ANNEX 1

Guidance levels of activity for procedures in nuclear medicine for a typical adult patient[a]

Test	Radionuclide	Chemical form[b]	Max. usual activity per test[c] (MBq)
Bone			
Bone imaging	$^{99}Tc^{m}$	Phosphonate and phosphate compounds	600
Bone imaging by single photon emission computerized tomography (SPECT)	$^{99}Tc^{m}$	Phosphonate and phosphate compounds	800
Bone marrow imaging	$^{99}Tc^{m}$	Labelled colloid	400
Brain			
Brain imaging (static)	$^{99}Tc^{m}$	TcO_4^-	500
	$^{99}Tc^{m}$	Diethylenetriaminepentaacetic acid (DTPA), gluconate, and glucoheptonate	500
Brain imaging (SPECT)	$^{99}Tc^{m}$	TcO_4^-	800
	$^{99}Tc^{m}$	DTPA, gluconate, and glucoheptonate	800
	$^{99}Tc^{m}$	Exametazime	500
Cerebral blood flow	^{133}Xe	In isotonic sodium chloride solution	400
	$^{99}Tc^{m}$	Hexamethyl propylene amine oxime (HM-PAO)	500
Cisternography	^{111}In	DTPA	40
Lacrimal			
Lacrimal drainage	$^{99}Tc^{m}$	TcO_4^-	4
	$^{99}Tc^{m}$	Labelled colloid	4
Thyroid			
Thyroid imaging	$^{99}Tc^{m}$	TcO_4^-	200
	^{123}I	I^-	20
Thyroid metastases (after ablation)	^{131}I	I^-	400
Parathyroid imaging	^{201}Tl	Tl^+, chloride	80
Lung			
Lung ventilation imaging	$^{81}Kr^{m}$	Gas	6000
	$^{99}Tc^{m}$	DTPA-aerosol	80
Lung ventilation study	^{133}Xe	Gas	400
	^{127}Xe	Gas	200
Lung perfusion imaging	$^{81}Kr^{m}$	Aqueous solution	6000
	$^{99}Tc^{m}$	Human albumin (macroaggregates or microspheres)	100
Lung perfusion imaging (with venography)	$^{99}Tc^{m}$	Human albumin (macroaggregates or microspheres)	160
Lung perfusion studies	^{133}Xe	Isotonic solution	200
	^{127}Xe	Isotonic chloride solution	200
Lung imaging (SPECT)	^{99}Tc	Macroaggregated albumin (MAA)	200
Liver and spleen			
Liver and spleen imaging	$^{99}Tc^{m}$	Labelled colloid	80
Functional biliary system imaging	$^{99}Tc^{m}$	Iminodiacetates and equivalent agents	150
Spleen imaging	$^{99}Tc^{m}$	Labelled denatured red blood cells	100
Liver imaging (SPECT)	$^{99}Tc^{m}$	Labelled colloid	200
Cardiovascular			
First pass blood flow studies	$^{99}Tc^{m}$	TcO_4^-	800
	$^{99}Tc^{m}$	DTPA	800
	$^{99}Tc^{m}$	Macroaggregated globulin 3	400
Blood pool imaging	$^{99}Tc^{m}$	Human albumin complex	40
Cardiac and vascular imaging/probe studies	$^{99}Tc^{m}$	Human albumin complex	800

Test	Radionuclide	Chemical form[b]	Max. usual activity per test[c] (MBq)
Myocardial imaging/probe studies	$^{99}Tc^{m}$	Labelled normal red blood cells	800
Myocardial imaging	$^{99}Tc^{m}$	Phosphonate and phosphate compounds	600
Myocardial imaging (SPECT)	$^{99}Tc^{m}$	Isonitriles	300
	^{201}Tl	Tl^{+} chloride	100
	$^{99}Tc^{m}$	Phosphonate and phosphate compounds	800
	$^{99}Tc^{m}$	Isonitriles	600
Stomach, gastrointestinal tract			
Stomach/salivary gland imaging	$^{99}Tc^{m}$	TcO_4^-	40
Meckel's diverticulum imaging	$^{99}Tc^{m}$	TcO_4^-	400
Gastrointestinal bleeding	$^{99}Tc^{m}$	Labelled colloid	400
	$^{99}Tc^{m}$	Labelled normal red blood cells	400
Oesophageal transit and reflux	$^{99}Tc^{m}$	Labelled colloid	40
	$^{99}Tc^{m}$	Non-absorbable compounds	40
Gastric emptying	$^{99}Tc^{m}$	Non-absorbable compounds	12
	^{111}In	Non-absorbable compounds	12
	$^{113}In^{m}$	Non-absorbable compounds	12
Kidney, urinary system, and adrenals			
Renal imaging	$^{99}Tc^{m}$	Dimercaptosuccinic acid	160
Renal imaging/renography	$^{99}Tc^{m}$	DTPA, gluconate, and glucoheptonate	350
	$^{99}Tc^{m}$	Macroaggregated globulin 3	100
	^{123}I	*o*-Iodohippurate	20
Adrenal imaging	^{75}Se	Selenocholesterol	8
Miscellaneous			
Tumour or abscess imaging	^{67}Ga	Citrate	300
	^{201}Tl	Chloride	100
Tumour imaging	$^{99}Tc^{m}$	Dimercaptosuccinic acid	400
Neuroectodermal tumour imaging	^{123}I	*m*-Iodobenzylguanidine	400
	^{131}I	*m*-Iodobenzylguanidine	20
Lymph node imaging	$^{99}Tc^{m}$	Labelled colloid	80
Abscess imaging	$^{99}Tc^{m}$	Exametazime labelled white cells	400
	^{111}In	Labelled white cells	20
Thrombus imaging	^{111}In	Labelled platelets	20

[a]Source: IAEA (1996). *International basic safety standards for protection against ionizing radiation and for the safety of radiation sources*. Vienna, International Atomic Energy Agency (Safety Series, No. 115); used with permission.
[b]In some countries, some of the compounds are considered obsolete.
[c]In some countries the typical values are lower than those indicated in the table.

ANNEX 2

Chemical destruction methods for cytostatic drugs

Note: The text of Methods 1–11, with minor editorial changes, is taken from the following publications with the permission of IARC:

IARC (1983). *Laboratory decontamination and destruction of carcinogens in laboratory wastes: some hydrazines*. Lyon, International Agency for Research on Cancer (IARC Scientific Publications, No. 54).

IARC (1985). *Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents*. Lyon, International Agency for Research on Cancer (IARC Scientific Publications, No. 73).

Introduction

Use of the methods described in this annex requires precautions in the handling both of cytostatic drugs and of some corrosive chemicals; for example, it is essential to wear gloves for the work.

A number of guidelines for the safe handling of antineoplastic agents have been published elsewhere (Knowles & Virden, 1980; David, 1981; Harrison, 1981; Zimmerman et al., 1981; Anderson et al., 1982; National Institutes of Health, 1982; Jones et al., 1983; Solimando, 1983; Stolar et al., 1983; National Study Commission on Cytotoxic Exposure, 1984; American Society of Hospital Pharmacists, 1985); the following warnings and precautions should also be observed during performance of the tests described here:

- Concentrated sulfuric and hydrochloric acids and sodium hydroxide are corrosive and should be handled with care. All reactions should be carried out in a well ventilated fume cupboard.
- Care should be taken in the preparation of solutions of potassium permanganate in sulfuric acid: solid potassium permanganate should never be added to concentrated sulfuric acid.
- The dilution of concentrated sulfuric acid with water is an extremely exothermic reaction; the acid should always be added to the water (never the reverse) and the heat of reaction removed by cooling in a cold-water bath.
- Potassium permanganate is a strong oxidizing agent; care must be taken not to mix it with concentrated reducing agents.
- In case of skin contact with corrosive chemicals, the skin should be washed under running water for at least 15 minutes.
- Dry sodium nitrate is highly combustible.

All the methods described in this annex have been tested for efficiency of degradation and absence of mutagenic activity of the residues. If more

information is required for testing, details of the methods can be found in IARC Scientific Publications, Nos 54 (1983) and 73 (1985).

Method 1. Destruction of doxorubicin and daunorubicin using potassium permanganate/sulfuric acid

Doxorubicin or daunorubicin, 30 mg, dissolved in 3 mol/litre sulfuric acid, 10 ml, is destroyed by potassium permanganate, 1 g, in 2 hours.

1. Reagents

Potassium permanganate:	technical grade
Sulfuric acid (concentrated):	relative density 1.84 (about 18 mol/litre); technical grade
Sulfuric acid (dilute):	3 mol/litre, aqueous

Note: The dilution of concentrated sulfuric acid is an extremely exothermic reaction. Always add the acid to the water, never the reverse, and remove heat by cooling in a cold-water bath.

Potassium permanganate/ sulfuric acid solution:	to 100 ml of 3 mol/litre sulfuric acid, add 4.7 g solid potassium permanganate

Note 1: To avoid frothing, add the potassium permanganate in small increments.

Note 2: The reagent should always be freshly prepared on the day of use.

Ascorbic acid or sodium bisulfite:	technical grade
Ascorbic acid solution or sodium bisulfite solution	~50 g/litre, aqueous
Sodium hydroxide:	technical grade
Sodium hydroxide solution	~2 mol/litre (~8 g/100 ml), aqueous
Sodium carbonate:	technical grade

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.1)

3.1 Solid compounds

3.1.1 Estimate the amount of drug to be destroyed, and dissolve in 3 mol/litre sulfuric acid to obtain a maximum content of 3 mg/ml.

3.1.2 Place flask on a magnetic stirrer; add about 1 g potassium permanganate per 10 ml of solution from 3.1.1.

Note: To avoid frothing, add the potassium permanganate in small increments.

3.1.3 Allow to react for 2 hours with stirring.

3.1.4 Neutralize with 8 g/100 ml sodium hydroxide solution, and discard.

3.2 Aqueous solutions

3.2.1 Estimate the amount of drug to be destroyed, and dilute with water if necessary to obtain a maximum concentration of 3 mg/ml.

3.2.2 Add slowly, with stirring, enough concentrated sulfuric acid to obtain a 3 mol/litre solution, and allow to cool to room temperature.

3.2.3 Proceed as in 3.1.2 to 3.1.4.

3.3 Pharmaceutical preparations

Note: To avoid frothing, add potassium permanganate in small increments.

3.3.1 *Liquids*: proceed as in 3.2, using twice the amount of potassium permanganate.

3.3.2 *Solids*: dissolve in water and proceed as in 3.2, using twice the amount of potassium permanganate.

3.4 Glassware

3.4.1 Immerse in a freshly prepared solution of potassium permanganate/sulfuric acid. Allow to react for 2 hours.

3.4.2 Clean the glass by immersion in a solution of ascorbic acid or sodium bisulfite.

3.5 Spills of solid compounds

3.5.1 Isolate the area, and put on suitable protective clothing.

3.5.2 Pour an excess of potassium permanganate/sulfuric acid solution over the contaminated area. If the purple colour fades, add more potassium permanganate. Allow to react for 2 hours.

3.5.3 Decolorize the surface with a solution of ascorbic acid or sodium bisulfite.

3.5.4 Neutralize by addition of solid sodium carbonate.

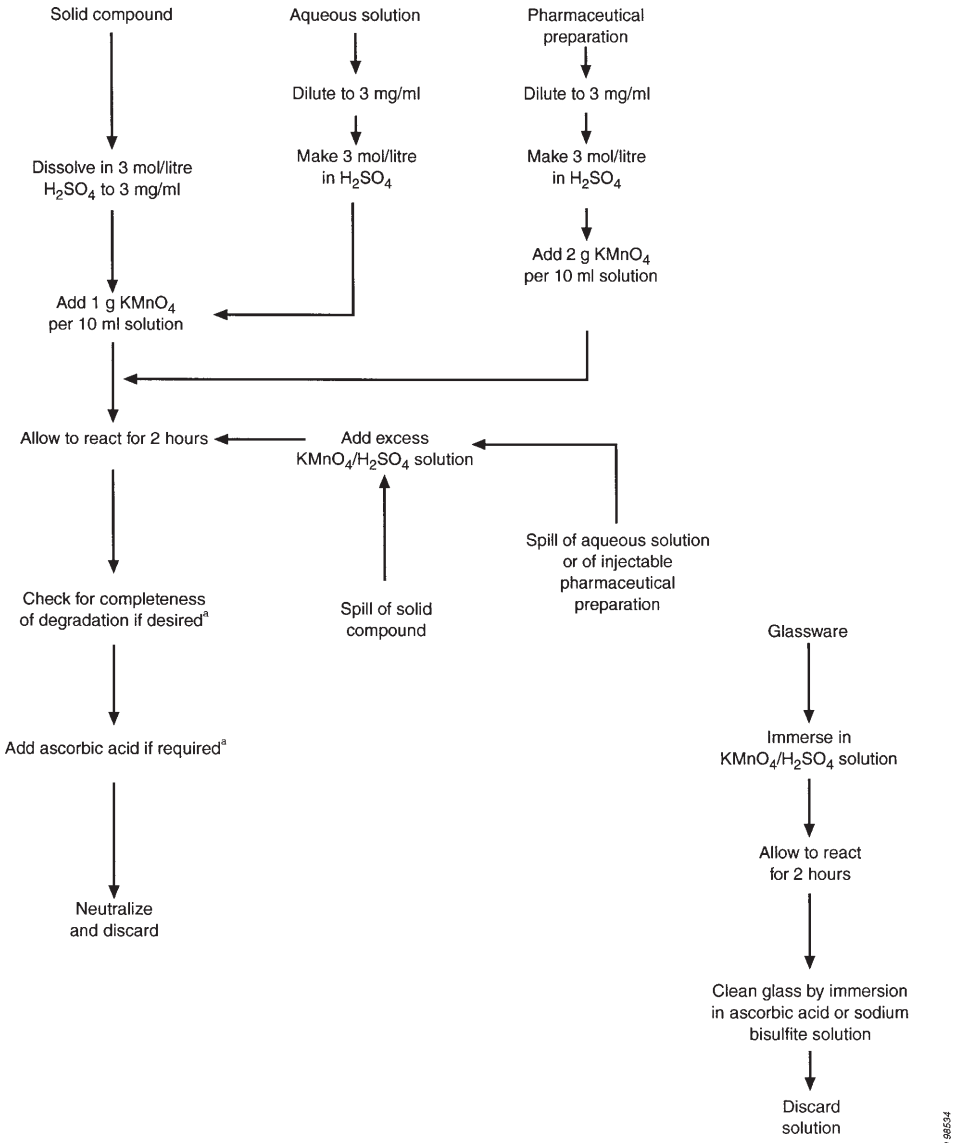
3.5.5 Remove the decontamination mixture with an absorbent material.

