Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

23-Jul-2001

English - Or. English

ENV/JM/MONO(2001)7
Unclassified

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

OECD SERIES ON TESTING AND ASSESSMENT
Number 26

REVISED ANALYSIS OF RESPONSES RECEIVED FROM MEMBER COUNTRIES TO THE QUESTIONNAIRE ON DATA REQUIREMENTS FOR ACUTE ORAL TOXICITY

JT00111079

English - Or. English

OECD Environmental Health and Safety Publications

Series on Testing and Assessment

No. 26

Revised Analysis of Responses Received from Member Countries to the Questionnaire on Data Requirements for Acute Oral Toxicity

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris

November 2000

Also Published in the Series Testing and Assessment:

No. 1, *Guidance Document for the Development of OECD Guidelines for Testing of Chemicals* (1993; reformatted 1995)

No. 2, *Detailed Review Paper on Biodegradability Testing* (1995)

No. 3, *Guidance Document for Aquatic Effects Assessment* (1995)

No. 4, *Report of the OECD Workshop on Environmental Hazard/Risk Assessment* (1995)

No. 5, *Report of the SETAC/OECD Workshop on Avian Toxicity Testing* (1996)

No. 6, *Report of the Final Ring-test of the* Daphnia magna *Reproduction Test* (1997)

No. 7, *Guidance Document on Direct Phototransformation of Chemicals in Water* (1997)

No. 8, *Report of the OECD Workshop on Sharing Information about New Industrial Chemicals Assessment* (1997)

No. 9, *Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application* (1997)

No. 10, *Report of the OECD Workshop on Statistical Analysis of Aquatic Toxicity Data* (1998)

No. 11, *Detailed Review Paper on Aquatic Testing methods for Pesticides and industrial Chemicals* (1998)

No. 12, *Detailed Review Document on Classification Systems for Germ Cell Mutagenicity in OECD Member Countries* (1998)

No. 13, *Detailed Review Document on Classification Systems for Sensitising Substances in OECD Member Countries* (1998)

No. 14, *Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries* (1998)

No. 15, *Detailed Review Document on Classification Systems for Reproductive Toxicity in OECD Member Countries* (1998)

No. 16, *Detailed Review Document on Classification Systems for Skin Irritation/Corrosion in OECD Member Countries(1998)*

No. 17, *Environmental Exposure Assessment Strategies for Existing Industrial Chemicals in OECD Member Countries (in preparation)*

No. 18, *Report of the OECD Workshop on Improving the Use of Monitoring Data in the Exposure Assessment of Industrial Chemicals (in preparation)*

No. 19, *Guidance Document on the Recognition, Assessment,and Use of Clinical Signs as Humane Endpoints for Experimental AnimalsUsed in Safety Evaluation*

No. 20, *Revised Draft Guidance Document for Neurotoxicity Testing*

No. 21, *Detailed ReviewPaper: Appraisal of Test Methods for Sex Hormone Disrupting Chemicals (2000)*

No. 22, *Guidance Document for the Performance of Out-door Monolith Lysimeter Studies (June 2000)*

No. 23, *Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures* (2000)

No. 24, *Draft Guidance Document on Acute Oral Toxicity Testing* (2000)

No. 25, *Detailed Review Document Hazard Classification Systems for Specific Target Organ Systemic Toxicity Following Single or Repeated Exposure in OECD Member Countries (August 2000)*

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 29 industrialised countries in North America, Europe and the Pacific, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised Committees and subsidiary groups composed of Member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's Workshops and other meetings. Committees and subsidiary groups are served by the OECD Secretariat, located in Paris, France, which is organised into Directorates and Divisions.

The work of the OECD related to chemical safety is carried out in the **Environment, Health and Safety Programme**. As part of its work on chemical testing, the OECD has issued several Council Decisions and Recommendations (the former legally binding on Member countries), as well as numerous Guidance Documents and technical reports. The best known of these publications, the **OECD Test Guidelines**, is a collection of methods used to assess the hazards of chemicals and of chemical preparations. These methods cover tests for physical and chemical properties, effects on human health and wildlife, and accumulation and degradation in the environment. The OECD Test Guidelines are recognised world-wide as the standard reference tool for chemical testing.

More information about the Environment, Health and Safety Programme and its publications (including the Test Guidelines) is available on the OECD's World Wide Web site (see page 8).

The Environment, Health and Safety Programme co-operates closely with other international organisations. This document was produced within the framework of the Inter-Organisation Programme for the Sound Management of Chemicals (IOMC).

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, FAO, WHO, UNIDO and the OECD (the Participating Organisations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. UNITAR joined the IOMC in 1997 to become the seventh Participating Organisation. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

OECD Environment Directorate,
Environment, Health and Safety Division

2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 45 24 16 75

E-mail: ehscont@oecd.org

REVISED ANALYSIS OF RESPONSES RECEIVED FROM MEMBER COUNTRIES ON THE QUESTIONNAIRE ON DATA REQUIREMENTS FOR ACUTE ORAL TOXICITY

A Summary of National Data Requirements and Required Level of Confidence of Acute Oral Toxicity Data for the Purpose of Hazard Characterisation

Twenty Member countries (Australia-AUS, Austria-AT, Belgium-BE, Canada-CA, Denmark-DK, Finland-FI, France-FR, Germany-GER, Hungary-HUN, Ireland-IR, Italy-IT, Japan-JP, Netherlands-NL, New Zealand-NZ, Norway-NO, Poland-PL, Sweden-SE, Switzerland-CH, UK and USA) and Slovenia-SLO responded to the questionnaire that was circulated on 11th February 1999.

The analysis of the questionnaire responses are summarised in a series of tables as follows:

- **Table 1:** List of countries who responded to the questionnaire, broken down according to chemical application/use.
- **Table 2:** Number of countries accepting any of the alternative methods for a particular purpose.
- **Table 3:** Number of countries requiring the respective data elements for each of the chemical use areas.
- **Table 4:** Identification of countries requiring the respective data elements for each of the chemical use areas.
- **Table 5:** Listing of countries' regulatory requirements.

Table 1: Listing of countries who responded to the questionnaire broken down according to chemical application/use

Application area	**No. of countries responded**	*Countries*
Workplace	19[1,2]	Australia, Belgium, Canada, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, New Zealand, Norway, Poland, Sweden, Switzerland, UK, USA and Slovenia
Transport	11[3]	Austria, Finland, Germany, Hungary, Ireland, Italy, Netherlands, Poland, UK, USA and Slovenia
Pesticides	20[4]	Australia, Austria, Belgium, Canada, Denmark, Finland, Germany, Hungary, Ireland, Italy[5], Japan, The Netherlands, New Zealand, Norway, Poland, Sweden, Switzerland, UK, USA and Slovenia
Consumer products	16	Australia, Austria, Denmark, Finland, Germany, Hungary, Italy, Netherlands, New Zealand, Norway, Poland, Sweden, Switzerland, UK, USA and Slovenia
Pharmaceuticals	16[6,7]	Australia, Austria, Canada, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, New Zealand, Poland, Sweden, USA and Slovenia
Industrial chemicals	17	Australia, Austria, Denmark, Finland, Germany, Hungary, Ireland, Italy[8], Netherlands, New Zealand, Norway, Poland, Sweden, Switzerland, UK, USA and Slovenia
Military	0[9]	
Other	7	Australia, *France, Hungary, Netherlands, Norway, Switzerland and USA*
• *Community right to know - emergency response provisions*	4	Hungary, Norway, Switzerland, USA
• *Determine doses for repeat dose studies*	6	Australia, France, Hungary, Netherlands, Norway, Switzerland
• *Pesticides for public health use*	1	Hungary
• *Hazardous waste* • *Hazardous leachetes*	1	Hungary

Footnotes are provided at the end of the document.

Table 2. Number of countries accepting any of the alternative methods for a particular purpose

REQUIREMENTS/APPLICATION AREA	No. of countries responded	Would any of the alternative methods suffice?					
		Yes	Which?			No	This question was not or unclearly answered
			420	423	425		
Workplace							
Classification	19	17	16	17	16	1[10]	1
Labelling	18	16	15	16	15	1[10]	1
Safety data sheet	15	13	13	12	13	1[10]	1
Chemical specific standards	7	7	7	7	7	0	0
Other						0	0
IDLH (Immediately Dangerous to Life and Health	1	0	0	0	0	1[11]	0
Transport							
Classification	10	8	7	7	8	1[10]	1
Labelling	10	8	7	7	8	1[10]	1
Packing groups	8	6	6	6	6	1[10]	1
Emergency response information and steps	7	5	5	4	4	1[10]	1
Classification to initiate training	5	4	4	4	4	1[10]	0
Regulated material provisions on the vehicle and driver	3	2	2	2	2	1[10]	1

Table 2. Number of countries accepting any of the alternative methods for a particular purpose (cont.)

REQUIREMENTS/APPLICATION AREA	No. of countries responded	Would any of the alternative methods suffice?					
		Yes	Which?			No	This question was not or unclearly answered
			420	423	425		
Pesticides							
Classification	20	16	13	13	15	2[12, 13]	2[14]
Labelling	19	15	12	12	14	2[13, 15]	2[14]
Placarding workplace	8	7	6	6	7	1[15]	0
Categorization for restricted use or general use	17	13	11	10	12	2[10,13]	2[14]
Child resistant packaging	12	11	10	9	10	1[10]	0
Restricted entry interval	9	8	7	6	7	1[10]	0
Inform poison control centers for diagnostic purposes	13	9	7	5	7	2[13, 16]	2[14]
Ecological risk assessment	13	9	7	6	8	2[17, 18]	2
Other							0
Risk assessment for human health	1	0	0	0	0	1[19]	0
Endangered Species - ecological risk assessment needed for impact analysis	1	0	0	0	0	1[20]	0
Microbial pest control agents	1	0	0	0	0	1[21]	0
Biochemical pest control agents	1	0	0	0	0	1[22]	0

Table 2. Number of countries accepting any of the alternative methods for a particular purpose (cont.)

REQUIREMENTS/APPLICATION AREA	No. of countries responded	Would any of the alternative methods suffice?					
		Yes	Which?			No	This question was not or unclearly answered
			420	423	425		
Pesticides (cont.)							
Other (cont.)							
Range-finding for repeat dose, in vivo mutagenicity, and acute mammalian neurotoxicity studies	1		0	0	0	1[23]	0
Consumer products							
Classification	15	13	13	13	13	0	2[24]
Labelling	15	12	12	12	12	1[25]	2[24]
Precautionary measures for emergencies	12	10	10	9	9	1[26]	1
Child resistant packaging/labelling	12	10	10	10	10	1[27]	1[28]
Identification of hazardous ingredient which meets cut off points	12	10	10	10	10	0	2[29]
Risk assessment for exemptions of other actions	10	9	9	8	8	1[30]	0
Special consumer products:							
cosmetics	10	9	8	7	8	0	1
medical devices	6	6	6	5	5	0	0
food additives	10	9	7	6	8	0	1
Pharmaceuticals							
Classification	8	5	4	4	4	1[31]	2[32]
Labelling	7	6	5	5	5	0	1
Specific pharmaceuticals:	6	5	5	3	4	0	1

Table 2. Number of countries accepting any of the alternative methods for a particular purpose (cont.)

