The Toxicologist's Pocket Handbook

Second Edition

Michael J. Derelanko

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About the Author

Michael J. Derelanko, Ph.D., D.A.B.T., F.A.T.S., has spent most of his career as a toxicologist in the chemical and pharmaceutical industries with experience in general mammalian toxicology and risk assessment. He is currently principal research investigator in the safety assessment department of Adolor Corporation in Exton, Pennsylvania, a pharmaceutical company specializing in the discovery and development of novel drugs to treat pain and the side-effects associated with pain management. Dr. Derelanko received a B.S. degree from St. Peter's College in 1973. He was a National Institute of Health predoctoral trainee in the Albert S. Gordon Laboratory of Experimental Hematology at New York University, achieving M.S. and Ph.D. degrees. In 1976, he received the New York University Gladys Mateyko Award for Excellence in Biology. Following a two-year postdoctoral fellowship in gastrointestinal pharmacology at Schering–Plough Corporation, he began his career in industrial toxicology as a research toxicologist in the laboratories of Allied Chemical Corporation in Morristown, New Jersey, which eventually became Allied–Signal and later Honeywell International. Dr. Derelanko was most recently corporate manager of toxicology and risk assessment at Honeywell.

Dr. Derelanko is a diplomate of the American Board of Toxicology and a fellow of the Academy of Toxicological Sciences. He is a member of the Society of Toxicology, the Society for Experimental Biology and Medicine, and the honorary research society Sigma Xi. He has served on the content advisory committee of the New Jersey Liberty Science Center, has chaired or been a member of industrial and government toxicology advisory committees, and serves on the speaker's bureau of the New Jersey Association for Biomedical Research.

Dr. Derelanko has authored numerous papers in experimental hematology, gastrointestinal pharmacology, and toxicology. He has been actively involved in educating the public about toxicology, particularly at the middle school level. He has delivered invited lectures on this subject at national meetings. In 2003, he received the Society of Toxicology award presented for contributions to public awareness of the importance of animals in toxicology research. He is co-editor along with Dr. Mannfred Hollinger of the first and second editions of the *CRC Handbook of Toxicology* and author of CRC's *Toxicologist's Pocket Handbook*.

Dedication

To the Memory of My Father, Frank Derelanko

Preface to the First Edition

Toxicologists rely on a large information base to design, conduct, and interpret toxicology studies, and to perform risk assessments. Reference books such as the *CRC Handbook of Toxicology* kept in the toxicologist's office facilitate ready access to this information. However, reference books of this nature tend to be quite large in size and are not easily carried in a briefcase. This puts the traveling toxicologist at a loss when the need for toxicological reference information arises at meetings, conferences, workshops, or when auditing studies at a contract laboratory. My goal was to produce a toxicological reference source in a convenient pocket-sized format that can supply needed toxicology reference information to the toxicologist traveling outside the lab or office.

The Toxicologist's Pocket Handbook provides a small, easily carried reference source of basic toxicological information for toxicologists and other health and safety professionals. This book contains selected tables and figures from the larger *CRC Handbook of Toxicology* that I previously edited along with Dr. Mannfred Hollinger. These tables and figures contain the most frequently used toxicology reference information. An abbreviated glossary of commonly used toxicological terms is also included. As with the larger handbook, this book has been designed to allow basic reference information to be located quickly. Tables and figures have been placed in sections specific to various subspecialties of toxicology. The detailed table of contents contains a listing of all of the tables and figures contained in the book. As many of the tables and figures originally obtained for the *CRC Handbook of Toxicology* were reprinted directly from or contain information from numerous previously published sources, I cannot attest to the accuracy and completeness of such information and cannot assume any liability of any kind resulting from the use or reliance on the information provided. Mention of vendors, trade names, or commercial products does not constitute endorsement or recommendation for use.

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Preface to the Second Edition

The goal of the first edition was to produce a small, easily carried reference source of frequently needed basic toxicology and related information for practicing toxicologists in industry, contract labs, regulatory agencies, and academia, other health and safety professionals and students. The first edition contains selected tables and figures from the much larger *CRC Handbook of Toxicology*. The hardest part of the task was not deciding which information should be included in the book but, rather, which information to leave out to maintain the compact size of the book. When approached by the publisher to update the first edition, it was difficult to resist the temptation to significantly add to the information presented in the book, especially those tables and figures that just seemed to be too important to again be left out. Nonetheless, the need for including more information had to be balanced against the desire to keep the book "pocket-sized."

In addition to updating the information in a number of tables from the first edition, the second edition contains nearly 60 new tables and 10 new figures, many from the second edition of the *CRC Handbook of Toxicology* as well as several new tables and figures that have not appeared in the previous handbooks. There are two new sections related to pharmaceutical toxicology and human clinical toxicology. Information on differences in physiology and metabolism between children and adults has been added to the section on risk assessment. The sections on lab animals and general toxicology have been significantly expanded, and most of the other sections from the first edition have additional information added. The glossary has been reorganized and expanded. It is now presented both by subject category and alphabetically to make it easier to locate a term or definition. It is hoped that a good balance was reached in providing this additional information while still maintaining a reasonably small and portable reference book. The format remains the same as the first edition with the information placed in sections specific to subspecialties of toxicology. The table of contents lists all tables and figures contained in the book by section.

The reader may occasionally note that there may be slight disagreement between data presented in a table in one section with similar data presented in other sections. For example, a range given for a hematological parameter such as erythrocyte count may differ slightly in tables in different sections. Such information was obtained from

different sources and is presented for different comparative purposes. The differences represent normal laboratory variation and the information is presented solely for the purpose of making relative comparisons. Therefore, as to not compromise the relative relationships being presented, no attempt was made to standardize the information between tables.

As with the first edition, although the information presented was obtained from reliable and respected sources, I cannot attest to the accuracy and/or completeness of such information and cannot assume any liability of any kind resulting from the use of or reliance on the information provided. Mention of vendors, trade names or commercial products does not constitute endorsement or recommendation for use.

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Section 1
Lab Animals

Table 1 Guiding Principles in the Use of Animals in Toxicology

1. The use, care, and transportation of animals for training and for toxicological research and testing for the purpose of protecting human and animal health and the environment must comply with all applicable animal welfare laws.
2. When scientifically appropriate, alternative procedures that reduce the number of animals used, refine the use of whole animals, or replace whole animals (e.g., *in vitro* models, invertebrate organisms) should be considered.
3. For research requiring the use of animals, the species should be carefully selected and the number of animals kept to the minimum required to achieve scientifically valid results.
4. All reasonable steps should be taken to avoid or minimize discomfort, distress, or pain to animals.
5. Appropriate aseptic technique, anesthesia, and postoperative analgesia should be provided if a surgical procedure is required. Muscle relaxants or paralytics are not to be used in place of anesthetics.
6. Care and handling of all animals used for research purposes must be directed by veterinarians or other individuals trained and experienced in the proper care, handling, and use of the species being maintained or studied. Veterinary care is to be provided in a timely manner when needed.
7. Investigators and other personnel shall be qualified and trained appropriately for conducting procedures on living animals, including training in the proper and humane care and use of laboratory animals.
8. Protocols involving the use of animals are to be reviewed and approved by an institutional animal care and use committee before being initiated. The composition and function of the committee shall comply with applicable animal welfare laws, regulations, guidelines, and policies.
9. Euthanasia shall be conducted according to the most current guidelines of the American Veterinary Medical Association (AVMA) Panel on Euthanasia or similar bodies in different countries.

Source: From Society of Toxicology (1999). With permission.

Table 2 Guiding Principles for Humane Treatment of Animals in Toxicology Studies

- Animals should be considered to experience comparable pain and distress in situations and procedures where pain and distress would occur in humans.
- Death, severe pain, and distress should be avoided where possible.
- Studies should be designed so that animals experience no more pain and distress than necessary to achieve the scientific objectives of the study.
- The duration of the study should be no longer than necessary to achieve its objectives.
- Specific endpoints for humanely terminating an animal should be established prior to the start of the study based on previous experience with the material being tested. Input should come from scientists, veterinarians, animal care personnel, and IACUC or similar ethical review board.
- Staff should be properly trained to recognize signs of pain and distress in the species being investigated.
- Clear roles, responsibilities, and authority should be established for making decisions on humane termination of an animal.
- Animals should be monitored with sufficient frequency to allow termination as soon as possible when humane endpoints have been reached.

Source: OECD (2000), Demers, G., et al. (2006).

Table 3 Signs Indicative of Pain, Suffering, and Distress in Animals[a]

Behavioral
- Vocalization in animals that do not normally vocalize on handling
- Writhing
- Tremors
- Lethargy, decreased activity, and reluctance to move
- Abnormal aggressive behavior, restlessness, agitation, and abnormal reaction to handling
- