, commencing at 09.30 on Wednesday 23 June

1. **Welcome and introduction of participants**
2. **Election of Chair and Rapporteur**
3. **Objectives of Workshop and overview of sessions**

Session 1 – The Globally Harmonized System for the Classification and Labelling of Chemicals

4. **Overview of the Globally Harmonized System for the Classification and Labelling of Chemicals (GHS)**
 - The Globally Harmonized System of Classification and Labelling of Chemicals (Powerpoint presentation by Catherine Masson, UNECE)
5. **Update on relevant country/regional initiatives for implementation of the GHS**
 - Presentation by Jonathan Krueger, UNITAR
 - Presentation by Diego Gotelli, Argentina
6. **Discussion of Session 1**

Session 2 – First-aid advice for chemical poisonings

6. **First-aid as an element of the GHS system for precautionary statements**
 - Status of the work of the UN Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals (ST/AG/AC.10/C4/2004/08e dated 30 April 2004)

7. **Availability of and scope of existing sources of first-aid advice on chemical poisoning**

- Discussion Paper

8. Conclusions and recommendations of session 2

Session 3 – Development of an IPCS INTOX Training Manual for Poisons Centres

9. IPCS INTOX Poisons Centre Training Manual - overview; scope and session objectives

- Background paper and presentation (Joanna Tempowski, IPCS)

10. Presentation of 11 draft chapters for review at meeting

11. Break-out groups to review and discuss draft chapters

12. Conclusions of break-out groups on draft chapters

13. Recommendations on future chapters and format for training manual

Session 4 - Closure of Workshop

14. Endorsement of conclusions and recommendations from Freiburg Workshop

15. Official closure

**WORLD HEALTH ORGANIZATION
INTERNATIONAL LABOUR ORGANIZATION
UNITED NATIONS ENVIRONMENT PROGRAMME**

IPCS WORKSHOP FOR POISONS CENTRES

**THE GLOBALLY HARMONIZED SYSTEM FOR THE CLASSIFICATION AND
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MATERIALS,
23-25 JUNE 2004, FREIBURG, GERMANY**

**AVAILABILITY AND SCOPE OF FIRST AID ADVICE FOR CHEMICAL
POISONING**

DISCUSSION PAPER

PURPOSE

The purpose of this document is to:

- provide an overview of current sources of first-aid advice for chemical poisonings;
- discuss the scope of current first aid advice in the context of the GHS work on precautionary statements,
- identify any advice specific to individual chemical(s); and
- enable a discussion of any issues arising

REQUESTED ACTION

Based on this review, Workshop participants may wish to discuss :

- *How to improve knowledge and awareness of the GHS and precautionary statements among poisons centres given the increased that prominence that implementation of the GHS will give to their services.*
- *Whether there is a need for the GHS to include information on the role of poisons centres in relation to first-aid advice such as the application of first-aid in certain situations.*
- *Whether there are certain settings where additional first-aid guidance is available e.g. large scale incidents involving large groups of persons. If so, the best way of providing this guidance*

- *Whether all chemicals for which specific first-aid advice have been identified.*
- *What degree of consensus exists for the need for specific first-aid advice for certain chemicals and if consensus exists the best way of providing this advice.*

SOURCES OF FIRST-AID ADVICE ON CHEMICAL POISONING

1. There are a number of international, regional and national contemporary sources of first-aid advice for chemical poisonings including

International

- IPCS INTOX Poisons Information Monographs (PIMS)
- IPCS Handbook on the Management of Poisoning
- IPCS Series of International Chemical Safety Cards and associated Compilers Guide
- International Maritime Organization Medical First Aid Guide for Use in Accidents Involving Dangerous Goods (IMO MFAG)

Regional

- EC Council Directive 67/548/EEC of 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances:
- Emergency Response Guidebook, US, Canada, Mexico

National

- First Aid and Safety Directions Handbook, Australian Government
- Labelling Guide for Toxic Substances, New Zealand Toxic Substances Regulations

2. Annex 1 provides further bibliographic information about these sources and describes the scope of coverage. Some of the sources of information provide general guidelines, standard phrases and advice for chemical poisoning emergencies while others provide specific guidance for certain chemicals. There are differences in the purpose of the guidance particularly the type of chemical emergencies covered e.g. workplace, consumer and large scale chemical incidents. Annex 2 identifies some of the chemicals for which non/standard first aid advice is provided.

FIRST-AID AND THE GHS

3. A Status report of the work of the Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals is given in document ST/SG/AG.10/C4/2004.8. The task of the Sub-Committee is to develop a proposal for a harmonized set of precautionary statements for chemicals to be implemented as part of the GHS. A precautionary statement is a phrase that describes recommended measures that should be taken to minimize or prevent adverse effects resulting from exposures to a hazardous product or improper storage or handling of a hazardous product. Different types of precautionary statements are included covering **prevention, response** in the case of accidental spillage or exposure, **storage, and disposal**.
4. A proposal for a harmonized set of precautionary statements have been developed based on those in current use, namely the IPCS International Chemical Safety Cards Compliers Guide, the American National Standards (ANZI Z129.1) and the EU system of safety phrases associated with classification and labelling directives.
5. The precautionary statements have been categorized according to the hazard classes of the GHS to increase the likelihood of consistent application and to enable the increased understanding of the need for different precautions for different chemicals.
6. First-aid statements are included in the proposed set of precautionary statements, linking their application as far as possible to the specific GHS hazards involved e.g. corrosivity, acute toxicity and so on. General first-aid advice is referred to by the GHS including the need to contact a poisons centre or medical practitioner. The degree of urgency of taking additional advice is linked to the severity of the hazard.

DETERMINING THE ACTIONS WHICH FALL UNDER THE DEFINITION OF FIRST-AID

7. The purpose of first-aid is to minimise or lessen any harmful consequence from exposure to a hazardous material. First-aid is the first action that should be taken when a person is suffering from chemical exposure before regular medical help can be provided.
8. It is sometimes difficult to determine where first-aid stops and medical intervention starts. Generally first-aid does not include invasive procedures, such as intravenous fluids or medications. However, first-aid recommendations may include more complicated techniques such as oxygen administration, under certain circumstances depending on the availability of materials or equipment. There appears to be two criteria for including these procedures:
 - The intervention must be essential to sustain life or prevent other serious consequences and must not introduce new risks.
 - It must be legally acceptable for the first-aider to perform the procedure.

TYPES OF FIRST-AID

9. Generally most sources of first-aid advice for chemical exposures subdivide the information according to the different routes of exposure, i.e. inhalation, skin and eye contact and ingestion. The proposed set of GHS precautionary statements include general measures such as removal from exposure, decontamination, the use of artificial respiration, induction of vomiting, and activated charcoal.

2.1 Artificial respiration

10. This applies to serious cases where the patient has stopped breathing altogether or nearly altogether. Artificial respiration is also indicated in cases of acute laboured breathing with a risk of suffocation. In many cases where the ICSC recommends artificial respiration, an obvious first choice would be to administer oxygen, but this form of treatment has been left out deliberately. The use of oxygen has commonly been recommended as a first aid procedure for any inhalation exposure, however, it is now recognised that administering oxygen can be harmful if performed improperly or in the wrong circumstances. For example, oxygen in a concentration greater than 24% may stop breathing in patients with chronic obstructive disease, such as chronic bronchitis or emphysema. It should therefore be administered exclusively by specially trained first aid and medical personnel or doctors. It is useful to have oxygen resuscitation apparatus available near to sites where the risk is high and where on-the-spot treatment could be given by properly qualified first aid personnel.

2.2 Induction of Vomiting

11. The induction of vomiting as a first aid measure is a controversial subject. In 1993 the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) agreed to collaborate in the preparation and dissemination of Position Statements on key issues in clinical toxicology, including the role of syrup of ipecac as a method of inducing vomiting, to take advantage of the expertise and experience available in both societies.

12. The AACT and EAPCCT recommended that “Syrup of ipecac should not be administered routinely in the management of poisoned patients. In experimental studies the amount of marker removed by ipecac was highly variable and diminished with time. There is no evidence from clinical studies that ipecac improves the outcome of poisoned patients and its routine administration in the emergency department should be abandoned. There are insufficient data to support or exclude ipecac administration soon after poison ingestion. Ipecac may delay the administration or reduce the effectiveness of activated charcoal, oral antidotes, and whole bowel irrigation. Ipecac should not be administered to

a patient who has a decreased level or impending loss of consciousness or who has ingested a corrosive substance or hydrocarbon with high aspiration potential.”

13. They concluded that ipecac should be considered only in an alert conscious patient who has ingested a potentially toxic amount of a poison and that as the effect of ipecac diminishes with time and as clinical studies have demonstrated no benefit from its use, it should be considered only if it can be administered within 60 minutes of the ingestion. Even then clinical benefit has not been confirmed.

14. Induction of vomiting is included in the GHS proposal based on the ICSC Compilers Guide which states that this type of first-aid may be considered for substances with an oral LD50 < 200 mg/kg combined with a high resorption rate, e.g., certain pesticides. In these cases the aspiration danger does not prevail. The guide does not specify the manner of inducing vomiting.

15. In the absence of the availability of ipecac other techniques such as the stimulation of the back of the throat with a finger, spoon or some other blunt object, or use of outmoded agents like copper sulfate or salt water may be employed by the inexperienced first-aider and may cause further harm to the patient.

16. The administration of household liquid detergent has been proposed as a useful alternative emetic, when ipecac syrup is not available.

17. Clearly if medical follow-up is not readily available and the chemical is very acutely toxic then induction of vomiting should be considered, however, ideally the advice of a poison centre or physician should be sought prior to performing this action.