REQUIREMENTS/ APPLICATION AREA	No. of countries responded	Would any of the alternative methods suffice?					
		Yes	Which?			No	This question was not or unclearly answered
			420	423	425		
Pharmaceuticals (cont.)							
Anticancer	15	10	8	6	9	2[31, 33]	3
Imaging agents	14	9	8	5	7	2[31, 33]	3
Specific application:	5	4	4	2	3	0	1
Drugs for single dose administration	14	9	7	5	6	2[31, 33]	3
Other:							
Highly toxic pharm.	1	1	1	1	1	0	0
Preclinical safety assessment	1	1	1	1	1	0	0
Drugs for multiple administration	1	1	0	0	1	0	0
Industrial chemicals							
Classification	16	15	15	14	15	0	1
Labelling	15	14	14	13	14	0	1
Supply and use	11	11	11	11	11	0	0
Other:							
Toxicity assessment	1	0	0	0	0	0	1
Data needs under TSCA, including section 5 Significant New Use Rules and Section 4 test rules	1	1	0	0	1	0	0

Table 2. Number of countries accepting any of the alternative methods for a particular purpose (cont.)

REQUIREMENTS/ APPLICATION AREA	No. of countries responded	Would any of the alternative methods suffice?					
		Yes	Which?			No	This question was not or unclearly answered
			420	423	425		
Industrial chemicals (cont.)							
Community right to know - emergency response provisions	4	1	1	1	1	1[10]	2
Determine doses for repeat dose studies	6	6	4	4	5	0	0
Pesticides for public health use	1	1	0	0	1	0	0
Hazardous waste Hazardous leachetes	1	1	0	1	0	0	0

Table 3: Number of countries out of a total number of countries requiring the respective data elements for each of the chemical use areas

REQUIREMENTS / APPLICATION AREA	No. of countries responded	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50[34]	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which?				Rationale/ Justification for requiring conventional acute Test (401)
						2000	5000				Yes/ No	420	423	425	
Workplace [1, 2]															
Classification	19	17	3			13	1	14		11	17/1	16	17	16	1
Labelling	18	17	3			10	1	11		8	16/1	15	16	15	1
Safety data sheet	15	13	3	1		7	1	11		7	13/1	12	12	13	1
Chemical specific standards	7	7				2	1	5		5	7/0	7	7	7	
Other															
IDLH (Immediately Dangerous to Life and Health	1		1	1	1	1		1	1	1	0/1				1
Transport [3]															
Classification	10	8	4			4	2	2		2	8/1	7	7	8	1
Labelling	10	8	3			4	1	2		2	8/1	7	7	8	1
Packing groups	8	7	1			4	1	3		2	6/1	6	6	6	1
Emergency response information and steps	7	4	1			3	1	5		4	5/1	5	4	4	1
Classification to initiate training	5	5	1			3	1	1		1	4/1	4	4	4	1
Regulated material provisions on the vehicle and driver	3	2	1			3		2		1	2/1	2	2	2	1

Table 3: Number of countries out of a total number of countries requiring the respective data elements for each of the chemical use areas (cont.)

REQUIREMENTS / APPLICATION	No. of countries responded	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which?				Rationale/ Justification for requiring conventional acute Test (401)
						2000	5000				Yes / No	420	423	425	
Pesticides [4]															
Classification	20	14	7	2	1	14	4	15		12	16/2	13	13	14	2
Labelling	19	11	7	1		10	4	12		9	15/2	12	12	14	2
Placarding workplace	8	8	2		1	2	2	4	1	4	7/1	6	6	7	1
Categorization for restricted use or general use	17	13	5	1		11	2	11		9	13/2	11	10	12	2
Child resistant packaging	12	9	2	1		9		9		6	11/1	10	9	10	1
Restricted entry interval	9	10	1			7	1	8		6	8/1	7	6	7	1
Inform poison control centers for diagnostic purposes	13	8	5	2	1	6	3	11	1	7	9/2	7	5	7	2
Ecological risk assessment	13	10	6	3	3	7	1	6	2	7	9/2	7	6	8	1
Other															
Risk assessment for human health	1		1	1	1		1	1	1	1	0/1				1
Endangered Species - ecological risk assessment needed for impact analysis	1		1	1	1	1			1	1	0/1				1
Microbial pest control agents	1		1	1				1		1	0/1				1
Biochemical pest control agents	1		1	1	1		1	1	1	1	0/1				1

Table 3: Number of countries out of a total number of countries requiring the respective data elements for each of the chemical use areas (cont.)

REQUIREMENTS/ APPLICATION AREA	No. of countries responded	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which?				Rationale/ Justification for requiring conventional acute Test (401)
						2000	5000				Yes / No	420	423	425	
Pesticides[4] (cont.)															
Other (cont.)															
Range-finding for repeat dose, in vivo mutagenicity, and acute mammalian neurotoxicity studies	1		1	1	1		1	1							1
Consumer products															
Classification	15	13	2			10	2	12		8	13/0	13	13	13	
Labelling	15	13	3	1		9	3	11		7	12/1	12	12	12	1
Precautionary measures for emergencies	12	10	2	1		6	2	9	1	6	10/1	10	9	9	1
Child resistant packaging/ labelling	12	12	1	1		7	3	9		6	10/1	10	10	10	1
Identification of hazardous ingredient which meets cut off points	12	8	3			6	2	8		6	10/0	10	10	10	
Risk assessment for exemptions of other actions	10	8	2	1	1	5	2	6		6	9/1	9	8	8	1
Special consumer products:															
cosmetics	10	8	2			5	1	8		5	9/0	8	7	8	
medical devices	6	6				5	1	4		3	6/0	6	5	5	
food additives	10	7	3	1		4	1	7		6	9/0	7	6	8	

Table 3: Number of countries out of a total number of countries requiring the respective data elements for each of the chemical use areas (cont.)

REQUIREMENTS / APPLICATION AREA	No. of countries responded	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which?				Rationale/ Justification for requiring conventional acute Test (401)
						2000	5000				Yes / No	420	423	425	
Pharmaceuticals [6,7]															
Classification	8	4	4		1	5		6		6	5/1	4	4	4	1
Labelling	7	3	3		1	3		5		5	6/0	5	5	5	
Specific pharmaceuticals:	6	3	2		1	2		6	1	3	5/0	5	3	4	
Anticancer	15	7	6	3	4	5		14	5	13	10/2	8	6	9	2
Imaging agents	14	7	5	3	4	4		13	4	13	9/2	8	5	7	2
Specific application:	5	2	2		1	2		5	1	3	4/0	4	2	3	
Drugs for single dose administration	12	7	4	2	4	4		13	4	12	9/2	7	5	6	2
Other:															
Highly toxic pharm.	1	1				1		1		1	1/0	1	1	1	
Preclinical safety assessment	1	1	1		1			1		1	1/0	1	1	1	
Drugs for multiple administration	1				1			1		1	1/0			1	
Industrial chemicals															
Classification	16	15	2		1	11	1	13		10	15/0	15	14	15	
Labelling	15	14	2			9	1	11		8	14/0	14	13	14	
Supply and use	11	11			1	6	1	9		7	11/0	11	11	11	
Other:															
Toxicity assessment	1	1			1	1		1		1					

Table 3: Number of countries out of a total number of countries requiring the respective data elements for each of the chemical use areas (cont.)

REQUIREMENTS/ APPLICATION	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which?				Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000				Yes / No	420	423	425	
Industrial Chemicals (cont.)														
Data needs under TSCA, including section 5 Significant New Use Rules and Section 4 test rules	1	1			1					1/0			1	
Community right to know - emergency response provisions	4	1			2	1	2		1	1/1	1	1	1	1
Determine doses for repeat dose studies	6	1	1	1	2	1	5	1	5	6/0	4	4	5	1
Pesticides for public health use	1	1	1			1				1/0			1	
Hazardous waste Hazardous leachetes	1					1			*1*	1/0		1		

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Workplace [1, 2]											
Classification No. of countries responded: 19 *(AUS, BE, CA, CH, DK, FI, FR, GER, HUN, IR, IT, NL, NZ, NO, PL, SE, UK, USA, SLO)*	AUS, BE, CA, CH, DK, FI, FR, GER, HUN, IR,, NL, NZ, NO, PL, SE, UK[35], USA	IT, USA, SLO			AUS, BE, CH, DK, FI FR, GER, IR, NL, NZ NO, SE USA	HUN	AUS, BE CH, DK, FI, FR, GER, IR, IT, NO, NZ, PL, SE, UK, SLO		AUS, BE, CH, DK, FI, FR, IT, NZ, NO, SE, UK	**Any** of the above: AUS, CA[36], CH, DK, FI[37], FR, GER[38], HUN, IR, NL, NZ, NO[39], PL, SE, UK **423/425:** IT **420/423:** BE **None:** USA **No answer**: SLO	USA[40]
Labelling No. of countries responded: *18* *(AUS, BE, CA, CH, DK, FI, FR, GER, HUN, IR, IT, NL, NZ, NO, PL, UK, USA, SLO)*	AUS, BE CA, CH, DK, FI, FR, GER, HUN, IR, NL, NZ, NO, PL, UK[35], USA	IT, USA, SLO			BE, DK, FI, FR, GER, IR, NL, NO, NZ USA	HUN	AUS, BE, DK, FI, FR, GER, IR, IT, NZ, PL, UK, SLO		AUS, BE, DK, FI, FR, IT, NZ, UK	**Any** of the above: AUS, CA[36], CH, DK, FI[37], FR, GER[38], HUN, IR, NL, NZ, NO[39], PL, UK **423/425:** IT **420/423:** BE **None:** USA **No answer:** SLO	USA[40]
Safety data sheet No. of countries responded: 15*(AUS, CA, CH, FI, FR, GER, HUN, IR, NL, NZ, NO, PL, UK, USA, SLO)*	AUS, CA, CH, FI, FR, GER, IR, NL, NZ, NO, PL, UK[35], USA	HUN, USA, SLO	HUN		FI, FR GER, IR, NO, NZ USA	HUN	AUS, CA, FI, FR, GER, IR, NL, NZ, NO, PL, UK, SLO		AUS, FI, FR NL, NZ NO, UK	**Any** of the above: AUS, CA[36], CH, FI[37],FR, GER[38], IR, NL, NZ, NO[39], PL, UK **425:** HUN **None:** USA **No answer**: SLO	USA[40]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are Required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Workplace[1,2] (cont.)											
Chemical specific standards No. of countries responded: 7 *(CH, FI, GER, HUN, NL, NO, UK)*	CH, FI, GER, HUN, NL, NO, UK[35]				FI, NO	HUN	FI, GER, HUN, NO, UK		FI, GER HUN, NO, UK	**Any** of the above: CH, FI[37], GER[38], HUN, NL, NO[39], UK	
Other											
IDLH (Immediately Dangerous to Life and Health0		USA	USA	USA	USA		USA	USA	USA	**None:** USA	USA[41]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are Required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Transport[3]											
Classification *No. of countries responded: 10 (AT, FI, GER, HUN, IR, IT, NL, PL, UK, USA)*	FI, GER, HUN, IR, NL, PL, UK, USA[42]	AT[43], IT, PL, USA			FI, GER, NL USA	HUN IR	FI, UK		FI, UK	**Any** of the above: FI[37], GER[38], HUN, IR, IT, NL, UK **425: PL**[44] **None:** USA **No answer:** AT	USA[40]
			AT[43]	A[43]T	AT[43]						
Labelling *No. of countries responded: 10* *(AT, FI, GER, HUN, IR, IT, NL, PL, UK, USA)*	FI, GER HUN, IR, NL, PL, UK, USA[42]	IT, PL, USA			FI, GER, NL USA	HUN	FI, UK		FI, UK	**Any** of the above: FI[37], GER[38], HUN, IR, IT, NL, UK **425:** PL[44]None**: USA** **No answer**: AT	USA[40]
		AT[43]	AT[43]	AT[43]	AT[43]						
Packing groups *No. of countries responded: 8* *(AT, FI, GER, HUN, IR, NL, UK, USA)*	FI, GER, HUN, IR, NL, UK, USA[42]	USA			FI, GER, NL USA	HUN	FI, UK, SLO		FI, UK	**Any** of the above: FI[37], GER[38], HUN, IR, NL, UK **None:** USA No answer: **AT**	USA[40]
		AT[43]	AT[43]	AT[43]	AT[43]						
Emergency response information and steps *No. of countries responded: 7 (AT, FI, GER, HUN, NL, UK, USA)*	FI, HUN, UK, USA[42]	USA			FI, NL USA	HUN	FI, GER, NL, UK, SLO		FI, GER, NL, UK	**Any** of the above: FI[37], GER, HUN, UK **420:** NL **None:** USA **No answer**: AT	USA[40]
		AT[43]	AT[43]	AT[43]	AT[43]						