3.5.6 Discard.

3.6 Spills of aqueous solutions or of pharmaceutical preparations

Proceed as in 3.5.

Fig. A2.1 *Schematic representation of procedure for destruction of doxorubicin or daunorubicin*



[a]Details of this optional step may be found in IARC Scientific Publication No. 73.

Method 2. Destruction of methotrexate and dichloromethotrexate using potassium permanganate/sulfuric acid

Methotrexate, 50 mg, or dichloromethotrexate, 10 mg, solid compound, dissolved in 3 mol/litre sulfuric acid, 10 ml, is destroyed by potassium permanganate, 0.5 g, in 1 hour.

Note: In the case of pharmaceutical preparations of dichloromethotrexate, up to 50 mg can be dissolved in 10 ml of 3 mol/litre sulfuric acid and can be satisfactorily destroyed with 0.5 g of potassium permanganate.

1. Reagents

Potassium permanganate:	technical grade
Sulfuric acid (concentrated):	relative density 1.84 (about 18 mol/litre); technical grade
Sulfuric acid (dilute):	3 mol/litre, aqueous

Note: The dilution of concentrated sulfuric acid is an extremely exothermic reaction. Always add the acid to the water, never the reverse, and remove heat by cooling in a cold-water bath.

Potassium permanganate/ sulfuric acid solution:	to 100 ml of 3 mol/litre sulfuric acid, add 4.7 g solid potassium permanganate

Note 1: To avoid frothing, add the potassium permanganate in small increments.

Note 2: The reagent should always be freshly prepared on the day of use.

Ascorbic acid or sodium bisulfite:	technical grade
Ascorbic acid solution or sodium bisulfite solution:	~50 g/litre, aqueous
Sodium hydroxide:	technical grade
Sodium hydroxide solution:	~2 mol/litre (~8 g/100 ml), aqueous

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.2)

3.1 Solid compounds

3.1.1 For each 50 mg methotrexate or about 10 mg dichloromethotrexate, add 10 ml of 3 mol/litre sulfuric acid.

3.1.2 Place on a magnetic stirrer, and add 0.5 g potassium permanganate per each 10 ml solution.
Note: To avoid frothing, add the potassium permanganate in small increments.

3.1.3 Continue stirring for 1 hour.

3.1.4 Neutralize with 8 g/100 ml sodium hydroxide solution and discard.

3.2 Aqueous solutions

3.2.1 Dilute with water to obtain a maximum concentration of 5 mg/ml methotrexate or 1 mg/ml dichloromethotrexate.

3.2.2 Add slowly, with stirring, enough concentrated sulfuric acid to obtain a 3 mol/litre solution.

3.2.3 Proceed as in 3.1.2 to 3.1.4.

3.3 Injectable pharmaceutical preparations

Note: This method has been tested using solutions containing 2–5% glucose and 0.45% saline.

3.3.1 Dilute with water to obtain a maximum concentration of 2.5 mg/ml of either compound.

3.3.2 Add slowly, with stirring, enough concentrated sulfuric acid to obtain a 3 mol/litre solution.

3.3.3 Add 1 g potassium permanganate for each 10 ml solution and continue stirring for 1 hour.

Note: To avoid frothing, add potassium permanganate in small increments.

3.4.4 Proceed as in 3.1.4.

3.4 Glassware

3.4.1 Immerse in a freshly prepared solution of potassium permanganate/sulfuric acid. Allow to react for 1 hour or more.

3.4.2 Clean the glass by immersion in a solution of ascorbic acid or sodium bisulfite.

3.5 Spills of solid compounds

3.5.1 Isolate the area, and put on suitable protective clothing.

3.5.2 Collect the solid, place it in a beaker and treat as in 3.1.

3.5.3 Rinse the area with an excess of 3 mol/litre sulfuric acid. Take up the rinse with absorbent material.

3.5.4 Place the absorbent material in a beaker and cover with potassium permanganate/sulfuric acid solution. Allow to react for 1 hour or more. If the purple colour fades, add more potassium permanganate.

3.5.5 Neutralize by addition of solid sodium carbonate. Discard.

3.6 Spills of aqueous solutions or of injectable pharmaceutical preparations

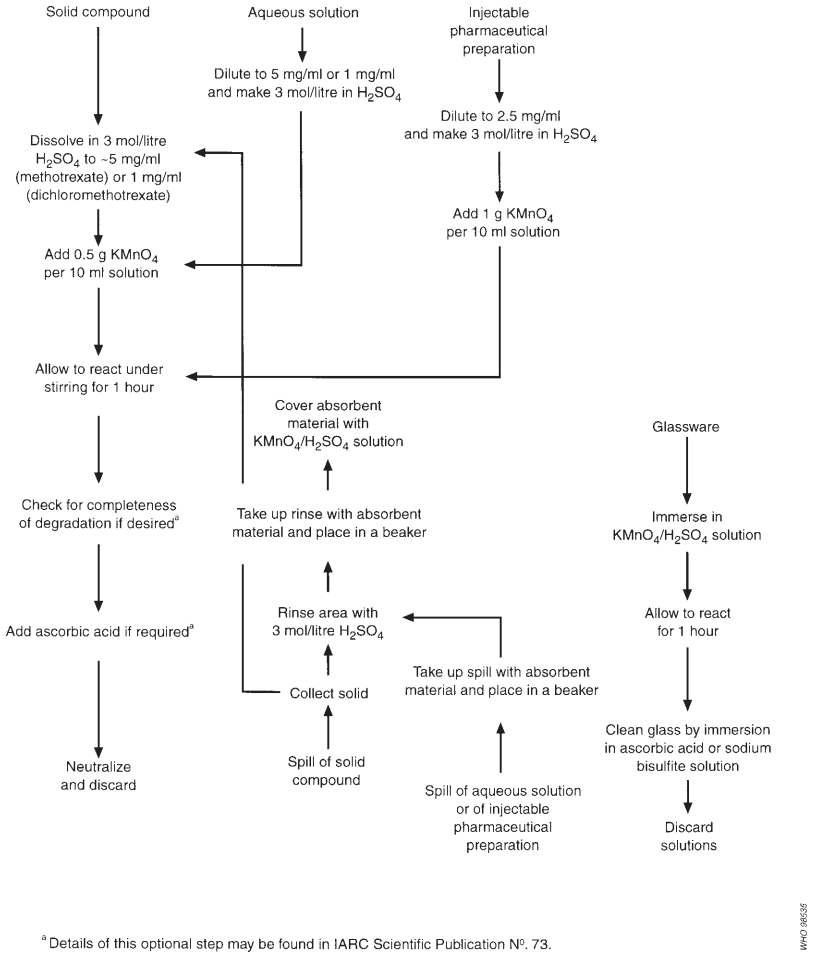
3.6.1 Isolate the area, and put on suitable protective clothing.

3.6.2 Take up the spill with absorbent material. Place the material in a beaker for inactivation.

3.6.3 Rinse the area with 3 mol/litre sulfuric acid and take up the rinse with absorbent material. Place the material in the same beaker as the other waste.

3.6.4 Proceed as in 3.5.4 and 3.5.5.

Fig. A2.2 *Schematic representation of procedure for destruction of methotrexate or dichloromethotrexate using potassium permanganate/sulfuric acid*



[a] Details of this optional step may be found in IARC Scientific Publication No. 73.

Method 3. Destruction of methotrexate using aqueous alkaline potassium permanganate

Methotrexate, 50 mg, dissolved in 4 g/100 ml sodium hydroxide solution, 50 ml, is destroyed by 1 g/100 ml potassium permanganate solution, 5.5 ml, in 30 minutes.

1. Reagents

Potassium permanganate:	technical grade
Sodium hydroxide:	technical grade
Sodium bisulfite:	technical grade
Potassium permanganate solution:	0.06 mol/litre (1 g/100 ml), aqueous

Sodium bisulfite solution:	0.1 mol/litre (1 g/100 ml), aqueous
Sodium hydroxide solutions:	1 mol/litre (4 g/100 ml), aqueous 2 mol/litre (8 g/100 ml), aqueous
Sodium hydroxide/potassium permanganate solution	1 g/100 ml potassium permanganate, in 4 g/100 ml sodium hydroxide

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.3)

3.1 Solid compound

3.1.1 Dissolve in 4 g/100 ml sodium hydroxide solution to obtain a concentration of not more than 1 mg/ml.

3.1.2 Add potassium permanganate solution until the purple colour persists for 30 minutes.

3.1.3 Add sodium bisulfite solution to the reaction mixture until the purple colour disappears.

3.1.4 Discard.

3.2 Aqueous solutions, including injectable pharmaceutical preparations

3.2.1 Add an equal volume of 8 g/100 ml sodium hydroxide solution.

3.2.2 Proceed as in 3.1.2 to 3.1.4.

3.3 Glassware

3.3.1 Immerse in potassium permanganate/sodium hydroxide solution. Allow to react for 30 minutes.

3.3.2 Clean the glass by immersion in sodium bisulfite solution.

3.4 Spills of solid compound

3.4.1 Isolate the area, and put on suitable protective clothing.

3.4.2 Collect the solid and place it in a beaker.

3.4.3 Rinse the area with 4 g/100 ml sodium hydroxide solution.

3.4.4 Take up the rinse with absorbent material. Place the material in the same beaker as the solid.

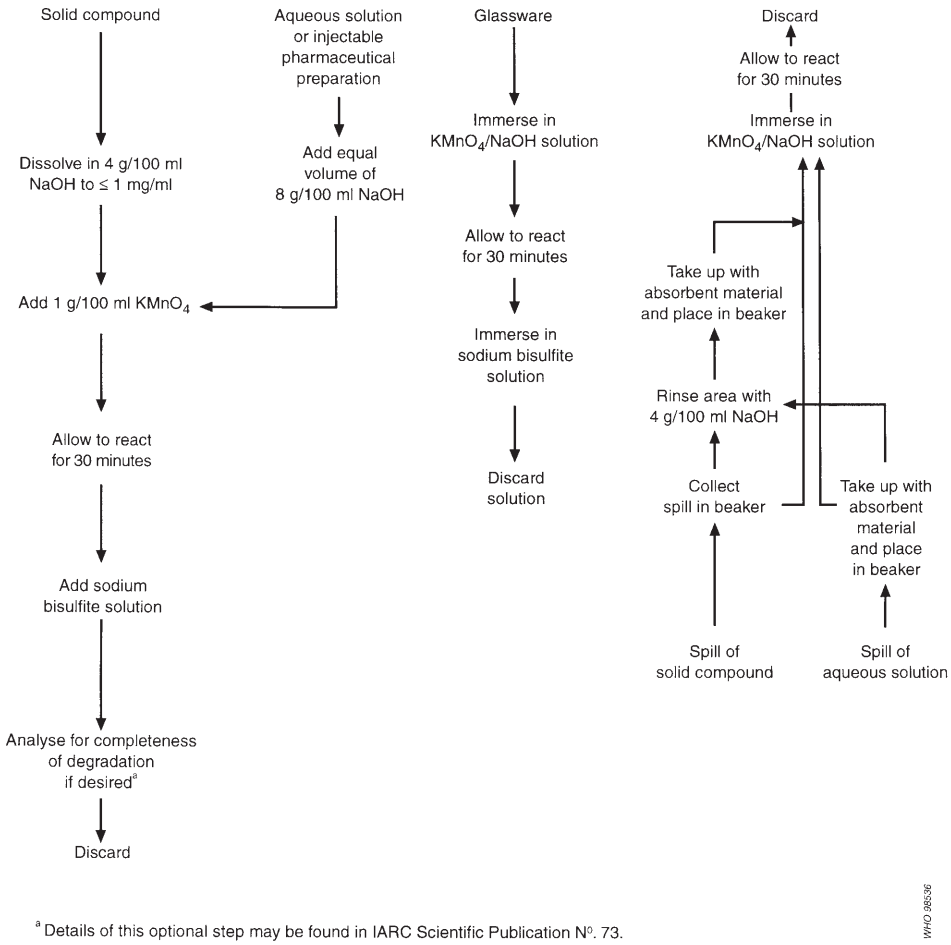
3.4.5 Cover the waste in the beaker with potassium permanganate/sodium hydroxide solution and allow to react for 30 minutes.

3.4.6 Discard.

3.5 Spill of aqueous solutions

3.5.1 Isolate the area, and put on suitable protective clothing.

Fig. A2.3 *Schematic representation of procedure for destruction of methotrexate using aqueous alkaline potassium permanganate*



[a] Details of this optional step may be found in IARC Scientific Publication Nº. 73.

3.5.2 Take up the spill with absorbent material. Place the material in a beaker and cover with potassium permanganate/sodium hydroxide solution.

3.5.3 Proceed as in 3.4.3 to 3.4.6.

Method 4. Destruction of methotrexate using aqueous sodium hypochlorite

Methotrexate, 50 mg, dissolved in 4 g/100 ml sodium hydroxide solution, 100 ml, is destroyed by 5% sodium hypochlorite solution, 4.6 ml, in 30 minutes.

1. Reagents

Sodium hypochlorite solution: commercial grade, 5%

Sodium hydroxide: technical grade

Sodium hydroxide solution: 1 mol/litre (4 g/100 ml), aqueous

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.4)

Note 1: Solutions of sodium hypochlorite tend to deteriorate and it is therefore essential to check their active chlorine content. The strength of sodium hypochlorite solutions may be given as weight/weight or weight/volume, which is an additional reason for estimating the concentration of available chorine.

Note 2: Percent (%) available chlorine = mass of chlorine in grams liberated by acidifying 100 g of sodium hypochlorite solution.

Note 3: The sodium hypochlorite solution used for this determination should contain not less than 25 g and not more than 30 g of active chlorine per litre. Assay: pipette 10.00 ml sodium hypochlorite solution into a 100-ml volumetric flask and fill to the mark with distilled water. Pipette 10 ml of the resulting solution into a conical flask containing 50 ml distilled water, 1 g potassium iodide, and 12.5 ml acetic acid (2 mol/litre). Rinse and titrate with 0.1 mol/litre sodium thiosulfate solution, using starch as indicator; 1 ml of 0.1 mol/litre sodium thiosulfate solution corresponds to 3.545 mg active chlorine.

3.1 Solid compound

3.1.1 Dissolve in 4 g/100 ml sodium hydroxide solution to obtain a concentration of not more than 50 mg/100 ml.

3.1.2 Estimate the amount of sodium hypochlorite solution required.

3.1.3 Add at least twice this estimated amount, i.e. approx. 10 ml sodium hypochlorite solution for each 50 mg methotrexate. Allow to react for 30 minutes.

3.1.4 Discard.

3.2 Aqueous solutions, including injectable pharmaceutical preparations

3.2.1 Estimate the amount of methotrexate to be degraded.

3.2.2 Proceed as in 3.1.2 to 3.1.4.

3.3 Glassware

3.3.1 Immerse in sodium hypochlorite solution. Allow to react for 30 minutes.

3.3.2 Discard the solution.

3.4 Spills of solid compound

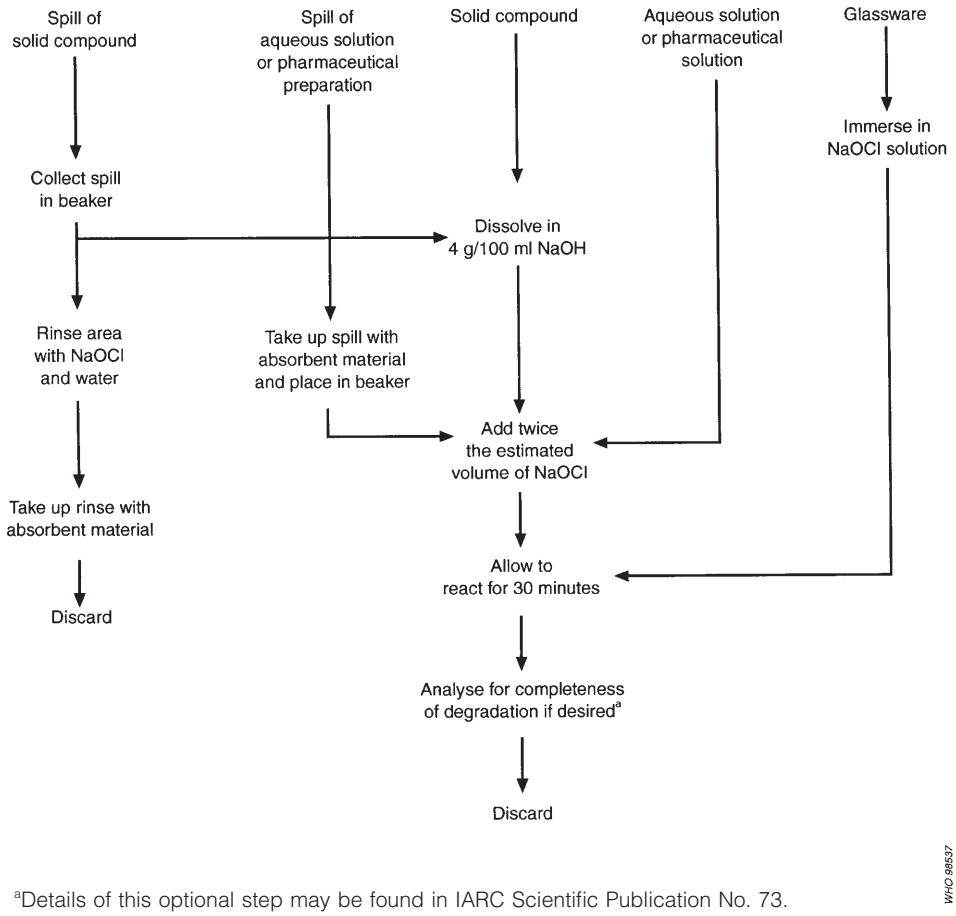
3.4.1 Isolate the area, and put on suitable protective clothing.

3.4.2 Collect the solid, place it in a beaker, and treat as in 3.1.

3.4.3 Rinse the area with sodium hypochlorite solution and then with water.

3.4.4 Take up the rinse with absorbent material and discard.

Fig. A2.4 *Schematic representation of procedure for destruction of methotrexate using aqueous sodium hypochlorite*



[a]Details of this optional step may be found in IARC Scientific Publication No. 73.

3.5 Spills of aqueous solutions, including injectable pharmaceutical preparations

3.5.1 Isolate the area, and put on suitable protective clothing.

3.5.2 Take up the spill with absorbent material. Place the material in a beaker.

3.5.3 Proceed as in 3.1.2 to 3.1.4.

Method 5. Destruction of cyclophosphamide and ifosfamide using alkaline hydrolysis in the presence of dimethylformamide

Cyclophosphamide or ifosfamide, 100 mg, in dimethylformamide, 20 ml, is destroyed by 12 g/100 ml sodium hydroxide solution, 10 ml, when refluxed for 4 hours.

1. Reagents

Sodium hydroxide:	technical grade
Sodium hydroxide solution:	~10 mol/litre (40 g/100 ml), aqueous ~3 mol/litre (12 g/100 ml), aqueous

Dimethylformamide (DMF):	analytical grade
DMF/sodium hydroxide solution:	freshly prepared solution containing 2 volumes of DMF and 1 volume of 12 g/100 ml sodium hydroxide

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.5)

3.1 Solid compounds

3.1.1 For each 100 mg of sample, add 30 ml DMF/sodium hydroxide solution.

3.1.2 Reflux for 4 hours.

3.1.3 Dilute with water and discard.

3.2 Aqueous solutions and pharmaceutical solutions

3.2.1 Dilute with 40 g/100 ml sodium hydroxide solution to obtain a maximum cyclophosphamide and/or ifosfamide content of 10 g/litre and a minimum sodium hydroxide concentration of 12 g/100 ml.

3.2.2 Add 2 ml DMF for each ml of solution from 3.2.1.

3.2.3 Proceed as in 3.1.2 to 3.1.3.

3.3 Glassware

3.3.1 Rinse with two successive portions of 12 g/100 ml sodium hydroxide, then two successive portions of water (enough to wet all the glass). Drain completely between each rinse.

3.3.2 Treat rinses as in 3.2.

3.4 Spills of solid compounds

3.4.1 Isolate the area, and put on suitable protective clothing.

3.4.2 Collect the solid, place it in a beaker and treat as in 3.1.

3.4.3 Rinse the area twice with an excess of 12 g/100 ml sodium hydroxide solution.

3.4.4 Take up the rinse with absorbent material, and immerse the material in a freshly prepared DMF/sodium hydroxide solution.

3.4.5 Repeat steps 3.4.3 and 3.4.4.

3.4.6 Reflux for 4 hours.

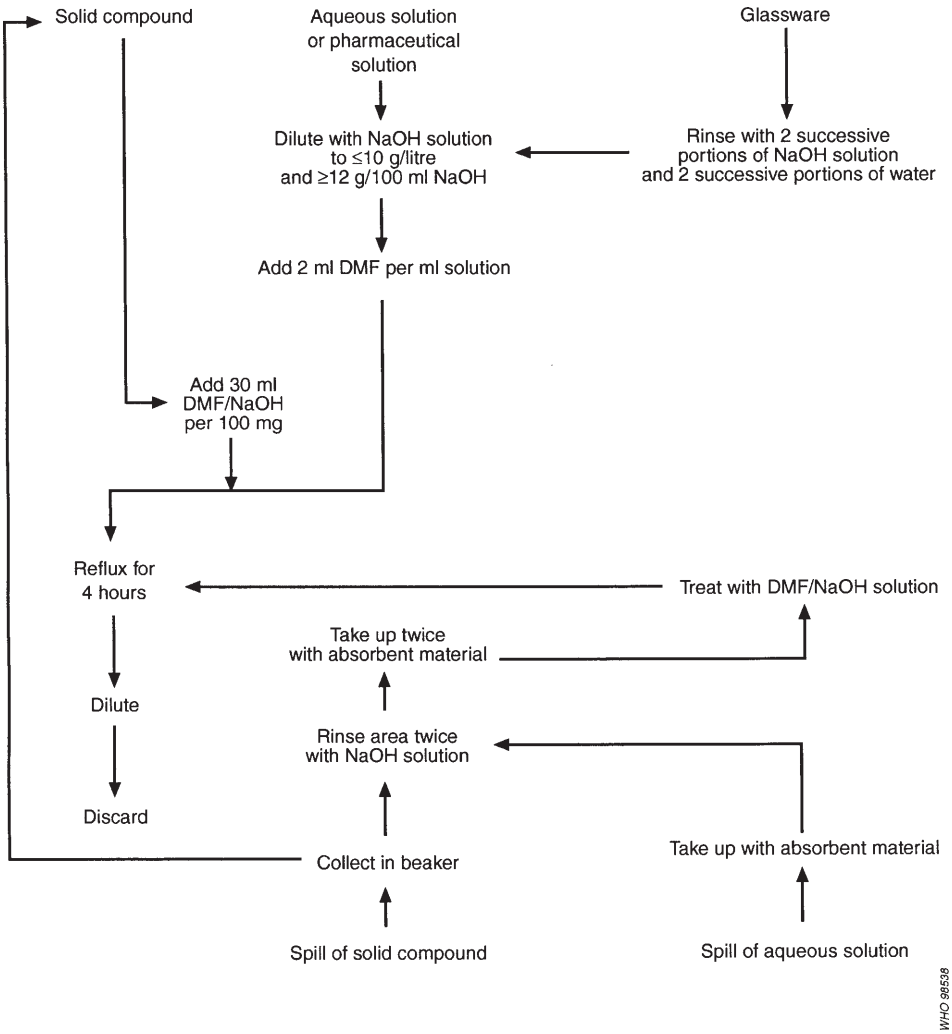
3.5 Spills of aqueous solutions

3.5.1 Isolate the area, and put on suitable protective clothing.

3.5.2 Take up the spill with absorbent material, and immerse the material in a freshly prepared DMF/sodium hydroxide solution.

3.5.3 Proceed as in 3.4.3 to 3.4.6.

Fig. A2.5 *Schematic representation of procedure for destruction of cyclophosphamide and ifosfamide using alkaline hydrolysis in the presence of dimethylformamide*



Method 6. Destruction of cyclophosphamide using acid hydrolysis followed by addition of sodium thiosulfate and alkaline hydrolysis

A sample of 250 mg cyclophosphamide dissolved in 10 ml of 1 mol/litre hydrochloric acid is completely hydrolysed when refluxed for 1 hour. After addition of 1.5 g sodium thiosulfate to the neutralized reaction mixture, the medium is made strongly alkaline with 20 g/100 ml sodium hydroxide solution and the reaction is allowed to proceed for 1 hour.

1. Reagents

Sodium hydroxide: technical grade

Sodium hydroxide solution: 5 mol/litre (20 g/100 ml), aqueous

Sodium thiosulfate: technical grade

Hydrochloric acid (concentrated):	relative density 1.19 (~12 mol/litre); technical grade
Hydrochloric acid (dilute):	1 and 2 mol/litre, aqueous
pH paper	

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.6)

3.1 Solid compound

3.1.1 For each 250 mg of sample, add 10 ml of 1 mol/litre hydrochloric acid.

3.1.2 Reflux for 1 hour. Allow to cool to room temperature.

3.1.3 Add 20 g/100 ml sodium hydroxide solution until a pH of about 6 is obtained. Allow to cool to room temperature.

3.1.4 Add 1.5 g sodium thiosulfate for each 250 mg cyclophosphamide and make strongly alkaline with 20 g/100 ml sodium hydroxide solution.

3.1.5 Allow to react for 1 hour.

3.1.6 Dilute with water and discard.

3.2 Aqueous solutions and injectable pharmaceutical preparations

3.2.1 Dilute if necessary to obtain a maximum cyclophosphamide content of 25 g/litre and add concentrated hydrochloric acid to obtain a 1 mol/litre hydrochloric acid solution.

3.2.2 Proceed as in 3.1.2 to 3.1.6.

3.3 Glassware

3.3.1 Rinse with four successive portions of 1 mol/litre hydrochloric acid solution (enough to wet all the glass). Drain completely between each rinse.

3.3.2 Treat rinses as in 3.1.2 to 3.1.6.

3.4 Spills of solid compound

3.4.1 Isolate the area, and put on suitable protective clothing.

3.4.2 Collect the solid and place in a beaker.

3.4.3 Rinse the area with four successive portions of enough 1 mol/litre hydrochloric acid to wet it. Take up each rinse with absorbent material. Place the material in the beaker containing the solid from 3.4.2.

3.4.4 Cover the contents of the beaker from 3.4.2 and 3.4.3 with 1 mol/litre hydrochloric acid solution.

3.4.5 Proceed as in 3.1.2 to 3.1.5.

3.4.6 Discard.

3.5 Spills of aqueous solutions

3.5.1 Isolate the area, and put on suitable protective clothing.

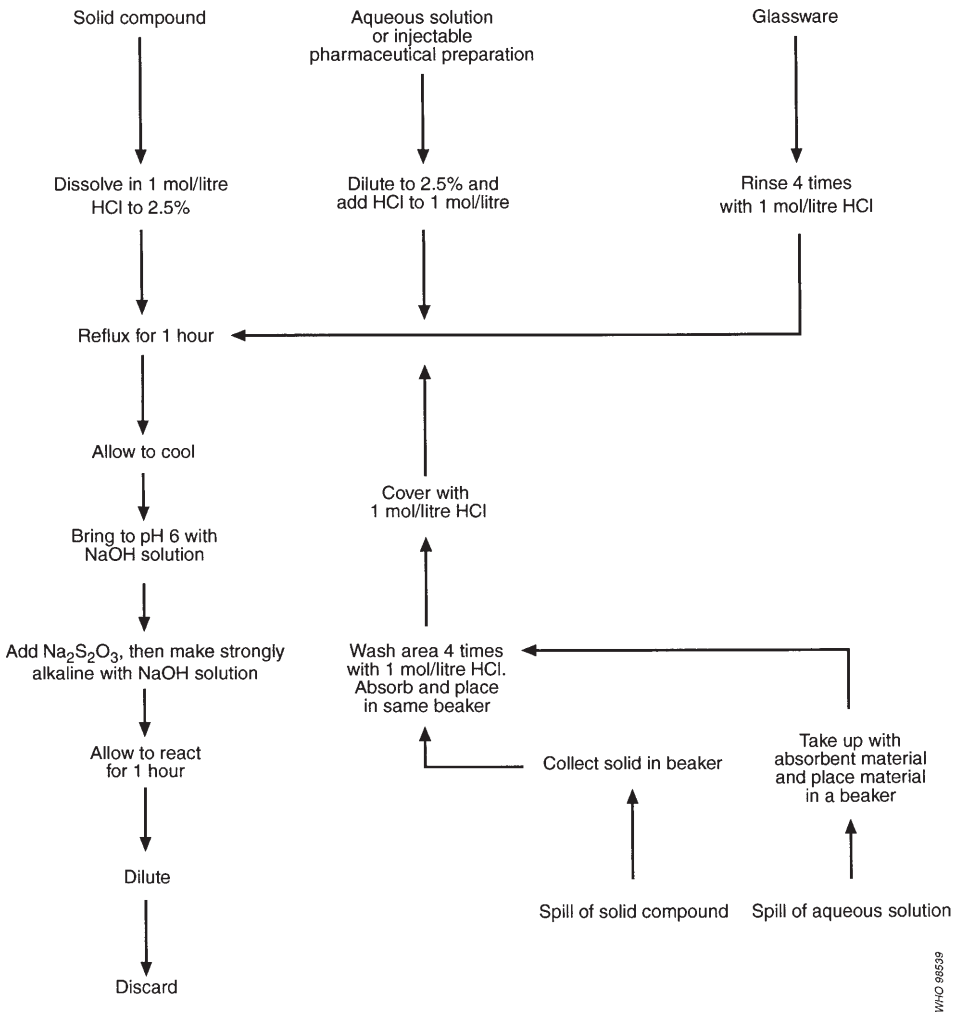
3.5.2 Take up the spill with absorbent material. Place the material in a beaker and cover with 1 mol/litre hydrochloric acid.

3.5.3 Rinse the area with four successive portions of enough 1 mol/litre hydrochloric acid to wet it.

3.5.4 Take up each rinse with absorbent material, and immediately immerse the material in the beaker containing the residues from 3.5.2.

3.5.5 Proceed as in 3.1.2 to 3.1.5.

Fig. A2.6 *Schematic representation of procedure for destruction of cyclophosphamide using acid hydrolysis followed by addition of sodium thiosulfate and aqueous hydrolysis*



Method 7. Destruction of vincristine sulfate and vinblastine sulfate using potassium permanganate/sulfuric acid

Vincristine sulfate or vinblastine sulfate, 10 mg, in 10 ml of 3 mol/litre sulfuric acid is completely destroyed by 0.5 g of potassium permanganate in 2 hours.

1. Reagents

Potassium permanganate: technical grade

Sulfuric acid (concentrated): relative density 1.84 (~18 mol/litre); technical grade

Sulfuric acid (dilute): ~3 mol/litre, aqueous

Note: The dilution of concentrated sulfuric acid is an extremely exothermic reaction. Always add the acid to the water, never the reverse, and remove heat by cooling in a cold-water bath.

Potassium permanganate/sulfuric acid solution: to 100 ml of 3 mol/litre sulfuric acid, add 4.7 g solid potassium permanganate

Note 1: To avoid frothing, add the potassium permanganate in small increments.

Note 2: The reagent should always be freshly prepared on the day of use.

Ascorbic acid or sodium bisulfite: technical grade

Ascorbic acid solution or sodium bisulfite solution: ~50 g/litre, aqueous

Sodium hydroxide: technical grade

Sodium hydroxide solution: ~2 mol/litre (~8 g/100 ml), aqueous

Sodium carbonate: technical grade

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.7)

3.1 Solid compounds

3.1.1 Estimate the amount of drug to be destroyed, and dissolve in 3 mol/litre sulfuric acid to obtain a maximum content of 1 mg/ml.

3.1.2 Place flask on a magnetic stirrer; add 0.5 g potassium permanganate per 10 ml of solution from 3.1.1.

3.1.3 Allow to react for 2 hours or more, with stirring.

3.1.4 Neutralize with 8 g/100 ml sodium hydroxide solution and discard.

3.2 Aqueous solutions

3.2.1 Estimate the amount of drug to be destroyed, and dilute with water, if necessary, to a maximum content of 1 mg/ml.

3.2.2 Add slowly, with stirring, enough concentrated sulfuric acid to obtain a 3 mol/litre solution, and allow to cool to room temperature.

3.2.3 Proceed as in 3.1.2 to 3.1.4.

3.3 Pharmaceutical preparations

Note: This method has been tested using the following preparation: 1 mg of compound + 1.275 mg methyl *p*-hydroxybenzoate + 1.225 mg propyl *p*-hydroxybenzoate + 100 mg mannitol.

3.3.1 Estimate the amount of drug to be destroyed, and dissolve in 3 mol/litre sulfuric acid to obtain a maximum content of 0.1 mg/ml.

3.3.2 Place on a magnetic stirrer; gradually add 0.5 g potassium permanganate per 10 ml of solution.

Note: To avoid frothing, add the potassium permanganate in small increments.

3.3.3 Proceed as in 3.1.3 to 3.1.4.

3.4 Glassware

3.4.1 Immerse in a freshly prepared solution of potassium permanganate/sulfuric acid. Allow to react for 2 hours or more.

3.4.2 Clean the glass by immersion in a solution of ascorbic acid or sodium bisulfite.

3.5 Spills of solid compounds

3.5.1 Isolate the area, and put on suitable protective clothing.

3.5.2 Collect the solid compound and place it in a beaker.

3.5.3 Rinse the area with water. Take up the rinse with absorbent material, and place the material in the beaker from 3.5.2.

3.5.4 Cover the contents of the beaker from 3.5.3 with potassium permanganate/sulfuric acid solution. Allow to react for 2 hours. If the purple colour fades, add more potassium permanganate.

3.5.5 Discard.

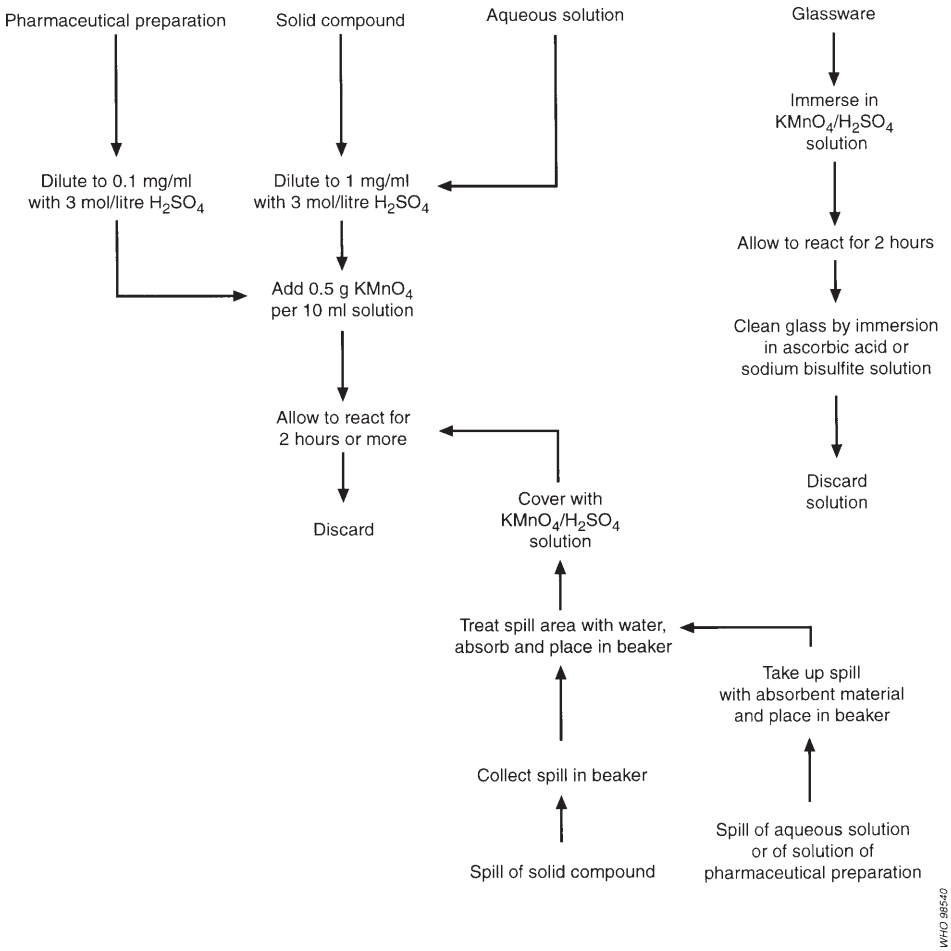
3.6 Spills of aqueous solutions or of solutions of pharmaceutical preparations

3.6.1 Isolate the area, and put on suitable protective clothing.

3.6.2 Take up the spill with absorbent material and place the material in a beaker. Rinse the area with water. Take up rinse with absorbent material, and place the material in the same beaker.

3.6.3 Proceed as in 3.5.4 to 3.5.5.

Fig. A2.7 *Schematic representation of procedure for destruction of vincristine sulfate and vinblastine sulfate*



Method 8. Destruction of 6-tioguanine and 6-mercaptopurine using potassium permanganate/sulfuric acid

6-Tioguanine or 6-mercaptopurine, 18 mg, dissolved in 20 ml of 3 mol/litre sulfuric acid is destroyed by 0.13 g potassium permanganate in 10–12 hours.

1. Reagents

Potassium permanganate: technical grade

Sulfuric acid (concentrated): relative density 1.84 (about 18 mol/litre); technical grade

Sulfuric acid (dilute): ~3 mol/litre, aqueous

Note: The dilution of concentrated sulfuric acid is an extremely exothermic reaction. Always add the acid to the water, never the reverse, and remove heat by cooling in a cold-water bath.

Potassium permanganate/ sulfuric acid solution: to 100 ml of 3 mol/litre sulfuric acid, add 4.7 g solid potassium permanganate

Note 1: To avoid frothing, add the potassium permanganate in small increments.

Note 2: The reagent should always be freshly prepared on the day of use.

Ascorbic acid or sodium bisulfite:	technical grade
Ascorbic acid solution or sodium bisulfite solution:	~50 g/litre, aqueous
Sodium hydroxide:	technical grade
Sodium hydroxide solution:	~2 mol/litre (~8 g/100 ml), aqueous
Sodium carbonate:	technical grade

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.8)

3.1 Solid compound

3.1.1 Estimate the amount of drug to be destroyed and dissolve in 3 mol/litre sulfuric acid to obtain a maximum concentration of 900 mg/litre.

3.1.2 Place flask on a magnetic stirrer; add 0.5 g potassium permanganate per 80 ml of solution from 3.1.1.

3.1.3 Allow to react overnight.

3.1.4 Neutralize with 8 g/100 ml sodium hydroxide solution and discard.

3.2 Aqueous solutions

3.2.1 Estimate the amount of drug to be destroyed and dilute with water if necessary to obtain a maximum concentration of 900 mg/litre.

3.2.2 Add slowly, with stirring, enough concentrated sulfuric acid to obtain a 3 mol/litre solution, and allow to cool to room temperature.

3.2.3 Proceed as in 3.1.2 to 3.1.4.

3.3 Oral preparations

3.3.1 Dissolve in 3 mol/litre sulfuric acid to a maximum concentration of 900 mg/litre.

3.3.2 Place flask on a magnetic stirrer; gradually add 4 g of potassium permanganate per 80 ml of solution.

Note: To avoid frothing, add the potassium permanganate in small increments.

3.3.3 Proceed as in 3.1.3 and 3.1.4.

3.4 Parenteral solutions

Note: This method has been tested using the following two preparations: 7.5 mg 6-tioguanine in 50 ml of 5% dextrose solution, and 10 mg 6-mercaptopurine in 10 ml of 5% dextrose solution.

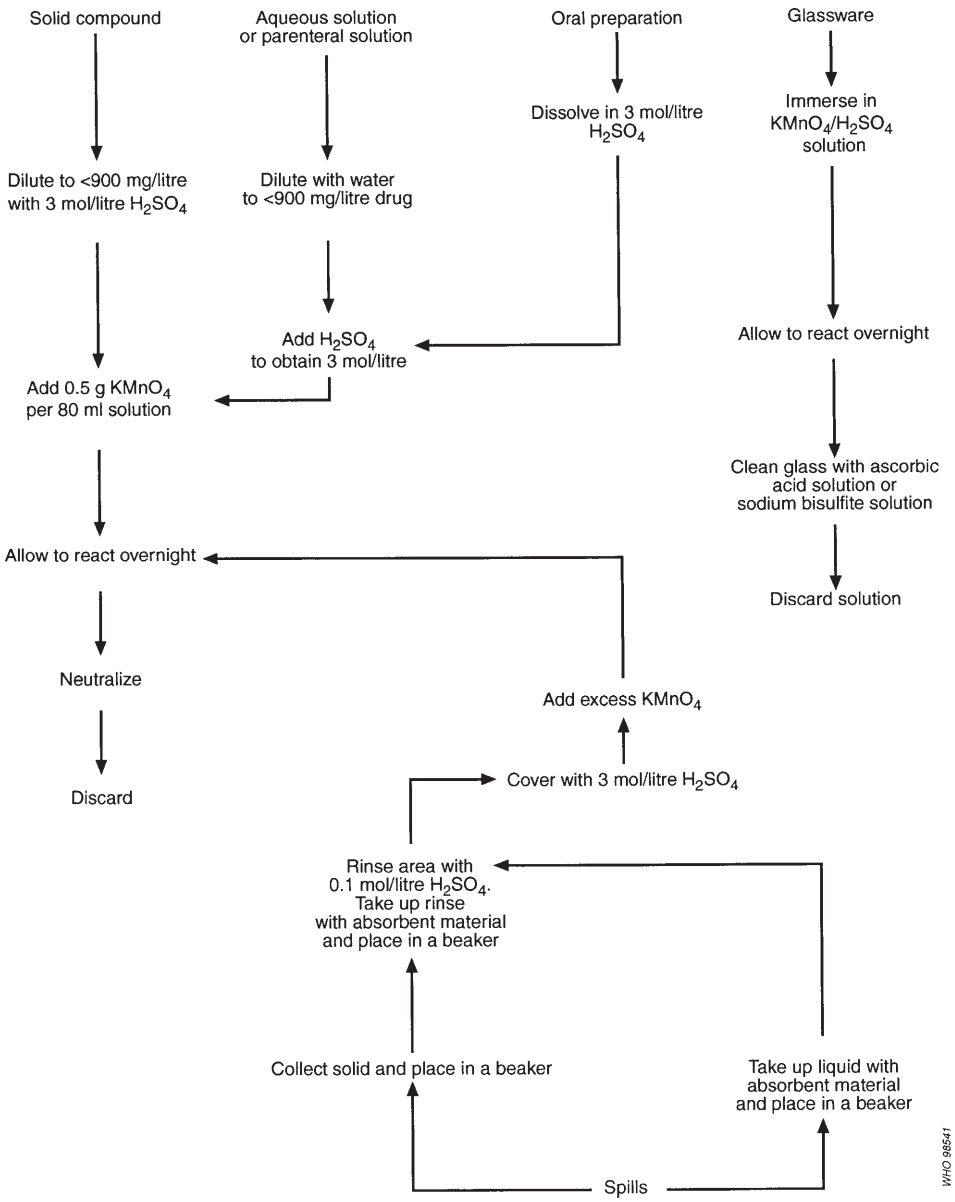
3.4.1 Add slowly with stirring, enough sulfuric acid to obtain a 3 mol/litre solution and allow to cool to room temperature.

3.4.2 Proceed as in 3.3.2 and 3.3.3.

3.5 Glassware

3.5.1 Immerse in a freshly prepared solution of potassium permanganate/sulfuric acid. Allow to react for 10–12 hours.

Fig. A2.8 *Schematic representation of procedure for destruction of 6-tioguanine and 6-mercaptopurine*



3.5.2 Clean the glass by immersion in a solution of ascorbic acid or sodium bisulfite.

3.6 Spills

3.6.1 Isolate the area, and put on suitable protective clothing.

3.6.2 Collect the solid, or take up the liquid with absorbent material, and place the material in a beaker.

3.6.3 Rinse the area with 0.1 mol/litre sulfuric acid. Take up the rinse with absorbent material, and place the material in the beaker from 3.6.2.

3.6.4 Cover the contents of the beaker from 3.6.3 with 3 mol/litre sulfuric acid and add, with stirring, an excess of potassium permanganate. Allow to react overnight.
Note: At the end of this period, some purple colour should remain; if not, add more potassium permanganate and continue to react.

3.6.5 Discard.

Method 9. Destruction of cisplatin by reduction with zinc powder

Cisplatin, 30 mg, dissolved in 2 mol/litre sulfuric acid, 50 ml, is destroyed by zinc powder, 1.5 g, in 10–12 hours.

1. Reagents

Sulfuric acid (concentrated):	relative density 1.84 (about 18 mol/litre); technical grade
Sulfuric acid (dilute):	~2 mol/litre and ~4 mol/litre, aqueous

Note: The dilution of concentrated sulfuric acid is an extremely exothermic reaction. Always add the acid to the water, never the reverse, and remove heat by cooling in a cold-water bath.

Zinc powder:	technical grade
Sodium hydroxide:	technical grade
Sodium hydroxide solution:	~2 mol/litre (~8 g/100 ml), aqueous

2. Apparatus

Standard laboratory equipment plus sintered glass funnel (porosity 4 or similar).

3. Procedure (see Fig. A2.9)

3.1 Solid compound

3.1.1 Dissolve in 2 mol/litre sulfuric acid solution to achieve a maximum concentration of 0.6 mg/ml.

3.1.2 Place flask on a magnetic stirrer; add 3 g zinc powder per 100 ml of solution from 3.1.1.

3.1.3 Stir overnight.

3.1.4 Neutralize with 8 g/100 ml sodium hydroxide solution.

3.1.5 Discard.

3.2 Aqueous solutions and injectable pharmaceutical preparations

Note: This method has been tested using solutions in 5% dextrose or 0.9% saline.

3.2.1 Dilute with water to obtain a maximum concentration of 0.6 mg/ml.

3.2.2 Add slowly, with stirring, enough concentrated sulfuric acid to obtain a 2 mol/litre solution, and allow to cool to room temperature.

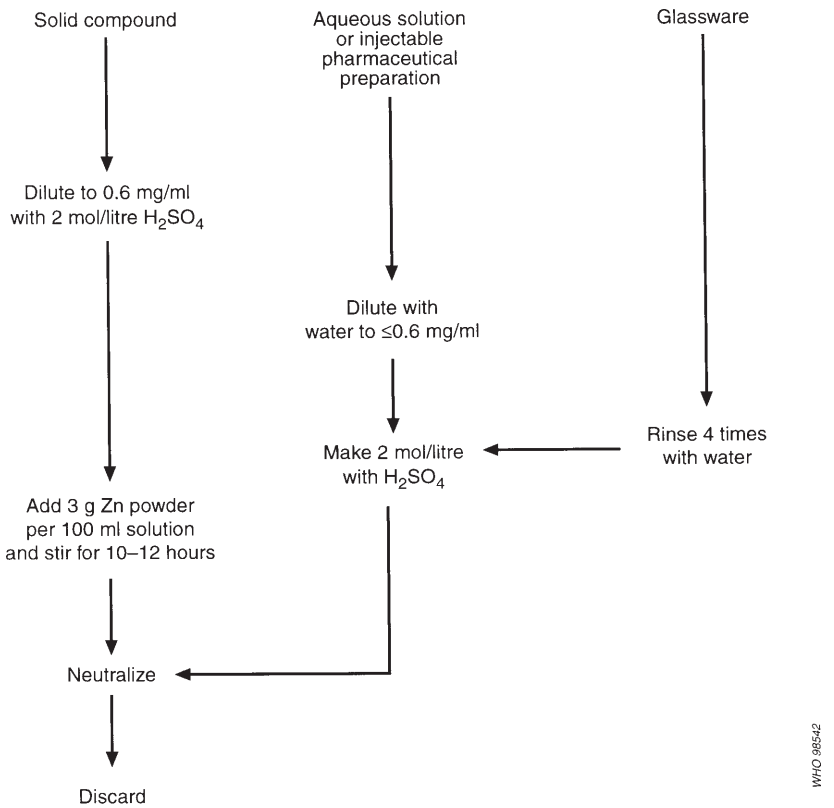
3.2.3 Proceed as in 3.1.2 to 3.1.5.

3.3 Glassware

3.3.1 Rinse at least four times with enough water to completely wet the glass.

3.3.2 Treat rinses as in 3.2.

Fig. A2.9 *Schematic representation of procedure for destruction of cisplatin by reduction with zinc powder*



Method 10. Destruction of cisplatin by reaction with sodium diethyldithiocarbamate

Cisplatin is destroyed by decomposition with sodium diethyldithiocarbamate.

1. Reagents

Sodium diethyldithiocarbamate:	technical grade
Sodium hydroxide:	technical grade
Sodium hydroxide solution:	0.1 mol/litre (0.4 g/100 ml), aqueous
Sodium nitrate:	technical grade
Sodium nitrate solution:	saturated, aqueous
Sodium diethyldithiocarbamate solution:	0.68 mol/litre (~1 g/100 ml) in 0.1 mol/litre sodium hydroxide solution

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.10)

3.1 Solid compound

3.1.1 Estimate the amount of drug to be destroyed.

3.1.2 Dissolve in water.

3.1.3 For every 100 mg cisplatin, add 3 ml sodium diethyldithiocarbamate solution.

3.1.4 Add an equal volume of sodium nitrate solution.
Note: A yellow precipitate of the complex of platinum II and diethyldithiocarbamate will form when the platinum concentration is greater than 100 µg/ml.

3.1.5 Discard.

3.2 Aqueous solutions, including injectable pharmaceutical preparations

Proceed as in 3.1.

3.3 Glassware

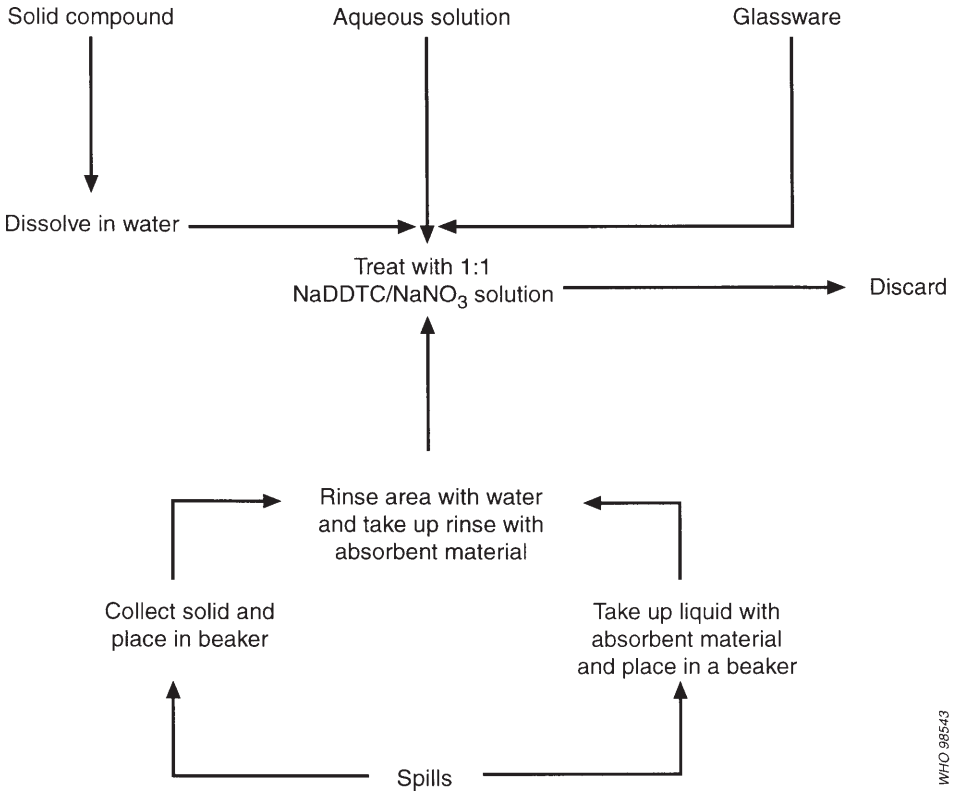
Immerse in a 1:1 mixture of sodium diethyldithiocarbamate solution and sodium nitrate solution.

3.4 Spills

3.4.1 Isolate the area, and put on suitable protective clothing.

3.4.2 Collect solid, or take up liquid with absorbent material, and place in a beaker.

Fig. A2.10 *Schematic representation of procedure for destruction of cisplation by reaction with sodium diethyldithiocarbamate*



3.4.3 Rinse the area with water and take up the rinse on absorbent material. Place the material in the beaker from 3.4.2.

3.4.4 Cover the contents of the beaker from 3.4.3 with a 1:1 mixture of sodium diethyldithiocarbamate solution and sodium nitrate solution.

3.4.5 Discard.

Method 11. Destruction of procarbazine in laboratory wastes using potassium permanganate in sulfuric acid

A 25-mg quantity of procarbazine can be degraded by 5 ml of a 0.3 mol/litre solution of potassium permanganate in 3 mol/litre sulfuric acid in 16 hours.

1. Reagents

Potassium permanganate: technical grade

Sulfuric acid (concentrated): relative density 1.84 (about 18 mol/litre)

Sulfuric acid (dilute): 3 mol/litre, aqueous

Note: The dilution of concentrated sulfuric acid is an extremely exothermic reaction. Always add the acid to the water, never the reverse, and remove heat by cooling in a cold-water bath.

Potassium permanganate/ sulfuric acid solution:	to 3 mol/litre sulfuric acid, add solid potassium permanganate to obtain a 0.3 mol/litre solution of potassium permanganate

Note 1: To avoid frothing, add the potassium permanganate in small increments.

Note 2: The reagent should always be freshly prepared on the day of use.

Ascorbic acid:	analytical grade

2. Apparatus

Standard laboratory equipment.

3. Procedure (see Fig. A2.11)

3.1 Undiluted procarbazine

3.1.1 Dissolve the procarbazine in 3 mol/litre sulfuric acid to obtain a maximum concentration of 5 g/litre. (Sulfate precipitate might form but will redissolve after addition of potassium permanganate in step 3.1.2.)

3.1.2 Add enough potassium permanganate to obtain a 0.3 mol/litre solution and to ensure that the purple colour remains after the reaction.

3.1.3 Allow to react overnight or longer.

3.1.4 Dilute with water and discard.

3.2 Aqueous solutions

3.2.1 Add slowly, with stirring, enough sulfuric acid to obtain a 3 mol/litre solution and a maximal procarbazine concentration of 5 g/litre.

3.2.2 Proceed as in 3.1.2 to 3.1.4.

3.3 Glassware

3.3.1 Rinse glassware with three successive portions of 3 mol/litre sulfuric acid solution. Drain completely between each rinse.

3.3.2 Treat rinses as in 3.1.2 to 3.1.4.

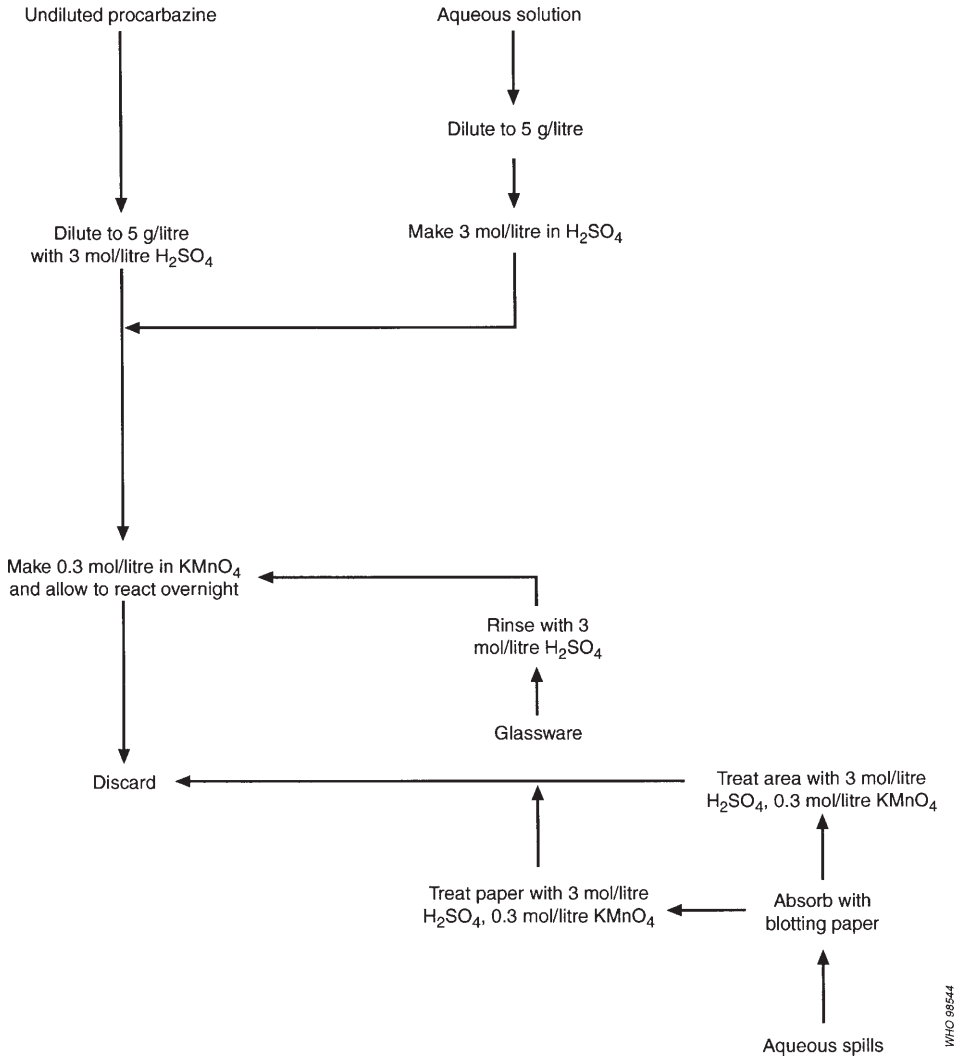
3.4 Spills of aqueous solutions

3.4.1 Isolate the area, and put on suitable protective clothing, including breathing apparatus if considered necessary. Add 3 mol/litre sulfuric acid solution to the spill area.

3.4.2 Take up the spill with an absorbent material, such as blotting paper; place it immediately in a beaker, and add a solution of 0.3 mol/litre potassium permanganate in 3 mol/litre sulfuric acid. Allow to react overnight or longer.

3.4.3 Pour some of the potassium permanganate/sulfuric acid solution over the contaminated area and allow to react overnight or longer; add some ascorbic acid to the area to clear the colour.

Fig. A2.11 *Schematic representation of procedure for destruction of procarbazine using potassium permanganate in sulfuric acid*



Methods of degradation of cytostatic drugs in hospital formulations

The three following degradation methods have been tested by a number of laboratories, coordinated by IARC, on 32 hospital formulations of cytostatic drugs (see Table A2.1). The efficiency of these methods is summarized in Table A2.2, which also indicates the mutagenic activity of the residues (tested using *Salmonella typhimurium* strains TA97, TA98, TA100, and TA102, with and without mutagenic activity). Degradation using sodium hypochlorite seems the most suitable method for these formulations.

Note: When reaction times were longer than those given in the following procedures, this is noted in Table A2.2.

(*Text continues on page 221.*)

Table A2.1 Formulation of reconstituted and administration solutions of cytostatic drugs

Note: After reconstitution of the drugs listed in this table, many are further diluted for administration to patients. However, the extent of this further dilution varies from country to country, as is evident from this table, which gives details for formulations used in France and the USA. The degradation methods given in this annex were tested on these formulations, in each instance using the "worst case", i.e. the stronger solution for administration, whenever there was a difference in national practice. It should be noted that the efficiency of degradation may be reduced if a particular method is used for a more concentrated formulation of a given drug.

Drug	Reconstituted solutions: solvents and additives		Drug concentration in reconstituted solution		Dilution for administration: diluents		Drug concentration in solution for administration	
	France	USA	France	USA	France	USA	France	USA
Aclarubicin 20 mg	Saline 0.9%		4 mg/ml		Saline 0.9% or glucose 5%		0.5 mg/ml	
Amsacrine 75 mg (contains 1.5 ml dimethyl acetamide)	Water 13.5 ml + (+)-lactic acid 42.93 mg	Water	5 mg/ml	5 mg/ml	Glucose 5%	Glucose 5%	0.15 mg/ml	0.15 mg/ml
Asparaginase	Water 2.5 ml + glycine 48.6 mg	Water	4000 U/ml	5000 U/ml	Saline 0.9% or glucose 5%	(no further dilution)	200 U/ml	5000 U/ml
Azathioprine[a]	Powder: lactose + starch + stearic acid +magnesium stearate	Water		10 mg/ml		Glucose 5%		2 mg/ml
Bleomycin 15 mg	Saline 0.9%, 5 ml	Water	3 U/ml	3 U/ml	Saline 0.9% or glucose 5%	(no further dilution)	0.05 U/ml or 3 U/ml	3 U/ml
Carboplatin	Water	Water	10 mg/ml	10 mg/ml	Saline 0.9%	Glucose 5%	1 mg/ml	0.5 mg/ml
Carmustine 100 mg	Ethanol (3 ml) + water (27 ml)	Water	3.3 mg/ml	33.3 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	0.2 mg/ml	0.5 mg/ml
Chlormethine[a] (mustine)	(Formulation contains 2 ml triethylene glycol)	Water	5 mg/ml	1 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	1 mg/ml	0.2 mg/ml
Cisplatin	Mannitol + saline + HCl (10%) to pH 4	Water	1 mg/ml	1 mg/ml	Saline	Saline	0.05 mg/ml	0.5 mg/ml

Cyclophosphamide	Saline 0.9%	Water	20 mg/ml	20 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	1 mg/ml	4 mg/ml
Cytarabine	Water + methyl *p*-hydroxybenzoate	Water	20 mg/ml	100 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9%	0.5 mg/ml	11 mg/ml
Dacarbazine 100 mg + citric acid 100 mg + mannitol 50 mg	Water (10 ml)	Water	10 mg/ml	10 mg/ml	Saline 0.9%	Saline 0.9% or glucose 5%	0.02 mg/ml	4 mg/ml
Daunorubicin 20 mg + mannitol	Water	Water	5 mg/ml	5 mg/ml	Saline 0.9% or glucose 5%	(no further dilution)	20 µg/ml	5 mg/ml
Doxorubicin 10 mg + lactose 5 mg	Water	Water	2 mg/ml	5 mg/ml	Saline 0.9% or glucose 5%	Glucose 5%	10 µg/ml	400 µg/ml
Epirubicin 10 mg + lactose	Water or saline 0.9%		2 mg/ml		Saline 0.9% or glucose 5%		0.2–2 mg/ml	
Etoposide, 20 mg + citric acid, 2 mg + benzyl alcohol, 30 mg + polysorbate 80/Tween 8'0, 80 mg + PEG 300, 650 mg + alcohol 30.5%, pH 3–4			20 mg/ml	5 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	200 µg/ml	150 µg/ml
Floxuridine	(not commercially available)	Water		100 mg/ml		Saline 0.9% or glucose 5%		0.3 mg/ml
Fludarabine[a]	Water	Water	25 mg/ml	10 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	1 mg/ml	0.4 mg/ml
5-Fluorouracil	Water (pH adjusted to 8.6–9.4 with NaOH)	Water (pH adjusted to 8.6–9.4 with NaOH)	50 mg/ml	50 mg/ml		(no further dilution)	0.01–40 mg/ml	50 mg/ml
Idarubicin[a] 5 mg + lactose 50 mg	Water or saline 0.9%	Water	1 mg/ml	1 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	0.5 mg/ml	40 µg/ml

Table A2.1 *(continued)*

Drug	Reconstituted solutions: solvents and additives		Drug concentration in reconstituted solution		Dilution for administration: diluents		Drug concentration in solution for administration	
	France	USA	France	USA	France	USA	France	USA
Ifosfamide	Water	Water	71.4 mg/ml	50 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	1 mg/ml	27 mg/ml
Lomustine—used without dilution. Contains: 40 mg/capsule lactose, talc, magnesium stearate								
6-Mercapto-purine—administered orally		Water		10 mg/ml		Saline 0.9% or glucose 5%		1 mg/ml
Methotrexate	Water + methyl *p*-hydroxybenzoate + propyl *p*-hydroxybenzoate	Water	2.5 mg/ml	100 mg/ml	Glucose 5%	Saline 0.9% or glucose 5%	0.5 mg/ml	2 mg/ml
Pirarubicin 10 mg + HCl 1 mol/litre + NaOH 0.2 mol/litre + lactose	Water (adjusted to 5 ml)		2 mg/ml		Glucose 5%		1 mg/ml	
Streptozocin 1 g + citric acid 220 mg	Saline 0.9% or glucose 5%, 9.5 ml	Water	100 mg/ml	100 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	0.1 mg/ml	14 mg/ml
Teniposide 50 mg + benzyl alcohol + dimethyl-acetamide + castor oil + ethanol	Non-aqueous solvent to 5 ml		10 mg/ml	10 mg/ml	Saline 0.9% or glucose 5%	Saline 0.9% or glucose 5%	500 µg/ml	1.8 mg/ml

Thiotepa 10 mg (contains saline and $NaHCO_3$)	Water	Water	5 mg/ml	10 mg/ml	Saline 0.9% or glucose 5%	Glucose 5%	1 mg/ml	60 µg/ml
Vinblastine sulfate 10 mg	Saline 0.9% or glucose 5%	Saline 9 mg in 1 ml of 0.9% benzyl alcohol in water, pH adjusted to 3-5–5.0	1 mg/ml	1 mg/ml	Saline 0.9% or glucose 5%	(no further dilution)	0.17 mg/ml	1 mg/ml
Vincristine sulfate 1 mg + methyl *p*-hydroxybenzoate 1.275 mg + propyl *p*-hydroxybenzoate 0.225 mg + acetic acid 0.2 mol/litre	Water (adjusted to 1 ml)	1.3 mg methylparaben in 1 ml water adjusted to pH 3.5–5.5	1 mg/ml	1 mg/ml	Saline 0.9% or glucose 5%	(no further dilution)	0.17 mg/ml	1 mg/ml
Vindesine sulfate 1 mg + mannitol 5 mg	Water		0.25 mg/ml		Saline 0.9% or glucose 5%		1 µg/ml	
Vinorelbine sulfate 10 mg	Water		10 mg/ml		Saline 0.9% or glucose 5%		100 µg/ml	

[a]Only the US formulations were tested.

Table A2.2 *Efficiency of the degradation methods tested on 32 cytostatic drug formulations*

Drug	Degradation by sodium hypochlorite		Degration by hydrogen peroxide		Degradation by Fenton reagent	
	Degradation	Mutagenicity	Degradation	Mutagenicity	Degradation	Mutagenicity
Aclarubicin	+	–	–		+	–
Amsacrine	+	–	–		+	–
Asparaginase	+	–	+	–	+	–
Azathioprine	+	–?	–		+	–
Bleomycin, 10 mg/ml	+	–	–		+/–[a]	+/–[a]
Carboplatin	+	–	+	–		
Carmustine:						
1 hour	+	+	+	–/T	+	+
4 hours	+	–	+	–/T	Not tested	
Chlormethine (mustine)	+	–	–		–	
Cisplatin	+	–	+	–(+)[b]	+	–
Cyclophosphamide	+	–	+	–	+	–(+)[c]
Cytarabine	+	–	+	–	+	–
Dacarbazine, 10 mg/ml	+	+	–		+/–[d]	+/–[d]
Dacarbazine, 4 mg/ml	+	–	Not tested		+	+/–
Daunorubicin	+	–	–		+	–
Doxorubicin	+	–	–		+	–
Epirubicin	+	–	+	–	+	–
Etoposide	+	–	–		+	+
Floxuridine	+	–	+	–	+	–
Fludarabine	+	–	+	–	+	–
5-Fluorouracil	+	–	+	Toxic	+	–
Idarubicin	+	–	–		+	–
Ifosfamide	+	–	+	–(+)[c]	+	–
Lomustine,[e] 5 mg/ml:						
1 hour	+	+	+	T[f]	+[g]/–	–[g]
4 hours	+	–	+	T[f]	Not tested	
Lomustine,[e] 1 mg/ml:						
1 hour	+	–	+	T[f]	+	–
4 hours	+	–	+	T[f]	Not tested	
6-Mercaptopurine	+	–	+	–	+	–
Methotrexate	+	–	+	–	+	–
Pirarubicin	+	–	+[h]	–	+	–
Streptozocin:						
NaCl, 0.9%	+	–	+	–	+	–/+
glucose, 5%	+	–	+	–	+/–[i]	+[i]
Teniposide	+	–(+)[c]	–		+	–
Thiotepa	+	–	+	–	+	–
Vinblastine sulfate	+	+	+	–	+	+
Vincristine sulfate	+	–	–		+	–
Vindesine sulfate	+	–	–		+	–
Vinorelbine sulfate	+	–	–		+	

[a]Residual concentration after degradation, 1.48%.
[b]Mutagenic activity detected for a US formulation, which was 10 times stronger than a French formulation also tested.
[c]Mutagenic activity detected when the reaction was performed in the presence of 5% glucose.
[d]Residual concentration after degradation, 0.04%.
[e]This drug is formulated as a powder; two concentrations were tested after dilution (5 and 1 mg/ml).
[f]Toxic activity detected, which may have resulted from a problem in preparation of the sample for mutagenicity testing.
[g]In one experiment, 1.22% residual drug was detected. The sample tested for mutagenicity was >99.5% degraded.
[h]A reaction time of 24 hours was found necessary for efficient degradation.
[i]Residual concentration after degradation, 0.7%.

Degradation by sodium hypochlorite

1. Measure the volume of the solution for administration of the cytostatic drug to be degraded.
2. Add an equivalent volume of a 5% sodium hypochlorite solution.
3. If necessary, shake to achieve complete homogeneity of the solution. (An ultrasound bath may be used for this purpose.)
4. Allow to react at room temperature for at least 1 hour.
5. If necessary, check for completeness of degradation.
6. Discard.

Degradation by hydrogen peroxide

1. Measure the volume of the solution for administration of the cytostatic drug to be degraded.
2. Add an equivalent volume of a 30% hydrogen peroxide solution.
3. If necessary, shake to achieve complete homogeneity of the solution. (An ultrasound bath may be used for this purpose.)
4. Allow to react at room temperature for at least 1 hour.
5. If necessary, check for completeness of degradation.
6. Dilute with water and discard.

Degradation by a Fenton reagent

1. Measure the volume of the solution for administration of the cytostatic drug to be degraded.
2. Place in a flask of at least 10 times the volume of solution to be degraded. Place the flask on ice.
3. Add slowly, with stirring, 0.3 g of ferrous chloride, $FeCl_2 \cdot 2H_2O$.
4. Add dropwise, with stirring, 10 ml of 30% hydrogen peroxide solution.
5. Allow to react at room temperature for at least 1 hour.
6. If necessary, check for completeness of degradation.
7. Dilute and discard.

References

Barek J et al. (1998). Chemical degradation of wastes of antineoplastic agents. Part 3: amsacrine, azathioprine, asparaginase and thiotepa. *Annals of occupational hygiene*, 42:259–266.

Castegnaro M et al. (1997). Chemical degradation of wastes of antineoplastic agents. Part 2: six anthracyclines: idarubicin, doxorubicin, epirubicin, pirarubicin, aclarubicin and daunorubicin. *International archives of occupational and environmental health*, 70:378–384.

Hansel S et al. (1997). Chemical degradation of wastes of antineoplastic agents. Part 1: cyclophosphamide, ifosfamide, melphalan. *International archives of occupational and environmental health*, 69:109–114.

ANNEX 3

Clearance levels for radioactive waste

The material in this annex has been produced by the International Atomic Energy Agency and is based on extracts from the following two publications, used with permission:

IAEA (1996). *Clearance levels for radionuclides in solid materials*. Vienna, International Atomic Energy Agency (TECDOC 855).

IAEA (1998). *Clearance of materials resulting from the use of radionuclides in medicine, industry and research*. Vienna, International Atomic Energy Agency (in press).

Table A3.1 *Generic clearance levels for solid waste*

Radionuclide	Clearance level (Bq/g) for moderate quantities	Radionuclide	Clearance level (Bq/g) for moderate quantities
H-3	1×10^6	Sr-89	1×10^3
C-14	1×10^4	Y-90	1×10^3
Na-22	1×10^1	Mo-99	1×10^2
Na-24	1×10^1	Tc-99	1×10^4
P-32	1×10^3	Tc-99m	1×10^2
S-35	1×10^5	In-111	1×10^2
Cl-36	1×10^4	I-123	1×10^2
K-42	1×10^2	I-125	1×10^3
Ca-45	1×10^4	I-131	1×10^2
Ca-47	1×10^1	Pm-147	1×10^4
Cr-51	1×10^3	Er-169	1×10^4
Fe-59	1×10^1	Au-198	1×10^2
Co-57	1×10^2	Hg-197	1×10^2
Co-58	1×10^1	Hg-203	1×10^2
Ga-67	1×10^2	Tl-201	1×10^2
Se-75	1×10^2	Ra-226	1×10^1
Sr-85	1×10^2	Th-232	1×10^0

Note: The generic clearance levels in Table A3.1 are given for moderate quantities of waste (i.e. less than 3 tonnes of cleared waste per year and per facility). They are identical to the exemption levels of the international basic safety standards for protection against ionizing radiation and for the safety of radiation sources (IAEA, 1996). Clearance levels for large quantities are one-tenth of the levels in Table A3.1.

Table A3.2 *Liquid discharge rates to sewers, rivers, or other large water bodies*

Radionuclide	Annual release rate (Bq/year)	Monthly release rate (Bq/month)	Daily release rate (Bq/day)
H-3	10^9	10^8	10^7
C-14	10^7	10^6	10^5
Na-22	10^2	10	1
Na-24	10^5	10^4	10^3
P-32	10^3	10^2	10
S-35	10^6	10^5	10^4
Cl-36	10^7	10^6	10^5
Ca-45	10^7	10^6	10^5
Ca-47	10^5	10^4	10^3
Fe-59	10^3	10^2	10
Co-57	10^6	10^5	10^4
Co-58	10^5	10^4	10^3
Ga-67	10^5	10^4	10^3
Sr-85	10^3	10^2	10^3
Sr-89	10^6	10^5	10^4
Y-90	10^7	10^6	10^5
Mo-99	10^5	10^4	10^3
Tc-99	10^7	10^6	10^5
Tc-99m	10^6	10^5	10^4
In-111	10^5	10^4	10^3
I-123	10^6	10^5	10^4
I-125	10^5	10^4	10^3
I-131	10^5	10^4	10^3
Pm-146	10^7	10^6	10^5
Er-169	10^7	10^6	10^5
Au-198	10^5	10^4	10^3
Hg-197	10^6	10^5	10^4
Hg-203	10^4	10^3	10^2
Tl-201	10^5	10^4	10^3
Ra-226	10^3	10^2	10
Th-232	10^3	10^2	10

Note 1: Table A3.2 provides annual release rates below which water-miscible liquid waste may be unconditionally discharged with normal wastewater by a pipe to a sewer, river, or other large water body. Since it would not necessarily be appropriate for the whole discharge to be made over a very short time, both monthly and daily limits have also been included. These are based on 1/10 and 1/100 of the annual limits respectively.

Note 2: The derivation of clearance levels for liquid releases is described elsewhere (IAEA, 1998). For discharge to sewers, two extreme possible scenarios were considered:

— no radioactive material is retained in sewage sludge but all is discharged to the water body in liquid form;
— all radioactive material discharged is retained in the sewage sludge at the sewage treatment works.

Radiation doses were calculated for both cases, and the more restrictive levels were used to derive the values in Table A3.2, after being divided by a conservative factor of 1000. This factor is intended to reflect the fact that:

— the models in the reference document (IAEA, 1998) were developed for application in temperate European and North American conditions, and the assumptions of diet, agriculture, and lifestyle may not be universally valid; and

— these models did not consider the transfer of radionuclides to terrestrial foodchains as a result of irrigation or use of sewage sludge in agriculture.

Note 3: Activity from patients' discharges, after diagnostic or therapeutic use of radionuclides, should also be considered. This may be achieved by comparing discharges with the clearance levels.

Note 4: For other radionuclides and higher levels of activity, any discharge made should be specifically authorized by the regulatory authority after assessment of all the relevant conditions.

Note 5: In reality, more than one radionuclide will often be involved. To determine whether a mixture of radionuclides is at or below the clearance level, a simple ratio expression can be used:

$$\sum_{i=1}^{n} \frac{C_i}{C_{Li}} \leq 1$$

where C_i is the concentration of radionuclide i in the material being considered (Bq/g)
C_{Li} is the clearance level of radionuclide i in the material (Bq/g)
n is the number of radionuclides in the mixture.

In the above expression, the ratio of the concentration of each radionuclide to the clearance level is summed over all radionuclides in the mixture. If this sum is less than or equal to 1, the material complies with the clearance requirements.

Table A3.3 *Gaseous releases into the open air*

Radionuclide	Annual release rate (Bq/year)	Monthly release rate (Bq/month)	Daily release rate (Bq/day)
H-3	10^8	10^7	10^6
C-14	10^7	10^6	10^5
Na-22	10^3	10^2	10
Na-24	10^6	10^5	10^4
P-32	10^5	10^4	10^3
S-35	10^5	10^4	10^3
Cl-36	10^4	10^3	10^2
K-42	10^7	10^6	10^5
Ca-45	10^5	10^4	10^3
Ca-47	10^6	10^5	10^4
Cr-51	10^6	10^4	10^3
Fe-59	10^5	10^4	10^3
Co-57	10^6	10^5	10^4
Co-58	10^6	10^5	10^4
Ga-67	10^7	10^6	10^5
Se-75	10^5	10^4	10^3
Sr-85	10^5	10^4	10^3
Sr-89	10^5	10^4	10^3
Y-90	10^7	10^6	10^5
Mo-99	10^6	10^5	10^4
Tc-99	10^4	10^3	10^2

Table A3.3 (*continued*)

Radionuclide	Annual release rate (Bq/year)	Monthly release rate (Bq/month)	Daily release rate (Bq/day)
Tc-99m	10^8	10^7	10^6
In-111	10^6	10^5	10^4
I-123	10^7	10^6	10^5
I-125	10^5	10^4	10^3
I-131	10^5	10^4	10^3
Xe-127	10^8	10^7	10^6
Xe-133	10^9	10^8	10^7
Pm-147	10^7	10^6	10^5
Er-169	10^7	10^6	10^5
Au-198	10^6	10^5	10^4
Hg-197	10^7	10^6	10^5
Hg-203	10^5	10^4	10^3
Tl-201	10^7	10^6	10^5
Ra-226	10^3	10^2	10
Th-232	10^2	10	1

Note 1: Table A3.3 provides annual release rates below which gaseous waste may be unconditionally discharged via ventilation systems (e.g. from laboratory fume cupboards) or other means to the open air. This may be done only in such a way and and in such a position as to prevent the gas from re-entering any building. Since it would not necessarily be appropriate for the entire discharge to be made over a very short time, monthly and daily limits have also been included; these are based on 1/10 and 1/100 of the annual limits respectively.

Note 2: The derivation of clearance levels for gaseous releases is described elsewhere (IAEA, 1998). It assumes that a person lives 20 m from the release point and obtains all crop-based foods from an area at least 100 m from the release point and all animal products from an area at least 800 m from the release point. Values in Table A3.3 were then based on radiation doses calculated from the summation of inhalation, injection, and external exposure pathways. The values in the table include a conservative factor of 1000 to reflect the fact that the models in the reference document (IAEA, 1998) were developed for temperate European and North American conditions and may differ for countries with significantly different diets, agriculture, and lifestyles.

Note 3: For other radionuclides and higher levels of activity, any discharge should be specifically authorized by the regulatory authority after assessment of all the relevant conditions.

Reference

IAEA (1996). *International basic safety standards for protection against ionizing radiation and for the safety of radiation sources.* Vienna, International Atomic Energy Agency (Safety Series, No. 115).

ANNEX 4

Procedure to be followed in the event of accidental contamination by mutagenic and carcinogenic products

The text of this annex has been reproduced, with minor editorial changes, from the following document:

> *Laboratory handling of mutagenic and carcinogenic products*. Geneva, World Health Organization, 1998 (unpublished document WHO/PCS/98.9; IPCS Training Module No. 2).

An accident involving contamination by a mutagenic or carcinogenic substance must be systematically planned for because it can affect the entire staff of a laboratory and the equipment. The substance in question may arise in a number of forms (liquid, solid, gas, volatile product, aerosol, etc.) and every eventuality must be catered for.

In every case:

- Emergency exits must be signposted and emergency telephone numbers (poison control centre, fire service, ambulance service, medical centre) must be prominently displayed.
- The emergency services must be notified of the existence of the hazard and of the proposed protocol.
- Emergency equipment must be to hand and trained first-aiders must be available.

A4.1 Immediate action

In every case, responsible persons, whose names and telephone numbers are clearly displayed on the door to the premises concerned, must be informed.

It is the responsibility of the supervisor to notify the medical service, which must record the accident in the register of accidents at work and contact outside services if necessary together with the health and safety committee/works council.

The immediate action taken by the supervisor has a number of objectives:

- to evacuate personnel quickly in accordance with a pre-arranged plan if the contamination is caused by a gas, volatile product, aerosol, powdery solid, or liquid;
- to avoid air currents: doors must be closed and ventilation hoods switched off if the contaminant is a powder;
- to restrict access to the contaminated area;
- to organize prompt decontamination of exposed personnel using appropriate methods;
- to organize prompt decontamination of the premises and exposed equipment.

Adequate precautions must be taken to prevent contamination of premises, equipment and individuals as far as possible.

A4.2 Evacuation of personnel

Personnel must be evacuated very promptly in serious cases of major contamination and where the contaminating product may easily disperse (in the case of gases, volatile products, or aerosols). This evacuation may require the assistance of persons from outside wearing protective clothing appropriate to the scale and type of contamination (gloves, goggles, cellulose mask, cartridge mask, self-contained breathing apparatus, overalls).

A4.3 Decontamination of personnel

Any signs of acute intoxication and/or of a life-threatening condition (injuries, breathing difficulties) must be attended to immediately. Thereafter, and depending on the type of contamination, there are a number of possible scenarios: in every case, clothing that has been soiled or is thought to have been soiled must be removed for decontamination and placed in special sacks.

Contamination of the skin and mucosa

Copious and immediate washing must be carried out on the spot for 20 minutes using cold or tepid water delivered by a shower, eye bath, or any other suitable method.

Never rub or scrub and never use a solvent, including alcohol, which may facilitate penetration of the contaminant through the skin.

The contaminant is diluted by this first rinsing, and the rinse water must be discarded together with mutagenic waste.

If the suspect products are lipophilic (solubility in water < 0.1%) mild detergents may be used on the skin to complete the decontamination. Use of detergents, however, must remain the exception, because they can make it easier for the contaminant to penetrate the skin or mucosa and they should never be used as the method of first resort.

In severe cases, contamination may be continued in hospital where any systemic effects can be treated.

Absorption by mouth

The process of decontamination follows medical or hospital practice (poison control centres). The mouth may, however, be rinsed out on the spot if the affected individual is conscious.

Never induce vomiting in an accident victim.

Inhalation

Individuals affected by inhalation of a contaminant should be evacuated immediately to a non-contaminated area; the process of decontamination will then require the attention of specialist personnel. Treatment of the toxic effects of the contaminant may require hospitalization.

A4.4 Decontamination of premises and equipment

In every case of contamination:

- The safety service must be notified.
- The contaminated area (floors, bench tops, etc.) must be marked off and isolated using a marker or adhesive tape.
- Appropriate protective clothing must be put on (gloves, cellulose mask or cartridge mask or self-contained breathing apparatus, overalls).
- Nothing must be picked up with the bare hands; decontamination must be carried out.

When the contaminant is a liquid:

Absorbent products (e.g. a universal drying agent) may be spread over the soiled surfaces. These absorbent products must then be disposed of in receptacles set aside for genotoxic materials. The affected area should then be copiously washed and rinsed using a solvent appropriate to the contaminant; rinsing and washing liquids should be disposed of as mutagenic effluent. The final rinsing liquid should be tested for mutagenicity (using a chemical analysis, which is faster than the mutagenicity test), and access to the contaminated area must be prohibited until test results are known.

In every case, solutions must be wiped up working from the outside edge of the soiled area in towards the point of first impact to prevent the hazardous product from spreading. These operations must be performed by a properly protected and competent individual.

When the contaminant is a powder:

All forms of ventilation must be switched off to reduce the risk of dispersion and the contaminated area must be cleaned using paper or a cloth impregnated with solvent. Filters must be changed after decontamination. The contaminated area must be covered by a cloth or compresses soaked in water or a neutralizing solution to prevent the generation of particulates which can be inhaled.

Premises and equipment may also be decontaminated using a wet method—initially, specific solvents, decontaminants, or detergents in an aqueous solution or soapy water. Solvents, decontaminants, or detergents should be spread on absorbent paper and discarded after use in the receptacles reserved for toxic substances. Surfaces should be copiously rinsed before the premises are used again.

In every case, solutions must be wiped up working from the outside edge of the soiled area in towards the point of first impact to prevent the hazardous product from spreading.

Small equipment of low cost may be disposed of without cleaning; alternatively it should be decontaminated using the method described above.

Clothing contaminated by accident or used during cleaning must be incinerated.

A4.5 Emergency stand-by equipment

An eye-bath and a shower should be available near a laboratory that uses mutagenic products.

A stock of latex gloves, cellulose masks, self-contained breathing apparatus, overalls, paper, disposable hooded coats, overshoes, and drying agents must be available to personnel. Ideally, a special spill control kit containing the various items of equipment needed should be assembled.

Lastly, it is vital to have a telephone in the immediate vicinity, with the telephone numbers of the supervisor, the medical service, fire service, ambulance service, poison control centre, etc. prominently displayed. This must not be located in the laboratory itself, but in the corridor outside for example.

A4.6 Acts of vandalism, theft, fire, flood

Procedures must be geared above all to prevention of accidents/incidents. However, the laboratory supervisor must be notified at once of any incident so that appropriate action can be taken. Information must be given at once to emergency teams that may have to be brought in from outside. All personnel must be made aware of any theft or act of vandalism; details should be posted so that everyone is informed of the hazards involved.

A4.7 Notification of accidental contamination

Accidental contamination must be notified using a standard-format document, a copy of which must in every case be sent to the medical service. The document must state:

- the day and date of the accident;
- the names of the persons concerned, including those who helped in the decontamination work;
- the premises and equipment contaminated;
- the name of the product that caused the contamination, its volume, presentation, and concentration;
- a description of the operations that resulted in the accident;
- a description of the actions taken after the accident.

All these details must be entered in the safety register.

A4.8 Responsibility

The laboratory supervisor has a duty to inform persons handling products that are known or suspected mutagens and/or carcinogens of the potential hazards.

Specific procedures must be available for personnel to follow.

In the event of an accident, a subsequent inquiry must determine the causes of the accident and establish means of ensuring that recurrences can be prevented.