18. The advice to use syrup of ipecac by poison centres has fallen dramatically in the last 10 years. This is because it has been replaced by activated charcoal alone in the emergency department context and by no intervention at home. Experience has more clearly defined the likelihood of ingestion and the threshold for risk in a variety of ingestion circumstances. As a result, many poison centres are more selective in the use of home decontamination or have ceased to use it altogether. The trend has been to define at-risk circumstances and in the paediatric context either refer children to an emergency department or to monitor them at home without intervention. Whether this strategy has resulted in a rise in emergency department referral or in morbidity is unknown. Recent age-specific, comparative, poison centre data are unavailable.

2.3 The use of Activated Charcoal

19. Activated charcoal use has been recommended by some first-aid guidelines following the ingestion of certain toxic agents and is proposed as part of the GHS precautionary statements based on the ICSC Compilers Guide. It is a commonly used agent in the emergency department for gastrointestinal decontamination.

20. The ICSC compilers guide notes that the use of activated charcoal may be considered following ingestions of solid toxic substances, soluble in water, with an oral LD50 < 200 mg/kg. The guide also notes that this use does not apply to liquids, because the quantity ingested accidentally is in general too large to be absorbed by a limited quantity of charcoal. Charcoal is not effective against mineral acids or alkalies and is less effective against substances such as DDT, cyanides, ethanol, methanol, water-insoluble, compounds and many metals.

21. Activated charcoal is contraindicated if the patient has an unprotected airway, such as in a patient with a depressed state of consciousness. Activated charcoal is also contraindicated if its use increases the risk and severity of aspiration (e.g., a hydrocarbon with a high aspiration potential).

22. According to the AACT/EAPCCT position statement regarding the use of activated charcoal, volunteer studies suggest that activated charcoal is more likely to reduce poison absorption if it is administered within 1 hour of ingestion. In the absence of satisfactorily designed clinical studies demonstrating benefit from its use, the administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of a poison up to 1 hour following ingestion. There are insufficient data to support or exclude the use of activated charcoal when more than 1 hour has passed since ingestion.

23. Ideally the advice of a poison centre or physician should be sought prior to the utilization of activated charcoal by the first-aider.

24. Recognition of activated charcoal's superior efficacy over syrup of ipecac has led to suggestions of administration of activated charcoal in the home particularly in the context of paediatric toxic ingestions. However, use in the home has not gained wide acceptance because of concern that it would not be administered properly by the untrained lay public and that many children would refuse to take activated charcoal.

3. Advice on first aid for specific chemicals

25. An examination of the identified sources of first-aid guidelines shows that there are some specific chemicals which may require more special first aid advice. These are identified in Annex 2 cross-referenced by reference to the source used to identify them. It can be seen that multiple sources refer to the specific chemicals listed.

3.1 Cyanide

26. Amyl nitrite, given by inhalation, has been used for many years as a simple first-aid measure for cyanide poisoning, although there is little scientific evidence that it is of significant benefit.

27. While the initial mode of action was thought to be due to generation of the cyanide binding methaemoglobin, it has subsequently been concluded that there may be another, possibly vasoactive, mechanism at work. Amyl nitrite is not a powerful methaemoglobin-forming agent in humans and therefore it has generally been used in combination with intravenous sodium nitrite.
28. It is also potentially dangerous, particularly in people with some forms of heart disease, although serious illness caused by misuse seems to be rare. It can be abused by 'sniffers'. It also has a limited shelf life and can be difficult to obtain as it is manufactured only in small quantities.
29. Its use is still described in safety data sheets and there may be circumstances, such as the use of cyanide preparations in the field for control of rodents, where it is the only treatment which can practicably be given, however, to be effective this antidote must be used at high inhalational doses, and in conjunction with high concentrations of oxygen.
30. The efficacy of intramuscular 4- dimethylaminophenol (DMAP) which has been advocated as a first-aid measure in cases of severe cyanide poisoning needs further evaluation.

(T.J Meredith, D Jacobsen, J.A Haines and J-C Berger Antidotes for Poisoning by Cyanide, volume 2, IPCS/CEC Evaluation of Antidote Series. WHO 1993)

3.2 Hydrofluoric Acid

31. Hydrofluoric acid is a highly corrosive agent. It causes tissue damage by two distinct mechanisms. Firstly, the high concentration of hydrogen ions produces a corrosive burn similar to that caused by hydrochloric and sulphuric acid. This occurs immediately. Secondly, the fluoride ions which are highly lipophilic penetrate the tissues deeply leading to painful liquefactive necrosis. Necrosis due to fluoride ions occurs progressively despite surface decontamination unless it is neutralized with the formation of the salts of calcium and/or magnesium. This can be by natural calcium or magnesium compounds or by those administered medically. Any person contaminated with hydrofluoric acid must have immediate first aid, followed by medical treatment from a physician as soon as possible.
32. The severity of hydrofluoric acid burns depends on the concentration of hydrofluoric acid in the offending agent, the surface area involved, and the duration of exposure. Massive exposure constitutes a life threatening situation. It is not widely known that massive exposure results from as little as a 1% total body surface area from a >50% hydrofluoric acid solution, or exposure of >5% total body surface area to hydrofluoric acid of any concentration.

33. The aim of treatment of hydrofluoric acid burns is to neutralize the fluoride ions with calcium and magnesium ions. The modalities used to achieve this goal vary widely and depends largely on the location and severity of the burn. The danger to first-aiders attending to patients who have had a massive exposure cannot be underestimated. Protective apparatus should be worn.

34. Calcium gluconate gel, applied after initial rinsing with water, has a documented effect as first aid treatment for hydrofluoric acid burns. Hexafluorine is a relatively new liquid compound developed especially for emergency decontamination of hydrofluoric acid eye and skin exposures. However, a 2002 Swedish Poison Centre study undertaken to compare Hexafluorine with water rinsing plus topical calcium and with water rinsing alone showed a consistent trend towards a worse outcome, both in comparison to water plus topical calcium and to water rinsing alone. Based on these observations it was concluded that water rinsing followed by topical calcium should remain the standard first aid treatment for skin exposure to hydrofluoric acid.

(Topical treatments for hydrofluoric acid burns: A blind controlled experimental study. Hojer, J.; Personne, M.; Hulten, P.; Ludwigs, U. *Journal of Toxicology, Clinical Toxicology* (2002), 40(7), 861-866)

35. A recent study has recommended treatment for hydrofluoric acid burns by commencing immediately with 30 minute lavage followed by the application of dimethyl sulphoxide 50% (penetration enhancer) + calcium gluconate 10% in surgical jelly.

(M. Hatzifotis , A. Williams, M. Muller and S. Pegg Hydrofluoric acid burns. [Burns Volume 30, Issue 2](#) , March 2004, Pages 156-159)

3.3 Phenol

36. Some first-aid guides recommend the use of undiluted polyethylene glycol (PEG) 300 to 400, glycerol or alcohol if readily available to decontaminate the phenol from the skin, prior to washing with water.

37. This advice presumably follows from animal experiments which showed that PEG 400 has an excellent decontamination capability. These studies also showed that irrigation of the skin with copious amounts of water has an effective decontaminating effect. It can prolong the time before phenol exposure produces mortality by up to three times. PEG increased this period by 25 times. Glycerine and zephirol (10% sodium bicarbonate and 4% tris buffer solution) were similar to water. PEG 300 was also found to be highly effective.

38. Unfortunately PEG 400 becomes a very viscous material at lower temperatures (i.e. in the winter season) and cannot be applied effectively to the skin in this condition. However, PEG 300 remains stable even at lower temperatures.

39. This has led to advice that initially an immediate irrigation with water should be preferred if larger skin areas are involved. However, water irrigation is not uniformly recommended unless a high density shower is available. Small amounts of water may dilute the phenol and expand the exposed area. The affected surface should be wiped with PEG until the smell of phenol has disappeared.

40. PEG has also been shown to produce a heat sensation caused by the moisture of the skin diluting the phenol. This effect was dependent on the diluent content of the PEG. At 50% PEG no heat effect was detected and it was found to be an effective washing agent. Ethanolic PEG solutions have a greater phenol solvent power but are flammable.

41. Whilst washing phenol contaminated skin with copious amounts of water is an effective decontaminant procedure it would seem that the use of PEG and other agents would be of benefit as a first-aid measure if available.

(R Horch, G Spilker and G.B. Stark. Phenol burns and intoxications. Burns 20(1):45-50 1994)

42. The use of PEG as a first-aid decontaminant for phenol exposures is dependant on its availability which may be subject to regional variation. For example, in Japan PEG is not usually available in workplaces so that flushing the skin with running water is the standard first-aid advice following dermal exposure.

3.4 Organophosphates/Carbamate Pesticides

Atropine tablets

43. The use of atropine tablets for poisoning with organophosphorus compounds is commonly found as a first-aid measure on many pesticide safety data sheets e.g. "If swallowed, give one atropine tablet every 5 minutes until dryness of the mouth occurs".

44. However, the use of atropine tablets in the first-aid management of organophosphate in significant poisoning seems unlikely to be of great benefit for the following reasons:

- Significant organophosphate poisoning often presents with diarrhoea and vomiting thus limiting the absorption of such tablets.
- Most patients with sufficient organophosphate poisoning will not be able to take the tablets orally and will require parenteral atropine bearing in mind that atropine

can be given intramuscularly as well as intravenously. The former technique can be used in a pre-hospital setting by first-aid personnel.

- Those patients significantly poisoned by organophosphate will often require enormous doses that cannot be administered by mouth.

Autoject devices containing atropine

45. These injectable atropine devices have also been recommended as a first aid measure in the event of organophosphate poisoning. Clearly they have an advantage over the use of atropine tablets but again have limited effectiveness particularly for significant poisonings. The availability of autoject devices is also somewhat variable in part due to large purchases by the military.

46. In view of the above the role of atropine tablets and autoject devices as a first-aid for organophosphate poisoning measure needs clarification.

3.4 Paraquat

47. The use of Fuller's Earth (15% solution) or activated charcoal as a gastrointestinal adsorbent is advocated as a first-aid measure following the ingestion of paraquat.

(Meredith, T. and Vale, J.A. (1995) Treatment of paraquat poisoning: gastrointestinal decontamination. In *Paraquat poisoning: mechanisms, prevention, treatment*, Ed Bismuth, C. and Hall, A.H., Marcel Dekker, New York, pp297-314.)

3.5 Cypermethrin (synthetic pyrethroid insecticide)

48. The IPCS PIM for Cypermethrin notes that the skin irritation and paraesthesia associated with dermal exposure is self-limiting and may be alleviated with topical vitamin E cream. This first-aid measure may also be of benefit with other synthetic pyrethroid insecticides which display cutaneous sensations.

(Flannigan SA (1985). Variation in cutaneous sensation between synthetic pyrethroid insecticides. *Contact Dermatitis*, 13(3):140-147)

3.6 Cyanoacrylates

49. These chemicals are widely used as adhesive agents and following skin contact the most likely hazard is bonding of skin surfaces or mucous membranes. The strong bonds which quickly form between adjacent skin surfaces, for example, fingers, may be separated relatively easily by soaking the bonded area in warm soapy water for several minutes, and then gently peeling the bond. Solvents such as acetone and dimethylsulfoxide have also been advocated for this purpose.

3.7 Methanol

50. The oral use of ethanol following the unintentional ingestion of methanol is an accepted first-aid measure. Ethanol competitively inhibits alcohol dehydrogenase (ADH) therefore blocking the metabolism of methanol to toxic metabolites. Ethanol has a very high affinity for ADH in comparison to other substrates (for example, 100 times the affinity of ethylene glycol and 20 to 30 times the affinity of methanol).

3.8 Toxic gases which compromise the use of oxygen by body tissues (carbon monoxide, hydrogen cyanide, hydrogen sulphide)

51. Oxygen administration following the inhalational exposure to these chemicals has been demonstrated to be of benefit as a general first-aid measure. The use of oxygen is justified by the mode-of-action of the chemical rather than the hazard class involved.

3.9 White Phosphorus

52. White phosphorus contact with the skin can cause serious burns since it readily ignites upon contact with air at 34°C. The affected area should be immersed or rinsed with cool water (warm water promotes the conversion of phosphorus to phosphoric acid) or covered with wet bandages until medical attention is received. (ERG 2000)

3.10 Inflammable metals (lithium, sodium, potassium)

53. These metals are corrosive and can cause serious burns due to almost immediate reaction with water, especially on moist skin. If the metal ignites, very deep burns and tissue destruction can occur. In case of contact with these substances, it is important to wipe them from the skin immediately then flush with running water for at least 20 minutes. (ERG 2000)

Antidotes

54. It is a common misperception that antidotes are available for most chemical exposures. This is the exception rather than the rule. There are not many antidotes available for the management of poisonings and in the context of first-aid only a few are recommended for use by first-aiders e.g. amyl nitrite for cyanide exposure. Both the availability of suitable antidotes and the adequacy of training for first-aiders are some of the factors which limit their use. The IPCS has established a programme to evaluate antidote effectiveness in clinical practice, disseminate evaluated information, and promote the availability of useful antidotes. The IPCS has undertaken the preparation of Antidote Monographs that summarize and assess the clinical use, mode of action, effectiveness, and other evaluated information and a consolidated IPCS List of

Antidotes that classifies antidotes and related drugs by their clinical effectiveness and urgency of need.

(Evaluation of antidotes: activities of the International Program on Chemical Safety. Pronczuk de Garbino, J; Haines, J A.; Jacobsen, D; Meredith, T. *Journal of Toxicology, Clinical Toxicology* (1997), 35(4), 333-343.)

4. Issues for Discussion

55. A number of sources of first-aid for chemical exposures have identified the need for specific protocols; however, these are not uniform and differences of opinion exist even for generally regarded standard first-aid measures such as the induction of vomiting, use of artificial resuscitation and activated charcoal. In addition, a number of chemicals have been identified which specific first-aid measures are needed over and above the general provisions.

56. Poison Centres are often the first place that people call for advice following a chemical exposure and they are able to provide guidance on the application of first-aid measures.

57. Poison Centres are becoming established in developing countries and their role being strengthened in developed countries. In both cases it is important to ensure that manufacturers preparing first-aid advice and first-aiders are aware of the services that they can provide.

58. In some cases it may be necessary to customize the general first-aid recommendations proposed based on situational factors such as the setting the emergency takes place in. For example the first-aid advice following exposure to hydrofluoric acid as a propriety rust removing agent in the home as compared to a workplace exposure to the acid may be different as compared to the workplace setting since it is unlikely that calcium gluconate gel would be available.

59. Each employee working at a plant or laboratory that handles cyanides, should receive instruction on the dangers of cyanides and be trained in appropriate first-aid measures, as should emergency-service personnel. However a person using cyanide for rodent control (e.g. rabbits, opossums) in the field is unlikely to have access to the same first-aid resources that would be available at an industrial workplace.

60. Injuries involving chemicals occur aboard merchant ships, since such agents are carried commonly on board either as cargo or as needed for running the ship.

61. The range of advice identified for a small number of specific chemicals shows variation among the reference sources consulted. The IPCS INTOX Project is in a position to build upon the joint efforts of professional groups such as the American Academy of Clinical Toxicologists (AACT), the European Association of Poisons

Centres and Clinical Toxicologists (EAPCCT) and the Asian Pacific Association of Medical Toxicology (APAMT). The IPCS Handbook of Poisoning already provides advice on the general and specific first-aid and could be revised, maintained and referenced by the GHS.

SOURCES OF FIRST-AID ADVICE FOR CHEMICAL POISONING

1.1 IPCS INTOX Poison Information Monographs

The IPCS INTOX Project provides a series of evaluated Poisons Information Monographs (PIMs). For each substance a PIM summarises the physico-chemical and toxicological properties, the medical features of the effects produced by various routes of exposure, the patient management, supporting laboratory investigations and first-aid procedures.

The PIMs can be found at <http://www.inchem.org/>

1.2 IPCS Handbook on Management of Poisoning

Henry J.A. and Wiseman H.M. Management of poisoning: a handbook for health care workers. WHO 1997. ISBN 92 4 154481 3

The This handbook has two main aims: to give people living in rural places, far from medical help, information on what to do when someone is poisoned; and to suggest ways of preventing poisoning in the community. Chapter 5 of this handbook gives general first-aid advice for chemical exposures.

Can be viewed at <http://www.intox.org/databank/documents/supplem/supp/sup1.htm>

1.3 ICSC Compilers Guide

These summarise essential information on chemical substances; developed cooperatively by the IPCS and the Commission of the European Union (EC).

An International Chemical Safety Card (ICSC) provides essential health and safety information on chemicals for their use at the "shop floor" level by workers and employers in factories, agriculture, construction and other work places. ICSCs consist of a series of standard phrases, mainly summarizing health and safety information collected, verified and peer reviewed by internationally recognized experts, taking into account advice from manufacturers and Poison Control Centres.

The Cards are peer-reviewed by an international group of experts. They are based on standard phrases, the criteria for which are given in the **Compiler's Guide**. The most recent version was published in November 2003 (Version 22-03).

The ISCS compilers guide can be found at:
<http://www.inchem.org/documents/icsc/icsc/icsguide.htm>

Examples of ISCS standard phrases for first-aid include:

18300000 Skin: FIRST AID.

18301000 Remove contaminated clothes.

Expl. Usually it makes sense to take off contaminated clothes and shoes as soon as possible to avoid further contact between them and the skin. It is better, however, to start with a rinse or a shower and to take off clothing during this treatment.

19300000 Eyes: FIRST AID.

19301000 First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.

Expl. Rinse continuously with water, preferably for at least 15 minutes. As a harmful substance could stay under contact lenses, they should be removed but only if they are not sticking to the eyes. Otherwise, extra damage could be done. After rinsing, the victim should see a doctor in all cases, whether for treatment or for a check-up only. He/she should be escorted if indicated.

Ind. Apply in all cases.

The ICSC Compilers Guide is used as a major source for selection of Precautionary Statements (and will be harmonized with the GHS).

1.4 EU Safety phrases

Safety Phrases Concerning Dangerous Chemical Substances and Preparations are used in the Countries of the EU.

The EU phrases can be viewed at:

<http://www.itcilo.it/actrav/actrav-english/telearn/osh/ip/safety.htm>

Examples of these phrases include:

S26. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

S46. If swallowed, seek medical advice immediately and show this container or label.

S62. If swallowed do not induce vomiting: seek medical advice immediately and show this container or label.

Commission Directive 91/155/EEC of 5 March 1991 defined and laid down detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC.

For Safety Data Sheets this Directive details the requirements for the provision of First aid measures and describes the first aid measures, specifying whether immediate medical attention is required.

The Directive requires that information on first aid is brief and easy to understand by the victim, bystanders and first-aiders. The instructions should indicate what is to be done on the spot in the case of an accident and whether delayed effects can be expected after exposure. The Directive specifies that the symptoms and effects should be briefly summarized by providing the information according to the different routes of exposure, i. e. inhalation, skin and eye contact and ingestion, under different subheadings. The first-aid information provided is to indicate whether professional assistance by a doctor is needed or advisable. For some substances or preparations it may be important to emphasize that special means to provide specific and immediate treatment must be available at the workplace.

1.5 The Emergency Response Guidebook (ERG2000)

The Emergency Response Guidebook (ERG2000) was developed jointly by the US Department of Transportation, Transport Canada, and the Secretariat of Communications and Transportation of Mexico (SCT) for use by firefighters, police, and other emergency services personnel who may be the first to arrive at the scene of a transportation incident involving a hazardous material. It is primarily a guide to aid first responders in (1) quickly identifying the specific or generic classification of the material(s) involved in the incident, and (2) protecting themselves and the general public during this initial response phase of the incident. The ERG is updated every three to four years to accommodate new products and technology. The next version is scheduled for 2004.

The ERG2000 website is located at
http://www.tc.gc.ca/canutec/erg_gmu/erg2000_menu.htm

An example of the ERG first aid advice:

SUBSTANCES - TOXIC AND/OR CORROSIVE (NON-COMBUSTIBLE/WATER-SENSITIVE)

FIRST AID

- Move victim to fresh air.
- Call 911 or emergency medical service.

- Apply artificial respiration if victim is not breathing.
- Do not use mouth-to-mouth method if victim ingested or inhaled the substance; induce artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device.
- Administer oxygen if breathing is difficult.
- Remove and isolate contaminated clothing and shoes.
- In case of contact with substance, immediately flush skin or eyes with running water for at least 20 minutes.
- For minor skin contact, avoid spreading material on unaffected skin.
- Keep victim warm and quiet.
- Effects of exposure (inhalation, ingestion or skin contact) to substance may be delayed.
- Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves.

1.6 IMO MFAG

Revision of the Supplement Medical First Aid Guide for Use in Accidents Involving Dangerous Goods (MFAG). Report of the Working Group. Amendment 29 to the IMDG Code, its annexes and supplements (EmS and MFAG) including harmonization of the IMDG Code with the UN recommendations on the transport of dangerous goods. DSC 2/3/19. International Maritime Organization 1996.

This publication contains the Medical First Aid Guide (MFAG) as an Annex.

The IMO/WHO/ILO MFAG is intended to provide advice necessary for initial management of chemical poisoning and diagnosis within the limits of the facilities available at sea.

The MFAG gives general information about the particular toxic effects likely to be encountered from exposure to a variety of chemicals and specifies the recommended treatment in tables and appendices.

1.7 Handbook of First Aid Instructions.

ISBN 0 642 36748 3 Handbook of First Aid Instructions, Safety Directions, Warning Statements and General Safety Precautions for Agricultural and Veterinary Chemicals. 3rd Edition, Australian Government, Department of Health and Aging. 2003

The FAISD Handbook is a consolidation of the advice provided to the Australian Pesticides and Veterinary Medicines Authority (APVMA) by the Office of Chemical Safety in the Therapeutic Goods Administration (TGA) of the Australian Department of Health and Ageing (DHAC) and the National Occupational Health and Safety

Commission (NOHSC) up to the date of amendment. The data on which these recommendations are based has been supplied largely by companies and persons seeking approval and registration of products from the APVMA. The recommendations are intended to provide guidance to these parties in the approval of labels for agricultural and veterinary chemical products.

The FAISD is located at: <http://www.tga.gov.au/docs/html/faisd.htm>

FAISD First-aid instructions are comprised of Standard Statements:

- a. If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 03 4747000;
- b. Discontinued
- c. If swallowed, do NOT induce vomiting. Give a glass of water.
- d. Avoid giving milk or oils.
- e. Avoid giving alcohol.
- f. If skin contact occurs, remove contaminated clothing and wash skin thoroughly.
- g. Remove from contaminated area. Apply artificial respiration if not breathing.
- h. If swallowed, give one atropine tablet every 5 minutes until dryness of the mouth occurs - if poisoned by skin absorption or through lungs, remove any contaminated clothing, wash skin thoroughly and give atropine tablets as above. Get to a doctor or hospital quickly.
- i. If poisoning occurs get to a doctor or hospital quickly.
- j. (Cresols, Xylenols or Phenols 25 per cent or less) - If spilt on skin, remove any contaminated clothing, wash skin thoroughly with soap and water, then methylated spirit. (Cresols, Xylenols or Phenols above 25 per cent) - If spilt on skin, remove any contaminated clothing, swab skin repeatedly with glycerine (glycerol), PEG (polyethylene glycol) or PEG - methylated spirit mixture or if necessary methylated spirit alone.
- k. Remove from contaminated area. Give oxygen and if necessary, artificial respiration. If giving mouth-to-mouth resuscitation wash out patient's mouth and lips - do not inhale patient's expired air. Remove contaminated clothing and wash contaminated skin thoroughly. Get to a hospital or doctor quickly.
- l. Give activated charcoal and keep patient quiet, in a dark place if possible.
- m. Discontinued
- n. If in eyes wash out immediately with water.
- o. If sprayed on skin, wash thoroughly. If sprayed in mouth, rinse mouth with water.
- p. Discontinued
- r. Discontinued
- s. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.
- t. Immediately apply calcium gluconate gel to affected skin.
- v. Discontinued
- w. Give plenty of water.

- x. If poisoned by skin absorption or through lungs, remove any contaminated clothing, wash skin thoroughly and give one atropine tablet every 5 minutes until dryness of the mouth occurs. Get to a doctor or hospital quickly.
- y. Do not give direct mouth-to-mouth resuscitation if swallowed. To protect rescuer, use air-viva, oxy-viva or one-way mask. Resuscitate in a well-ventilated area.
- z. No first aid directions are recommended for labelling purposes.

1.8 New Zealand Labelling Guide for Toxic Substances.

Toxic Substances Regulations 1983. Published in July 2001 by the Public Health Programmes, Public Health Directorate, Ministry of Health PO Box 5013, Wellington, New Zealand. ISBN: 0-478-26191-8.

The NZ Labelling Guide is available at: <http://www.moh.govt.nz/moh.nsf>

These guidelines assist the labelling of substances and detail specific statements for labels of toxic substances in different toxic substance schedules. They include standard statements for describing poisoning symptoms and detail the appropriate first aid to administer.

The first-aid statements described in this guide have been harmonised with Australia as part of a Trans-Tasman harmonisation (Australian/New Zealand) exercise. Three one day meetings were held during 1989-1999 and the following harmonized statements were developed :

Basic:

- A For advice, contact a Poisons Information Centre (Phone eg Australia 131 126; New Zealand 0800 764766) or a doctor (at once).
- Z First aid is not generally required. If in doubt, contact a Poisons Information Centre (Phone eg Australia 131 126; New Zealand 0800 764766) or a doctor.

General:

- G1 Urgent hospital treatment is likely to be needed. (Note- the words 'at once' to be added to instruction A).
- G2 If swallowed, give activated charcoal if instructed. (Note- the words 'at once' to be added to instruction A).
- G3 If swallowed, do NOT induce vomiting.
- G4 Immediately give a glass of water.
- G5 Avoid giving milk or oils.

G6 If sprayed in mouth, rinse mouth with water.

Eyes

E1 If in eyes, wash out immediately with water.

E2 If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by the Poison Information Centre or for at least 15 minutes.

Respiratory System

R1 If inhaled, remove from contaminated area. Apply artificial respiration if not breathing.

R2 If inhaled, remove from contaminated area. Apply artificial respiration if not breathing. Do not give direct mouth-to-mouth resuscitation. To protect rescuer, use air-viva, oxy-viva or one-way mask. Resuscitate in a well ventilated area.

Skin:

S1 If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

S2 If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water. Continue flushing with water until advised to stop by the Poisons Information Centre or doctor.

S3 If spilt on the skin, remove any contaminated clothing, wash skin thoroughly with soap and water, then methylated spirit if available. Contact the poisons Information Centre or a doctor.

S4 If spilt on the skin, immediately remove any contaminated clothing, wash skin with methylated spirit or PEG (polyethylene glycol) 300 or 400 if available, then flush under running water until advised to stop by the Poisons Information Centre or a doctor.

S5 If skin contact occurs, immediately remove contaminated clothing. Flush skin under running water for 15 minutes. Then apply calcium gluconate gel. Contact the Poisons Information Centre.

Special Purpose:

SP1 If swallowed, splashed on skin or in eyes, or inhaled, contact a Poisons Information Centre (Phone e.g. Australia 131 126; New Zealand 0800 764766) or a doctor at once. Remove any contaminated clothing and wash skin thoroughly. If swallowed, activated charcoal may be advised. Give atropine if instructed.

CHEMICALS FOR WHICH SPECIFIC FIRST-AID ADVICE EXISTS

Cyanide 1,2,3,7,8
Cyanoacrylates 2
Flammable metals (Li/Na/K) 5
Hydrofluoric acid 1,2,6,7,8
Methanol 1,2,6
Organophosphates/Carbamates 1,2,6,7,8
Paraquat 1,2,3
Phenol 1,2,3,7,8
Synthetic pyrethroids 1
Toxic gases (CO/HCN/H₂S) 2,3
White Phosphorus 5

Source of first-aid advice:

1. IPCS INTOX PIMs
2. IPCS Management of Poisoning
3. ICSC Compilers Guide
4. EU Safety phrases
5. The Emergency Response Guidebook (ERG2000)
6. IMO MFAG
7. FAISD Handbook
8. NZ Labelling Guide for Toxic Substances