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Transport[3] (cont.)											
Classification to initiate training *No. of countries responded: 5 (FI, GER, HUN, NL, USA)*	FI, GER, HUN, NL, USA[42]	USA			FI, NL USA	HUN	FI		FI	**Any** of the above: FI[37], GER, HUN, NL **None:** USA	USA[40]
Regulated material provisions on the vehicle and driver *No. of countries responded: 3 (FI, NL, USA)*	NL, USA[42]	USA AT[43]	AT[43]	AT[43]	FI, NL USA AT[43]		FI, SLO		FI	**Any** of the above: FI[37], NL **None:** USA **No answer:** AT	USA[40]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Pesticides[4]											
Classification No. of countries responded: 20 *(AUS, AT, BE, CA, CH, DK, FI, GER, HUN, IR, IT, JP, NL, NZ, NO, PL, SE, UK, US, SLO)*	AUS, AT, CA[45], CH, DK, FI, GER, IR, HUN, NL, NZ, SE UK, USA[46]	CA[45], IT[47] JP, NO, PL, USA, SLO	CA[48], USA	USA[49]	AUS AT, BE CA, CH, DK FI, GER IR, NL, NO, PL, UK, SE	HUN, JP, NZ, USA	AUS, AT, BE, CA[50], CH, DK, FI, IR, IT, NO, NZ, SE, UK, USA, SLO		AT, BE CA, CH, FI, IR, NO, NZ, PL, SE, UK, USA	**Any** of the above: AUS, AT, BE, CA[51], CH, FI, GER[38], IR, HUN, NL, SE, UK **420:** DK **425:** NO, PL[52] **423/425:** IT **None:** JP, USA **No answer**: SLO NZ[55]	JP[53], USA[54]
Labelling No. of countries responded: 19 *(AUS, AT, BE, CA, CH, DK, FI, GER, HUN, IR, IT, JP, NL, NZ, NO, PL, UK, US, SLO)*	AUS, AT, CA[45], CH, DK, FI, GER, IR, HUN, NL, NZ, UK USA	CA[45], IT, JP, NO, PL, USA, SLO	CA[48]		AUS, AT, BE, CA, CH, DK, FI, GER, IR, PL UK	HUN JP NZ USA	AUS, AT, BE, CA[50], CH, DK, FI, IR, IT, NZ, UK USA SLO		AT, BE, CA, CH, FI, IR, NZ, PL, UK, USA	**Any** of the above: AUS, AT, BE, CA[51], CH, FI, GER[38], IR, HUN, NL, UK **420:** DK **423/425**: IT **425:** NO, PL[52] **None:** JP, USA **No answer**: SLO NZ[55]	JP[53], USA[56]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if patholog y (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Pesticides[4] (cont.)											
Placarding workplace No. of countries responded: 8 *(AT, CH, FI, GER, HUN, NL, NO, USA)*	AT, CH, DK, FI, HUN, JP, NL, USA	NO, USA			CH, FI	HUN USA	CH, FI, GER, USA[57]	GER	AT, CH, FI, USA	**Any** of the above: AT, CH, FI, GER[38], HUN, NL **425:** NO **None:** USA	USA[56]
Categorization for restricted use or general use *No. of countries responded: 17* *(AUS, AT, CA, CH, DK, FI, GER, HUN, IR, JP, NL, NZ, NO, PL, UK, US, SLO)*	AUS, AT CA[45], CH, DK, FI, GER, HUN, IR, NL, NZ, UK, USA	CA[45], JP, NO, PL, SLO	CA[48]		AUS, AT, CA, CH, DK, FI, IR, NL, PL, UK USA	HUN NZ	AUS, AT, CA[50], CH, DK, FI, IR, NZ, PL, UK, USA		AT, CA, CH, FI, IR, NZ, PL, UK, USA	**Any** of the above: AUS, AT, CA[51], CH, FI, GER, HUN, IR, NL, UK **420:** DK **425:** NO, PL[52] **None:** JP, USA **No answer:** SLO NZ[55]	JP[53], USA[40]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Pesticides [4] (cont.)											
Restricted entry interval *No. of countries responded: 9* *(AT, CH, DK, FI, GER, HUN, IR, NO, USA)*	AT, CH, DK, FI, GER, IR, HUN, NL, UK, USA	NO			AT, CH, DK, FI, IR, UK, USA	HUN	AT, CH, DK, FI, GER, IR, UK, USA		AT, CH, FI, IR, UK, USA	**Any** of the above: CH, FI, GER, HUN, IR, UK **420:** DK **425:** NO **None:** USA	USA[40]
Inform poison control centers for diagnostic purposes No. of countries responded: 13 *(AUS, AT, CH, DK, FI, HUN, JP, NL, NZ, NO, UK, USA, SLO)*	AUS, AT CH, DK, FI, NL, NZ, UK	HUN, JP NO, USA SLO	HUN, USA	USA	AUS, AT, CH DK, FI, UK	HUN NZ USA	AUS, AT, CH, DK, FI, HUN, NL, NZ, UK, USA, SLO	USA	AT, CH, FI, NL, NZ, UK, USA	**Any** of the above: AUS, AT, CH, FI, UK **420:** DK, NL **425:** HUN, NO **None:** JP, USA **No answer:** SLO NZ[55]	JP[53], USA[58]
Ecological risk assessment *No. of countries responded: 13* *(AT, CA, CH, DK, FI, GER, HUN, NL, NZ, PL, UK, USA, SLO)*	AT, CA[59], CH, DK, FI, GER, HUN, NL[60], NZ, UK	CA[59], NL NO, PL USA, SLO	CA[48], NL USA	CA[61], NL, USA	AT, CA, CH DK, FI, NL, USA NZ[68]		AT, CA, CH, FI, NL, UK, SLO	CA[62], USA	AT, CA[63], CH, FI, NL, PL, UK	**Any** of the above: AT, CH, FI, GER, HUN, UK **420:** DK **425:** CA[64], PL[65] **None:** NL[66], USA **No answer:** NZ, SLO	USA[67]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Pesticides [4] (cont.)											
Other[69]											
Risk assessment for human health		USA	USA	USA		USA	USA	USA	USA	**None:** USA	USA[70]
Endangered Species - ecological risk assessment needed for impact analysis		USA	USA	USA	USA			USA	USA	**None:** USA	USA[71]
Microbial pest control agents		USA	USA			USA	USA		USA	**None:** USA	USA[72]
Biochemical pest control agents		USA	USA	USA		USA	USA	USA	USA	**None:** USA	USA[73]
Range-finding for repeat dose, in vivo mutagenicity, and acute mammalian neurotoxicity studies		USA	USA	USA			USA				USA[74]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Consumer products											
Classification *No. of countries responded: 15 (AUS, AT, CH, DK, FI, GER, HUN, IT, NL, NZ, NO, PL, SE, UK, SLO)*	AUS, AT, CH, DK, FI, GER, HUN, NL, NZ, NO, PL, SE, UK	IT, SLO			AUS, AT, CH, DK, FI, GER, NL, NO, SE[75], UK	HUN, NZ	AUS, AT, CH, DK, FI, IT, NZ, NO, PL, SE, UK, SLO		AT, CH, DK, FI, IT, NZ, NO, SE	**Any** of the above: AUS, AT, CH, DK, FI[37], GER[38], HUN, IT, NL, NO[39], PL, SE, UK **No answer:** SLO	
Labelling No. of countries responded: 15*(AUS, AT, CH, DK, FI, GER, HUN, IT, NL, NZ, NO, PL, UK, USA, SLO)*	AUS, AT, CH, DK, FI, GER, HUN, NL, NZ, NO, PL, UK, USA	IT, USA, SLO	USA		AUS, AT, CH, DK, FI, GER, NL, NO, UK	HUN, NZ, USA	AUS, AT, CH, DK, FI, IT, NZ, PL, UK, USA, SLO		AT, CH, DK, FI, IT, NZ, USA	**Any** of the above: AUS, AT, CH, DK, FI[37], GER[38], HUN, IT, NL, NO[39], PL, UK **None:** USA **No answer:** SLO	USA[76]
Precautionary measures for emergencies *No. of countries responded: 12 (AUS, AT, CH, DK, FI, GER, HUN, NL, NO, UK, USA, SLO)*	AUS, AT, CH, FI, GER, HUN, NL, NO, UK, USA	USA, SLO	USA		AUS, AT, CH, FI, NL, NO	HUN, USA	AUS, AT, CH, FI, NL, NO, UK, USA, SLO	USA	AT, CH, FI, NL, NO, USA	**Any** of the above: AUS, AT, CH, DK, FI[37], GER[38], HUN, NO[39], UK **420:** NL **None:** USA **No answer**: SLO	USA[77]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Consumer products (cont.)											
Child resistant packaging/labelling *No. of countries responded: 12 (AUS, AT, CH, DK, FI, GER, HUN, NL, NZ, NO, UK, USA)*	AUS, AT, CH, DK, FI, GER, HUN, NL, NZ, NO, UK, USA	USA	USA		AUS, AT, CH, FI, NL, NO, UK	HUN, NZ, USA	AUS, AT, CH, DK, FI, NZ, NO, UK, USA		AT, CH, FI, NZ, NO, USA	**Any** of the above: AUS, AT, CH, DK, FI[37], GER[38], HUN, NL, NO[39], UK **None:** USA NZ **Error! Bookmark not defined.**	USA[78]
Identification of hazardous ingredient which meets cut off points *No. of countries responded: 12 (AUS, AT, CH, FI, HUN, IT, NL, NZ, NO, PL, UK, SLO)*	AUS, AT, FI, HUN, NL, NZ, NO, UK	IT, PL, SLO			AUS, AT, CH, FI, NL, UK	HUN, NZ	AUS, AT, CH, FI, IT, NO, UK, SLO		AT, CH, FI, IT, NZ, NO	**Any** of the above: AUS, AT, CH, FI, HUN, IT, NL, NO[39], PL, UK **No answer:** SLO	
Risk assessment for exemptions of other actions *No. of countries responded: 10 (AUS, AT, CH, FI, GER, HUN, IT, NL, NO, USA)*	AUS, AT, FI, GER, HUN, IT, NL, NO	IT, USA	USA	USA	AUS, AT, CH, FI, NL	HUN, USA	AT, CH, FI, NL, NO, USA		AT, CH, FI, NL, NO, USA	**Any** of the above: AUS, AT, CH, FI, GER[38], HUN, IT, NO[39] **420:** NL **None:** USA	USA[79]

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Consumer products (cont.)											
Special consumer products											
• **cosmetics** No. of countries responded: 10 *(AUS, AT, FI, GER, HUN, NL, PL, SE, UK, SLO)*	AUS, AT, FI, GER, HUN, NL, SE, UK[80]	PL, SLO			AUS, AT, FI, NL, UK SE[82]	HUN	AUS, AT, FI, GER, NL, PL, UK, SLO SE[82]		AT, FI, GER, NL, PL SE[82]	**Any** of the above: AUS, AT, FI, GER[38], HUN, SE, UK **420:** NL **425:** PL[81] **No answer:** SLO	
• **medical devices** *No. of countries responded: 6* *(AUS, AT, FI, HUN, NL, UK)*	AUS, AT, FI, HUN, NL, UK[80]				AUS, AT, FI, NL UK	HUN	AT, FI, NL, UK		AT, FI, NL	**Any** of the above: AUS, AT, FI, HUN, UK **420:** NL	
• **food additives** *No. of countries responded: 10* *(AUS, AT, FI, GER, HUN, NL, PL, SE, UK, SLO)*	AUS, AT, FI, GER, NL, SE, UK[80]	HUN, PL, SLO	HUN		AUS, AT, FI, NL, UK	HUN	FI, HUN, NL, PL, SE, UK, SLO		AT, FI, GER, NL, PL, SE	**Any** of the above: AUS, AT, FI, GER, SE, UK **420:** NL **425:** HUN, PL[81] **No answer:** SLO	

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because they did not clearly respond to the question)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Pharmaceuticals[6,7]											
ClassificationNo. of countries responded: 8*(AUS, AT, FR, FI, HUN, NZ, P, SLO)*	AUS, AT, HUN, NZ	FI, FR, PL, SLO IT[87]		NZ	AUS, AT[83], FI, FR, NZ		AUS, AT, FI, FR, PL		AUS, AT, FI, FR, NZ, PL	**Any** of the above: AUS, FI[37], PL **420/425:** NZ[84] **423:** HUN **None:** AT[85] **No answer:** FR, SLO	FR[86]
Labelling No. of countries responded: 7*(AUS, DK, FI, HUN, NZ, PL, SLO)*	AUS, HUN, NZ	FI, PL, SLO		NZ	AUS, FI, NZ		AUS, DK, FI, PL		AUS, DK, FI, NZ, PL	**Any** of the above: AUS, DK, FI[37], PL **420/425:** NZ[84] **423:** HUN **No answer:** SLO	
Specific pharmaceuticals *No. of countries responded: 6* *(DK, FI, IT, NZ, SE, SLO)*	IT, NZ, SE	FI, SLO		NZ	FI, NZ		DK, FI, IT, SE, SLO	IT	IT, NZ, SE	**Any** of the above: DK, FI[37], SE **420:** IT, NZ[84] **425:** NZ[84] **No answer:** SLO	

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because the information they provided was unclear)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Pharmaceuticals [6,7] (cont.)											
• **anticancer** No. of countries responded: 15 *(AUS, AT, CA, DK, FR, FI, GER, HUN, IR, IT, NL, NZ, SE, USA, SLO)*	AUS, AT, GER, IT, NL, NZ, SE[88, 89]	FI, FR, HUN, IR[90], SE[88,89], SLO	FR, IR[91], USA	IR, NZ, SE[92], USA	AUS, AT[83], FI, GER[93], NZ USA[95]		AUS, AT, CA, DK, FI, FR, GER, IR, IT, NL, SE USA, SLO,	CA, FR, HUN, IT, USA NL[96]	AUS, AT, CA, DK, FI, FR, GER, IR, IT, NL, NZ, SE, USA	**Any** of the above: AUS, DK, FI[37], SE GER[38], NL[96] **420:** IT, NZ[84] **425:** HUN, IR, NZ[84] **None:** AT[85], USA **No answer**: CA, FR, SLO	FR[86], USA[94]
• **imaging agents** *No. of countries responded: 14* *(AUS, AT, CA, DK, FR, FI, HUN, IR, IT, NL, NZ, SE, USA, SLO)*	AUS, AT, HUN, IT, NL, NZ, SE[88]	FI, FR, IR[90], SE[88], SLO	FR, IR[91], USA	IR, NZ, SE[92], USA	AUS, AT[83], FI, NZ USA[95]		AUS, AT, CA, DK, FI, FR, IR, IT, NL, SE, USA, SLO	CA, HUN, IT, USA NL[96]	AUS, AT, CA, DK, FI, FR, IR, IT, NL, NZ, SE, USA	**Any** of the above: AUS, DK, FI[37], NL[96], SE **420:** HUN, IT, NZ[84] **425:** IR, NZ[84] **None:** AT[85], USA **No answer:** CA, FR, SLO	FR[86], USA[94]
Specific application: *No. of countries responded: 5* *(DK, FI, IT, NZ, SLO)*	IT, NZ	FI, SLO		NZ	FI, NZ		DK, FI, IT, SLO	IT	FI, IT, NZ	**Any** of the above: DK, FI[37] **420:** IT, NZ[84] **425:** NZ[84] **No answer:** SLO	

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because the information they provided was unclear)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423, 425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Pharmaceuticals [6,7](cont.)											
drugs for single dose administration No. of countries responded: 14 *(AUS, AT, CA, DK, FR, FI, HU, IR, IT, NL, NZ, SE, USA, SLO)*	AUS, AT, HUN, IT, NL, NZ, SE[88]	FI, FR, SE[88], SLO	FR, USA[97]	IR, NZ, SE[92], USA[97]	AUS, AT[83], FI, NZ USA[95]		AUS, AT, CA, DK, FI, FR, IR, IT, NL, SE, USA, SLO	CA, HUN, IT, USA NL[96]	AUS, AT, CA, DK, FI, FR, IR, IT, NL, NZ, SE, USA	**Any** of the above: AUS, DK, FI[37], SE **420:** IT, NL[96], NZ[84] **423:** HUN **425:** IR, NZ[84] **None:** AT[85], USA **No answer:** CA, FR, SLO	FR[86], USA[94]
Other[98]:											
Highly toxic pharm.	GER				GER [93]		GER		GER	***Any** of the above: GER[38]*	
Preclinical safety assessment	SE[88]	SE[88]		SE[92]			SE		SE	***Any** of the above: SE*	
Drugs for multiple administration				IR (preferred)			IR		IR	***425:** IR*	

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because the information they provided was unclear)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423,425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Industrial chemicals											
Classification No. of countries responded: 16 *(AUS, AT, CH, DK, FI, GER, HUN, IR, IT, NL, NZ, NO, PL, SE, UK, SLO)*	AUS, AT, CH, DK, FI, GER, HUN, IR, IT, NL, NZ, NO, PL, SE, UK	IT, SLO		IR[99]	AUS, AT, CH, DK, FI, GER, IR, NL, NZ, NO, SE	HUN	AUS, AT, CH, DK, FI, IR, IT, NZ, NO, PL, SE, UK, SLO		AUS, AT, CH, DK, FI, IT, NZ, NO, SE, UK	**Any** of the above: AUS, AT, CH, DK, FI[37], GER[38], HUN, IR, NL, NZ, NO[39], PL, SE, UK **420/425:** IT **No answer:** SLO	
Labelling No. of countries responded: 15 *(AUS, AT, CH, DK, FI, GER, HUN, IR, IT, NL, NZ, NO, PL, UK, SLO)*	AUS, AT, CH, DK, FI, GER, HUN, IR, IT, NL, NZ, NO, PL, UK	IT, SLO			AUS, AT, CH, DK, FI, GER, NL, NZ, NO	HUN	AUS, AT, CH, DK, FI, IR, IT, NZ, PL, UK, SLO		AUS, AT, CH, DK, FI, IT, NZ, UK	**Any** of the above: AUS, AT, CH, DK, FI[37], GER[38], HUN, IR, NL, NZ, NO[39], PL, UK **420/425:** IT **No answer:** SLO	
Supply and use No. of countries responded: 11 *(AUS, AT, CH, FI, GER, HUN, IR, NL, NZ, PL, UK)*	AUS, AT, CH, FI, GER, HUN, IR, NL, NZ, PL, UK			GER	AUS, AT, CH, FI, GER, NZ	HUN	AUS, AT, CH, FI, GER, IR, NZ, PL, UK		AUS, AT, CH, FI, GER, NZ, UK	**Any** of the above: AUS, AT, CH, FI[37], GER[38], HUN, IR, NL, NZ, PL, UK	

[1] **USA** has filled in the questionnaire for workplace (and therefore considered in the analysis) although the Occupational Safety and Health Administration does not require that studies be performed or submitted. Chemicals are classified in the work place on the basis of available toxicity data.

2 **Canada** has filled in the questionnaire for workplace (and therefore considered in the analysis) although the WHMIS (Workplace Hazard Management Information System) does not require any testing. WHMIS was designed to make the best use of existing toxicological data.

3 **Australia** did not answer the particular questions of the questionnaire but rather provided the information that the transport requirements follow the recommendations in the 10th Edition of the United Nations "Manual of Tests and Criteria". Therefore, Australia is not included in the analysis of transport application area.

4 The entries provided by UK cover biocides regulation only. However, UK has been considered in the analysis of pesticides.

5 **Italy**: only preparations

6 **UK** did not consider necessary to complete the questionnaire for pharmaceuticals because only occasionally is there a specific requirement for acute toxicity studies (Medicines Act UK, EU: 76/76/EEC). When they are required the emphasis is on signs of toxicity not lethality. There are no formal requirements for any of the OECD methods for acute oral toxicity.

7 **Norway** did not consider necessary to complete the questionnaire for pharmaceuticals but provided the information that Norway is implementing the EU legislation.

8 **Italy:** including active ingredient of pesticides.

9 Only **Poland** mentioned that military chemicals are generally classified and labelled on the basis of regulations on industrial and consumer chemicals

10 **USA**: Evaluation of alternative methods will await availability of the guidance document.

11 **USA:** IDLH's are assessed using risk assessments and involve expert judgement about total weight of evidence, including both animal and human data

12 **USA:** Risk management decisions (involving detailed acute toxicity information as noted) are needed for highly toxic active ingredients to determine risk reduction measures as conditions for registration. Formulations must be characterized up to 5000 mg/kg.

13 **Japan:** No rationale/justification provided.

14 **Slovenia** did not answer this question while NZ did not clearly answer if alternative methods would suffice for untested mixtures. The original NZ answer is: "Extrapolation from the toxicity of technical actives to their formulations is needed if data for the formulated product is not supplied. There is a need to extrapolate to find concentrations of the active ingredient at which the formulated product changes classification. Test must allow (ie. provide enough information to facilitate) these extrapolations to be done.

15 **USA:** Alternates do not provide for characterization up to 5000 mg/kg

16 **USA:** Complete quantitative and qualitative descriptions of toxicity are necessary for diagnosis and treatment of poisonings.

17 **The Netherlands:** It is not that we require the OECD 401, but information on the slope.

18 **USA:** Rats are used as surrogates for wild mammals. Dose response curve, including slope and low dose-effects information is necessary for ecological risk assessment in order to protect wildlife.

19 **USA:** Data on acute oral and dermal toxicity (slope, LD50, toxic signs, pathology) are used as part of weight of evidence with other studies,

e.g. to estimate dermal absorption. Especially important for pesticides with limited or tiered data bases (antimicrobials, biochemicals). The Food Quality Protection Act places increased emphasis on evaluation of worker and bystander risk.

20 **USA**: Alternates do not provide information about dose response needed for ecological risk assessment

21 **USA:** To save testing, microbial pesticides are subjected to combined infectivity/acute toxicity tests. Acute protocols require sufficient numbers of animals to handle variability of micro-organisms in formulations. Often, a limit test of 10 animals suffices at 5000 mg/kg. Natural product toxins such as Bt toxins are highly toxic and require slope and other acute toxicity data for risk assessment.

22 **USA:** Robust and complete acute toxicity data are required in order that human health and ecological risk assessments can be performed. With less complete acute toxicity data, additional subchronic, developmental toxicity, and ecotoxicity tests must be performed.

23 **USA**: Data on the highest non-lethal dose as determined in range-finding studies are used to establish benchmark doses.

[24] Slovenia did not answer the question while **NZ** did not clearly answer if alternative methods would suffice for untested mixtures. The original NZ answer is: Any of the new methods (420/423/425) would provide useful information for assessment of acute toxic effects of chemicals used in consumer products. However, the maximum dose regime of the new tests is 2000mg/kg of body weight, so there is the potential for lower toxicity materials not being classified using the new tests. In these circumstances it may be possible that if the 401 test had been used, some, relatively moderate, classification may have been imposed. It seems to me that this is most likely to occur with Consumer Products (rather than pesticides, therapeutic substances etc) since these substances are likely to have toxicity close to the lower end of the classification scheme. Using the new test systems a substance would be assigned an LD50 greater than 2000mg/kg, when the old method (401) may, after finding of lethality at 2000mg/kg, have carried out further testing and determined an LD50 between 2000 and 5000 mg/kg. Whether this results in a risk to the consumer depends on the attitude to the results obtained. The assumption for classification purposes will presumably be that the LD50 is greater than 2000mg/kg bwt. but some account needs to be taken of whether or not any adverse effects or lethality occurs at this dose level. The important point is that a finding of no toxic effects at the highest dose level (2000mg/kg) should not be considered to mean that the substance is without any toxic effects at all. Particularly if some, non-lethal toxicity is observed at 2000mg/kg, there is an indication of a risk to the consumer. In conclusion then, we consider the new test are useful, but some concerns on the implications for the materials which are at the lower toxicity levels".

[25] **USA:** Products must be characterized to 5000 mg/kg. LD50, slope, and confidence intervals are necessary for characterization of mixtures from data on components.

[26] **USA:** Toxic signs, dose-response curve, and pathology results are necessary to provide user guidance and directions for emergencies.

Products must be characterized to 5000 mg/kg

[27] **USA:** Products must be characterized to 5000 mg/kg.

[28] **NZ** did not clearly answer if alternative methods would suffice. The original NZ answer is provided in note 24.

[29] **Slovenia** did not answer the question if alternative methods would suffice while NZ did not answer it clearly. The original NZ answer is provided in note 14.

[30] **USA:** The LD50 value, slope, confidence interval, toxic signs, and pathology are used, to determine if further regulatory action is needed such as if product should be in a child resistant packaging, restricted for use, or banned.

[31] **Austria** did not provided any reason why the alternative methods would not suffice. On the other hand, **Austria** does not see any reason for using the "traditional' OECD 401.

[32] **Slovenia** and **France** did not answer the question if alternative methods would suffice. However, France ticked the box "Rational/Justification for requiring conventional acute Test 401" but did not provide the rationale or justification.

[33] USA: The acute toxicity dose-effect curve must be well-characterized, from NOELs or threshold toxicity, up through significant toxicity levels. Values must be characterized by confidence intervals.

34 The numbers provided under this question correspond to the total number of countries requiring a confidence level.

35 UK: Alternatively information on toxic signs as provided by OECD 420 would suffice.

36 Canada: WHMIS (Workplace Hazard Management Information System) does not require any testing. WHMIS was designed to make the best use of existing toxicological data. However, the OECD Guideline 401 is referenced in Section 46 of the Controlled Products Regulations (under the authority of the Hazardous Products Act). The deletion of this OECD Guideline will require a modification to this section of our regulations. Since the proposed methods (i.e. 420, 423, 425) allow for the calculation of an LD50 value or a range, the impact would be minimal. **However, the doses used in the guidelines cited above should be reviewed to reflect the cut-off doses used by the new harmonized classification system for acute toxicity.**

37 Finland: **Too little experience at the moment to make reliable comparative assessment for expressing** Finland's **preferences in the use of alternative OECD Guidelines.** As guidelines they are known to cover the main points of toxicity and the UP-and Down method to yield also the LD50 value. Finland trust guidance document to give more information on their use. Based on the coverage of alternative OECD guidelines, the 401 can be deleted. However, it is important that the data already produced with the OECD 401 should be valid to avoid redundant on their use.

38 Germany: Any of the method listed with preference to following order: 423/420/425

39 Norway: Any of the method listed with preference to following order: 423/425/(420)

40 USA: Evaluation of alternative methods will await availability of the guidance document.

41 USA: IDLH's are assessed using risk assessments and involve expert judgement about total weight of evidence, including both animal and human data

42 USA: for substances or actual mixture (may not be suitable for method of weighted averages)

43 Austria: LD/LC50 is required to assign those goods to class 6.1 “Toxic Substances“ which do not belong to the listed (by UN-N°) single substances or chemical families but are subject to the criteria of so called n.o.s. entries (see references below to regulatory requirements). Labelling and material provisions on the vehicle and driver follow the classification criteria. Classification criteria include assignment to packing groups. Emergency response information and steps: Do not specifically require testing as background for the information on the risks of a substance when released.

44 Poland: Polish transport regulations are in agreement with EU regulation and point estimate is required. Therefore, we would accept 425 as it provides a point estimate.

45 Canada: either point estimate data or range of lethality data are accepted - no preference; range of lethality data must fall within prescribed classification cutoff values noted in the Registration Handbook and study must be of acceptable quality.

46 USA: Prefer point estimate.

47 Italy: Pesticide preparations are classified according to Presidential Decree No. 223/1988. Active ingredients follow the same rules as for Consumer Products.

48 Canada: confidence intervals should be reported with point estimate data.

49 USA: Slope needed if highly toxic.

50 Canada: Information on toxic signs following acute dosing is considered along with other information when setting an acute reference dose.

51 Canada: Provided that range of lethality data allows for classification within prescribed classification cut-off values.

52 Poland: We would accept the 425 as it provides a point estimate of lethality which is required by the EU regulations.

53 Japan: No rationale/justification provided.

54 USA: Risk management decisions (involving detailed acute toxicity information as noted) are needed for highly toxic active ingredients) to determine risk reduction measures as conditions for registration. Formulations must be characterized up to 5000 mg/kg.

55 New Zealand: Extrapolation from the toxicity of technical actives to their formulations is needed if data for the formulated product is not supplied. There is a need to extrapolate to find concentrations of the active ingredient at which the formulated product changes classification. Test must allow (ie. provide enough information to facilitate) these extrapolations to be done.

56 USA: Alternates do not provide for characterization up to 5000 mg/kg

57 USA: If dermally toxic.

58 USA: Complete quantitative and qualitative descriptions of toxicity are necessary for diagnosis and treatment of poisonings.

59 Canada: point estimate data are currently used (and preferred) in risk assessments although there is no regulatory requirement for such; however, use of range estimates of lethality could be accommodate via use of a more conservative approach to risk assessment

60 The Netherlands: Under special circumstances a range would be sufficient, e.g. if the LD50 is greater 2000 or if the PEC is well below or above the toxicity range.

61 Canada: While details of slope are preferred, risk assessments can be performed in absence of this information (more conservative approach taken).

62 Canada: A similar value, the NOEC, is used

63 Canada: Details of significant detrimental effects only need be reported.

64 Canada: provides the preferred point estimate of lethality; the “assumed slope” is a limiting factor vis-a-vis preference for a derived slope in risk assessments.

65 Poland: In Poland data from laboratory animals generally are not used for this purpose. However, if so point estimate is helpful and would accept 425 as it provides it.

66 The Netherlands: It is not that we require the OECD 401, but information on the slope.

67 USA: Rats are used as surrogates for wild mammals. Dose response curve, including slope and low dose-effects information is necessary for ecological risk assessment in order to protect wildlife.

68 New Zealand: OECD upper cut-off

69 Austria, Japan and Norway have also checked the “other”box, however, no information of the application was provided. Therefore, their entries were not included.

70 USA: Data on acute oral and dermal toxicity (slope, LD50, toxic signs, pathology) are used as part of weight of evidence with other studies, e.g. to estimate dermal absorption. Especially important for pesticides with limited or tiered data bases (antimicrobials, biochemicals). The Food Quality Protection Act places increased emphasis on evaluation of worker and bystander risk.

71 USA: Alternates do not provide information about dose response needed for ecological risk assessment

72 USA: To save testing, microbial pesticides are subjected to combined infectivity/acute toxicity tests. Acute protocols require sufficient numbers of animals to handle variability of microorganisms in formulations. Often, a limit test of 10 animals suffices at 5000 mg/kg. Natural product toxins such as Bt toxins are highly toxic and require slope and other acute toxicity data for risk assessment.

73 USA: Robust and complete acute toxicity data are required in order that human health and ecological risk assessments can be performed. With less complete acute toxicity data, additional subchronic, developmental toxicity, and ecotoxicity tests must be performed.

74 USA: Data on the highest non-lethal dose as determined in range-finding studies are used to establish benchmark doses.

75 Sweden: Consumer products: Classification up to 5000 mg/kg, normally through extrapolation from limit dose.

76 USA: Products must be characterized to 5000 mg/kg. LD50, slope, and confidence intervals are necessary for characterization of mixtures from data on components.

77 USA: Toxic signs, dose-response curve, and pathology results are necessary to provide user guidance and directions for emergencies. Products must be characterized to 5000 mg/kg

78 USA: Products must be characterized to 5000 mg/kg.

79 USA: The LD50 value, slope, confidence interval, toxic signs, and pathology are used, to determine if further regulatory action is needed such as if product should be in a child resistant packaging, restricted for use, or banned.

80 UK: Only required in active ingredients (Cosmetics Directive 76/768/EEC).

81 Poland: No special requirement for testing methods. The law from 1939 still in force. Therefore, it depends on regulator. We would accept the 425 as it provides the point estimate.

82 Sweden: Cosmetics: Depends on the outcome of the range estimate and the expected exposure.

83 Austria: if non toxic

84 New Zealand desires for pharmaceuticals information on the slope of the curve, therefore, has a preference for use of guidelines 420 and 425, as it appears that these give an estimate of an LD50 or a minimum lethal dose more readily than 423.

85 Austria did not provided any reason why the alternative methods would not suffice. On the other hand, Austria does not see any reason for using the "traditional' OECD 401.

86 France: no rationale/justification was provided.

87 Italy: In Italy, a Ministerial Decree of July 28, 1977, requests to have LD50's (with confidence limits and slope) for new drugs never used clinically before. However, since many years, drug toxicity has been evaluated after a single oral dose, with no LD50 value reported.

88 **Sweden**: Pharmaceuticals: Quantitative evaluation of the approximate lethal dose should be obtained, but a high level of precision is not required.

89 **Sweden**: Pharmaceuticals: An assessment of those levels at which severe toxic symptoms or death occur (limit dose approach) should be performed in rodents with the administration route envisaged for clinical use.

90 **Ireland**: MTD

91 **Ireland**: the required confidence interval is 95%.

92 **Sweden**: Pharmaceuticals: Information on the dose-effect relationship should be obtained, but a high level of precision is not required.

93 **Germany**: much less than 2000

94 **USA**: The acute toxicity dose-effect curve must be well-characterized, from NOELs or threshold toxicity, up through significant toxicity levels. Values must be characterized by confidence intervals.

95 **USA**: As high as necessary to examine toxicity.

96 **Netherlands**: In general (but not legally obliged) some information concerning a LD10 value in mice is used for the design of human experiments

97 **USA**: anti-parasitics, antifungals, immunosuppressants

98 The **USA** also checked the "other" box but no information on the application was provided. Therefore, the USA was not included.

99 **Ireland**: It is useful but not necessary to know the slope of the curve for LD50 determination.

Table 4: Identification of countries requiring the respective data elements for each of the chemical use areas (cont.)

(Countries presented in a particular box under dotted line were not considered in the numbers of Table 3 because the information they provided was unclear)

REQUIREMENTS	Check box if range estimate of lethality would suffice	Check box if point estimate of lethality (LD50) would be required	Required confidence interval of LD50	Are details of the slope of the curve required?	Required upper testing limit (2000 or 5000 mg/Kg)		Check box if toxic signs should be reported	Check box if LD10, ED10 or similar values are required	Check box if pathology (Gross or Histo) should be reported	Would any of the alternative methods suffice? Which? (420, 423,425)	Rationale/ Justification for requiring conventional acute Test (401)
					2000	5000					
Industrial chemicals (cont.)											
Other[Error! Bookmark not defined.]											
Toxicity assessment	GER			GER	GER		GER		GER		
Data needs under TSCA, including section 5 Significant New Use Rules and Section 4 test rules		USA (preferred)			USA					**425:** USA (preferred)	
Community right to know - emergency response provisions	CH, HUN, NO, USA	USA			CH, USA	HUN	CH, NO		CH	**Any** of the above: CH **None:** USA **No answer:** HUN, NO	USA[40]
Determine doses for repeat dose studies	AUS, CH[100], FR, NL, NO	HUN	HUN	HUN	AUS, CH	HUN	AUS, CH, FR, HUN, NO		AUS, CH, FR, HUN, NO	**Any** of the above: AUS, CH, FR **420:** NL **423/425:** NO **425:** HUN	HUN[101]
Pesticides for public health use	HUN	HUN	HUN			HUN				**425:** HUN	
Hazardous wastes Leachetes of wastes	HUN					HUN			HUN	**423:** HUN	

Table 5: Listing of countries regulatory requirements

Country	Application area: Workplace
Australia	• National Occupational Health and Safety Commission • National Model regulations fir the Control of workplace Substances
Belgium	O.J. of EC, L110 A/53 (04.05.93) and L248/195 (30.09.96)
Canada	• WHMIS (Workplace Hazard Management Information System) • Controlled Products Regulations (under the authority of the Hazardous Products Act). Section 46.
Denmark	Directive 67/548/EEC
Finland	*Information not provided*
France	*Information not provided*
Germany	EU Regulations
Hungary	Decree 4/1997 (II.21) of the Minister of Welfare on the enforcement of the Governmental Decree 233/1996 (XII. 26) on rules concerning hazardous substances and preparations
Ireland	Directive 67/548/EEC on Classification, Packaging and labelling of Dangerous Substances
Italy	*Information not provided*
Netherlands	*Information not provided*
New Zealand	• Hazardous Substances and New Organisms Act 1996 • Health and Safety in Employment Act 1992
Norway	EU Directives
Poland	There no legal requirements for testing chemicals used in workplaces. Regulation of the Minister of Health and Social Welfare of 21 August 1997 on chemicals hazardous for the health or life (Dz. U. of 1997, No 105, item 671) comments: • the Regulation requires classification and labelling of chemicals for supply and elaboration of Safety Data Sheets for dangerous chemicals • no legal requirements for testing • the Regulation contains the provision stating that range estimate of lethality is sufficient for classification (strictly followes the Directive 93/21/EEC) • the Regulation approximates Polish law on classification, labelling and preparation of Safety Data Sheets to EU law (Directives 67/548/EEC, 88/379/EEC and 91/155/EEC)
Sweden	EU legislation
Switzerland	• Federal Law on Trade in Toxic Substances (Toxicity Law) • Order Relating to Safety Data Sheets for Toxic and Environmentally Hazardous Substances
UK	EU Directives: 67/548/EEC; 93/21/EEC; 96/54/EEC; 88/379/EEC
USA	Occupational Safety and Health Act, 1970. Hazard Communication Regulations at 19CFRPart 1910.1200.
Slovenia	Official Journal SFRJ No. 13/91

100 **Switzerland**: e.g. OECD TG 408.

[101] **Hungary:** It means that the use of TG 4O1 is to be considered, moreover, may be indicated by substances that need repeated dose toxicity studies, independently of the substances use fields. E.g., pesticide or food additive active ingredients need to the authorisation repeated dose toxicity studies. The pesticide formulations do not need repeat dose toxicity studies and in this case any of the alternative tests may be used. Regulatory requirements are the same as by "Industrial Chemicals".

Table 5: Listing of countries' regulatory requirements (cont.)

Application area: Transport	
Australia	The transport requirements follow the recommendations in the 10th Edition of the United Nations "Manual of Tests and Criteria".
Austria	International • Recommendations on the Transport of Dangerous Goods: Model Regulations, 11th revised edition (ST/SG/AC.10/1/Rev.11) ("UN- Recommendations", "Orange Book"), United Nations New York, 1999 (see in particular Chapters 2.0; 2.0.2, 2.6; 2.6.1-2.6.2, 3.1 and Appendix A) • Implementing International Agreements: IMDG-Code (Sea); ICAO T. I. (Air); RID (Rail); ADR (Road) • Implementing EC- Directives (94/55/EC, 96/49/EC) National implementation in Austria by "Federal Act on Transport of Dangerous Goods (GGBG)"
Finland	*Information not provided*
Germany	UN Transport Recommendations
Hungary	*Information not provided*
Ireland	Council Directive 94/55/EC –Transport of dangerous goods by road
Italy	Ministerial Decree of the Ministry of transport of November 4, 1996, in fulfilment of EEC Council Directive 94/55
Netherlands	*Information not provided*
Poland	Polish provisions on the transportation of dangerous goods and among them the toxic materials follow the UN and European provisions. Especially the European Agreement on Road Transport of Dangerous Goods comments: "in the future Polish provisions will adopt EU provisions on road transport of dangerous goods with EU requirements on classification and tests required"
UK	• UK Regulations: Classification and packaging of dangerous goods • EU Regulations: 67/548/EEC (Dangerous Substances Directive); 88/379/Eec (Dangerous Preparations Directive)
USA	49CFR.173.132, .133. Also, see UNCETDG Recommendations, 1997
Slovenia	Official Journal SFRJ No. 27/90

Table 5: Listing of countries' regulatory requirements (cont.)

Application area: Pesticides	
Australia	*Information not provided*
Austria	91/414/EC Pesticide Directive
Belgium	94/79/EC (21/12/94); JO L354 of 31/12/94 p.16-31
Canada	*Information not provided*
Denmark	Method B1 or B1a in Directive 92/69/EC
Germany	EU Regulations
Hungary	Decree 5/1988 (IV. 26) of the Minister of Food and Agriculture on the enforcement of the Act II of 1988 of the Parliament on plant protection
Ireland	Directive 91/414/EEC, Annex VI (Uniform principles for placing of plant protection products on the market)
Italy	• PRESIDENTIAL DECREE No. 223, of May 24, 1988. • LEGISLATIVE DECREE No. 194, of March 17, 1995, in fulfillment of EEC Directive 91/414.
Japan	*Information not provided*
Netherlands	For pesticides: EU 91/414/EC, CTB (Board for the authorization of pesticides) data requirements in framework of Dutch Pesticides Act, Risk assessment scheme.
New Zealand	• Hazardous Substances and New Organisms Act 1996 • Pesticides Act 1979 • Agricultural and Veterinary Medicines Act 1997
Norway	*Information not provided*
Poland	• Pesticides are placed on the market under the Regulation of the Minister of Agriculture and Food Economics of 12 March 1996 on detailed principles of granting authorization for placing on the market and use of plant protection products (Dz. U. of 1996, No 48, item 212) comments: – the Regulation contains the provision that LD_{50} test is required and – gross pathology is required – the Regulation does not contain provisions on child resistant packaging – toxic and very toxic plant protection products are not allowed for general use – the Regulation is based on EU requirements concerning placing of plant protection products on the market (apart of requirement of classification for toxicity in the range of 2000 mg/kg to 5000mg/kg) • There are discussions on amendments of the Regulation allowing the application of range estimate of lethality (alternative methods) for classification and labelling of pesticides - the EU provisions will be strictly followed
Sweden	EU Directive 91/414/EC
Switzerland	Toxicity Law
UK	*Information not provided*
USA	• Federal Insecticide, Fungicide and Rodenticide Act • Endangered Species Act
Slovenia	*Information not provided*

Table 5: Listing of countries' regulatory requirements (cont.)

Application area: Consumer products	
Australia	*Information not provided*
Austria	95/2/EEC Food Add. Directive; 76/768/EEC Cosm. Directive
Denmark	Directive 67/548/EEC
Germany	EU Regulations
Hungary	Decree 4/1997 (II.21) of the Minister of Welfare on the enforcement of the Governmental Decree 233/1996 (XII. 26) on rules concerning hazardous substances and preparations
Italy	• LEGISLATIVE DECREE of July 16, 1998, in acknowledgment of EEC Directive 88/379. • LEGISLATIVE DECREE of February 2, 1997, no. 52, in acknowledgment of EEC Directive 92/32. • MINISTERIAL DECREE of April 28, 1997. Technical Annexes, 22nd adjustment.
Netherlands	*Information not provided*
New Zealand	Food Act 1981; Consumer Guarantees Act 1993; Far Trading Act 1986
Poland	• Placing on the market of chemicals for general use is regulated by the Regulation of the Minister of Health and Social Welfare of 21 August 1997 on chemicals hazardous for the health or life (Dz. U. of 1997, No 105, item 671) comments: – the Regulation requires classification and labelling of chemicals for supply; – no legal requirements for testing – the Regulation contains the provision stating that range estimate of lethality is sufficient for classification (strictly followes the Directive 93/21/EEC) – the Regulation approximates Polish law on classification, labelling and preparation of Safety Data Sheets to EU law (Directives 67/548/EEC, 88/379/EEC and 91/155/EEC) – the Regulation does not introduce the EU provisions on notification of new chemicals • Cosmetics are placed on the market under the Regulation of the Minister of Social Welfare in agreement with the Minister of Industry and Trade of 18 January 1939 on supervision of manufacturing and marketing of cosmetics (Dz. U. of 1939 No 13, item 72) comments: – the Regulation requires certificates for cosmetics – LD_{50} test is required by the certifying institution – in the future the EU requirements for placing cosmetics on the market will be strictly followed • Food additives are placed on the market under the Regulation of the Minister of Health and Social Welfare of 17 December 1973 on authorization granted for production, placing on the market and importation of some food materials (Dz. U. of 1973 No 51, item 293) comments: – the Regulation requires authorization for new food additives – scope of testing is left for institution granting authorization – at present the LD_{50} point estimate is required – in the future the requirements will strictly follow the EU law on food additives
Sweden	• KIFS 1994:12 corresponding to EU directives 67/548 and 88/379. • Cosmetics: EU directive 76/768 • Besides the above EU regulations, Sweden has a national derogation concerning the endpoint acute oral toxicity: An additional category of danger "moderately harmful" covers certain preparations which do not fulfil the criteria for classification as "harmful".
Switzerland	Toxicity Law

Table 5: Listing of countries' regulatory requirements (cont.)

Application area: Consumer products (cont.)	
UK	EU Directives: • 88/379/EEC (Dangerous Preparations Directive); • 67/548/EEC (Dangerous Substances Directive); • 98/8/EEC (Biocides Directive); • 76/768/EEC (Cosmetics Directive)
USA	Federal Hazardous Substances Act, 16CFR Part 1500.3(b) and (c)
Application area: Pharmaceuticals	
Australia	*Information not provided*
Austria	EU Directive, 75/318/EEC
Canada	*Information not provided*
Denmark	• Directive 65/65/EEC • Directive 75/318/EEC • International Conference of Harmonization (ICH) No.1
Finland	*Information not provided*
France	*Information not provided*
Germany	EU regulations
Hungary	Act XXV of 1998 of the Parliament on pharmaceuticals for human use (Enforcement of the Act is to be expected in the near future)
Ireland	Directive 75/318/EEC associated EU/CPMP notes for guidance
Italy	LEGISLATIVE DECREE No. 178 of May 29, 1991, in acknowledgment of EEC Directive
Netherlands	*Information not provided*
New Zealand	• Medicines Act 1980 • Misuse of Drugs Act 1975 • Fair Trading Act 1986
Poland	In the nearest future the requirements will strictly follow the EU law on pharmaceuticals
Sweden	• EU directive 75/38/EEC • CPMP/SWP/997/96
USA	• Good and Cosmetic Act • Anticancer drugs are in regulations at 21CFR Part 312.20
Slovenia	O.J. RS No. 9/96

Table 5: Listing of countries' regulatory requirements (cont.)

Application area: Industrial chemicals	
Australia	*Information not provided*
Austria	EU Regulations: 67/548/EEC (Subst. Directive); 793/93 Exist. Chem. Regulation
Denmark	Directive 67/548/EEC
Finland	*Information not provided*
Germany	EU regulations
Application area: Industrial chemicals (cont.)	
Hungary	Decree 4/1997 (II.21) of the Minister of Welfare on the enforcement of the Governmental Decree 233/1996 (XII. 26) on rules concerning hazardous substances and preparations
Ireland	EU Directive 67/548/EEC on Classification, Packaging and labelling of Dangerous Substances, Regs 1994; Regs 1998.
Italy	• LEGISLATIVE DECREE of July 16, 1998, in acknowledgement of EEC Directive 88/379. • LEGISLATIVE DECREE of February 2, 1997, no. 52, in acknowledgement of EEC Directive 92/32. • MINISTERIAL DECREE of April 28, 1997. Technical Annexes, 22nd adjustment.
Netherlands	*Information not provided*
New Zealand	• Hazardous Substances and New Organisms Act 1996 • Health and Safety in Employment Act 1992
Norway	Norway has implemented the different EU directives
Poland	Industrial chemicals are placed on the market under the Regulation of the Minister of Health and Social Welfare of 21 August 1997 on chemicals hazardous for the health or life (Dz. U. of 1997, No 105, item 671) comments: – the Regulation requires classification and labelling of chemicals for supply and elaboration of Safety Data Sheets for dangerous chemicals – no legal requirements for testing – the Regulation contains the provision stating that range estimate of lethality is sufficient for classification (strictly followes the Directive 93/21/EEC) – the Regulation approximates Polish law on classification, labelling and preparation of Safety Data Sheets to EU law (Directives 67/548/EEC, 88/379/EEC and 91/155/EEC) – the Regulation does not adapt in Poland the EU law on notification of new chemicals
Sweden	KIFS 1994:12 corresponding to EU Directives 67/548/EEC and 88/379/EEC
Switzerland	Toxicity Law
UK	EU Directives: 67/548/EEC; 93/21/EEC; 96/54/EEC.
USA	Toxic Substances Control Act
Slovenia	O.J. SFRJ No.13/91

Table 5: Listing of countries' regulatory requirements (cont.)

Other application area	
Australia	*Information not provided*
Hungary	• ***Pesticides for public heath use***: Decree 3/1969 (V.16) of the Minister of Health on marketing and use of insecticides, rodenticides and repellents • ***For hazardous waste:*** Governmental Decree 102/1996 (VII. 12) on hazardous waste
Switzerland	*Information not provided*
France	*Information not provided*
Norway	*Information not provided*
USA	• ***Community right to know – emergency response provisions:*** Emergency Planning and Community Right to Know Act Sections 311, 312

ANNEX 2

STATISTICAL BASIS FOR ESTIMATING ACUTE ORAL TOXICITY COMPARISON OF OECD GUIDELINES 420, 423 AND 425

INTRODUCTION

1. This document describes the statistical strengths and limitations of the various methods for accurately determining a point estimate of the LD_{50}, slope of the dose-response curve for LD_{50}, confidence limits around the point estimate of LD_{50} and the slope, a point estimate of an LD_{10} and information on the dose-effect response. In this context, a dose-response curve applies to the estimation of lethality and a dose-effect response applies to the estimation of the change in the variety and distribution of all other types of toxicological signs with the change in dose. By design not all of the guidelines will provide estimates for all of these endpoints. This document allows the reader to quickly identify the tests that will meet his or her particular needs.

2. The statistical basis for all test methods is that lethality is a quantal response. Its measurement will give rise to a frequency distribution of responses reflecting the composite tolerances of the test population upon exposure to graded doses of the test chemical. In practice, most chemicals give rise to an approximately lognormal distribution of deaths versus dose, skewed toward hypersensitivity. When this frequency population is transformed to a logarithmic abscissa, a (symmetric) normal distribution generally results that can be characterized by two parameters, the median and the standard deviation, s. The median is the dose at which 50% of the animals are killed by the test chemical and is called the LD_{50}. Not all animals will react in the same way to the chemical and thus s represents the square root of the variance of the test populations' response to the chemical. The dose-response curve is sigmoidal in nature and represents the cumulative response of the test animals to the chemical. The inflection point of this sigmoidal curve coincides with the LD_{50} for the test population.

3. What follows is a brief description of the mathematical and biological principles underlying each acute oral toxicity method followed by a listing of how each test estimates or does not estimate the specific parameters mentioned above.

FIXED DOSE PROCEDURE, GUIDELINE 420

Principles Underlying The Test Method:

4. The Fixed Dose Procedure (FDP) is a method for assessing acute oral toxicity that involves the identification of a dose level that causes evidence of non-lethal toxicity (termed *evident* toxicity) rather than a dose level that causes lethality. *Evident toxicity* is a general term describing clear signs of toxicity following administration of test substance, such that an increase to the next highest fixed dose would be expected to result in the development of severe toxic signs and probably mortality.

5. Underpinning the FDP is a belief that the toxic profile of a substance can be characterized with sufficient reliability for most regulatory situations without the need for the identification of a lethal dose. That is, observations made at non-lethal doses will allow substances to be ranked, or classified, according

to their acute toxicity, provide information to aid dose level selection for repeat dose studies and provide hazard data for use in a risk assessment. The original FDP was subject to a number of validation and comparison studies, which showed that classification outcome was similar to that based on the outcome of traditional tests for determining an LD_{50} value (1,2,3,4,5).

6. Fixed dose levels of 5, 50, 300 and 2000 mg/kg and rules for the sequential procedure were adopted following a rigorous analysis using a statistical model (6,7). The analysis predicted the classification outcome (according to the EU scheme and the lethality-based GHS), numbers of animals used and number of substance-related deaths using a number of FDP design options for substances with a range of LD_{50} values and dose response slopes for lethality. On the basis of this analysis, the design of the FDP was optimised with respect to classification performance and animal welfare.

7. The statistical modelling showed that the FDP produces classification outcomes similar to that based on the LD_{50} value for substances with a steep (greater than 2) dose response curve for mortality. For substances with a relatively shallow (less than 2) dose response curve there is an increasing probability the FDP will produce a more stringent classification than that based on the LD_{50} value; however, the risk of a less stringent classification than that based on the LD_{50} value is negligible. The influence of the choice of starting dose on the classification outcome, which can be a problem with sequential procedures, is negligible.

Point Estimate of LD_{50}:

8. The FDP is not designed to determine a point estimate of LD_{50}. However, an approximate LD_{50} range can be inferred from the classification outcome. The ability of the FDP to correctly classify (i.e. assign to an LD_{50} range) is discussed above.

Confidence Limits on the Estimate of LD_{50} Estimate of the Slope of the Lethality Dose-Response Curve and its Confidence Limits:

9. The FDP is not designed to determine a point estimate of LD_{50}, confidence limits on the estimate of the LD_{50} or an estimate of the slope of the dose-response curve for lethality or its confidence limits. Some information on dose-response relationship may be available from the sighting study and when more than one fixed dose is used in the main study.

Dose-Effect Curve:

10. Since lethality is not the preferred endpoint for the FDP, information on toxicological effects seen only at dose levels close to a lethal dose will not always be available. However, it has been shown in a number of validation and comparative studies (1,2,3,4,5,6) that while there were instances where clinical signs observed in FDP tests differed from those observed in traditional LD_{50} tests, in only a few cases were these meaningful. In the majority of cases, the clinical signs not observed in the FDP tests were non-specific signs of approaching death.

Point Estimate Of An LD_{10}:

11. The ability of the FDP to predict the LD_{10} has not been assessed.

Acute Toxic Class, Guideline 423

Principles Underlying The Test Method:

12. The acute toxic class (ATC) method enables the toxicologist to allocate chemical substances to all classification systems currently in use (e.g.. the LD_{50} is between 50 and 500 mg/kg body weight) (8,9).

It is a group sequential procedure using three animals of one sex per step. Three pre-identified starting doses are possible.

13. The ATC Method is based on the probit model; i.e., the dose-response relationship follows the Gaussian distribution for log-dose values with two parameters, the mean (LD_{50}) and the slope ß in probit units based on the log-scaled dose-axis (logarithm according to base 10). Then, following the test scheme of the method, expected probabilities of a correct, of a lower and of a more stringent classification in dependence on the true oral LD_{50} value of a substance and its slope can be derived.

14. The test doses were selected with respect to the Globally Harmonized Classification system. It has been shown that the probabilities of correct classification is greatest when test doses and class limits are identical. The minimal distance factor between two neighboring toxic classes has to be 4 for slopes of ß³1 to achieve a probability of correct classification of at least 0.5 for at least one LD_{50} value in each class. For a slope of ß³1 the probability of an allocation to a lower than correct toxic class is limited to 0.256.

15. There is only a low dependence on the starting dose with respect to classification results, especially for slopes of ß>1. With increasing slopes or increasing LD_{50} values this influence decreases and tends toward zero for an unlimited increase of ß or LD_{50}. Also for infinitely low values of LD_{50} the influence becomes zero.

16. There is a strong dependence on the starting dose with respect to expected numbers of animals used and of moribund/dead animals. Therefore an appropriate starting dose should be near the true LD_{50} of the substance to be tested to minimise the number of animals used.

Point estimate of LD_{50}:

17. The ATC was not designed to determine a point estimate of LD_{50}. However, a point estimate of the LD_{50} can be calculated by the maximum likelihood method providing there are at least two doses with mortality rates not equal to 0% or 100%. However, the probability of this is rather low because the distance between two neighboring doses is 8- to 10-fold and no more than three animals per dose are used (10).

Confidence Limits On The Estimate Of LD_{50}, Estimate Of The Slope Of The Lethality Dose-Response Curve And Its Confidence Limits:

18. The ATC was not designed to determine a point estimate of LD_{50}, the slope of the lethality dose-response curve, or confidence limits for that slope. Providing there are at least three doses, two of which have mortality rates not equal to 0% or 100%, the maximum likelihood method can be used to calculate a slope estimate and broad confidence limits on the estimated LD_{50} and the estimated slope.

Dose-Effect Curve:

19. The ATC was not designed to determine a dose-effect curve for the LD_{50}. However, dose-effect curves can be calculated by the maximum likelihood method providing there are at least three doses, two with the specific toxic signs not present in 0% or 100% of the animals.

Point Estimate Of An LD_{10}:

20. The ATC was not designed to determine a point estimate of LD_{10}. However, a point estimate of the LD_{10} can be calculated by the maximum likelihood method providing there are at least two doses with different mortality rates not equal to 0% or to 100%.

Up-and-Down Method, Guideline 425

Principles Underlying the Test Method:

21. The concept of the up-and-down (UDP) testing approach (sometimes called a Staircase Design) was first described by Dixon and Mood (11,12). There have been papers on such issues as its use with small samples (13) and its use with multiple animals per dose (14). One of the most extensive discussions appears in a draft monograph prepared by W. Dixon and Dixon Statistical Associates for a U.S. National Institutes of Health [NIH] Phase I Final Report, Reduction in Vertebrate Animal Use in Research, produced under SBIR Grant No. 1-R43-RR06151-01(15). This draft monograph is available from its author for a fee or from the National Center for Research Resources of the NIH to individuals under the Freedom of Information Act.

22. In 1985, Bruce proposed the use of the UDP for the determination of acute toxicity of chemicals (16). While there exist several variations of the up-and-down experimental design, Guideline 425 is a modification of the procedure of Bruce as adopted by ASTM in 1987 (17). The guideline provides a primary test, simply for LD_{50} point estimation, and a supplemental test, used together with the primary to get slope and confidence intervals. The UDP calls for dosing individual animals of a single sex, usually females, in sequence at 48-hour intervals, with the initial dose set at "the toxicologist's best estimate of the LD_{50}," or at 175 mg/kg if no such estimate is possible. Following each death (or moribund state) the dose is lowered; following each survival, it is increased, according to a pre-specified dose progression factor. If a death follows an initial direction of increasing doses, or a survival follows an initial direction of decreasing dose, additional animals are tested following the same dose adjustment pattern and then testing is ended. The OECD 425 protocol calls for a default dose progression factor of 3.2 and default s for maximum likelihood calculations of 0.5 (i.e., log(3.2)). The supplemental test calls for several parallel up and down sequences, each stopped when its first death follows a survival or its first survival follows a death. Dosing levels and calculation details are provided in the guideline.

Point Estimate of the LD_{50}:

23. From the data a point estimate of the LD_{50} is calculated using the maximum likelihood method (18,19.).

Confidence Limits On The Estimate Of LD_{50}, Estimate Of The Slope Of The Lethality Dose-Response Curve And Its Confidence Limits:

24. Using the preliminary test confidence limits around the LD_{50} value can be calculated using the maximum likelihood method (18,19), provided a suitable historical or other sound estimate of the standard deviation can be employed. With the inclusion of the supplemental test, TG 425 can provide confidence limits on the estimate of LD_{50}, as well as an estimate of the slope of the dose-response curve for lethality and a confidence limit on the slope of the dose-response curve for lethality. The supplemental test requires increased numbers of animals.

Dose-Effect Curve:

25. A dose effect curve can be calculated using a two parameter probit model provided that the response is quantal and there is an overlapping of the range of doses that result in a positive and negative response.

Point estimate of an LD_{10}:

26. The UDP as described in Guideline 425 does not estimate an LD_{10}. Dixon (15) discusses the use of a staircase approach to the estimation of percentage points other than LD_{50}. Such an approach could be explored when LD10 estimates are needed.

REFERENCES

1. Van den Heuvel, M J, D G Clark, R J Fielder, P P Koundakjian, G J A Olier, D Pelling, N J Tomlinson, and A P Walker (1990). The international validation of a fixed-dose procedure as an alternative to the classical LD50 test. Fd. Chem. Toxicol., 28:469-482.

2. British Toxicology Society (1984). Special report: a new approach to the classification of substances and preparations on the basis of their acute toxicity. Human Toxicol., 3:85-92.

3. Van den Heuval, M J, A D Dayan and R O Shillaker (1987). Evaluation of the BTS approach to the testing of substances and preparations for their acute toxicity. Human Toxicol., 6:279-291.

4. Lipnick, R L, J A Cotruvo, R N Hill, R D Bruce, K A Stitzel, A P Walker, I Chu, M Goddard, L Segal, J A Springer, and R C Myers (1995). Comparison of the Up-and-Down, Conventional LD50, and Fixed-Dose Acute Toxicity Procedures. Fd Chem. Toxic. 33: 223-231.

5. Yam, J, P J Reer, and R D Bruce (1991). Comparison of the Up-and-Down Method and the Fixed-Dose Procedure for Acute Oral Toxicity Testing. Fd Chem. Toxic. 29:259-263.

6. Stallard N and A Whitehead (1995). Reducing numbers in the fixed-dose procedure. Human Expt. Toxicol., 14:315-323.

7. Stallard N, A Whitehead and P Ridgway (2000). Statistical evaluation of modifications to the fixed dose procedure (manuscript in preparation).

8. Diener, W; U Mischke, E Schlede and D Kayser (1995). The biometric evaluation of the OECD modified version of the acute toxic class method (oral). Arch.Toxicol. 69: 729-734.

9. Schlede, E; U Mischke, W Diener and D Kayser (1995). The international validation study of the acute-toxic-class method (oral). Arch.Toxicol. 69: 659-670.

10. Diener, W; L Siccha, U Mischke, D Kayser and E Schlede (1994). The biometric evaluation of the acute-toxic-class method (oral). Arch.Toxicol. 68: 599-610.

11. Dixon, W J, and A M Mood (1948). A method for obtaining and analyzing sensitivity data. J. Amer. Statist. Assoc. 43:109-126.

12. Dixon, W J (1991). Staircase Bioassay: The Up-and-Down Method. Neurosci. Biobehav. Rev. 15:47-50.

13. Brownlee, K A , J L Hodges, Jr., and M Rosenblatt (1953). J Amer. Stat. Assoc., 48:262-277.

14. Hsi, B P (1969). J Amer. Stat. Assoc., 64:147-162.

15. Dixon, W J (1991). Design and Analysis of Quantal Dose-Response Experiments (with Emphasis on Staircase Designs). Dixon Statistical Associates, Los Angeles CA, USA.

16. Bruce, R D (1985). An up-and-down procedure for acute toxicity testing. Fundam. Appl. Tox., 5:151-157.

17. ASTM (1987) E 1163-87, Standard test method for estimating acute oral toxicity in rats. American Society for Testing Materials, Philadelphia PA, USA.

18. Dixon, W J (1965). The up-and down method for small samples. J. Amer. Statist. Assoc., 60:967-978.

19. Finney, D J (1971). Probit Analysis, 3rd ed., Cambridge University Press, Cambridge, England, 50-80.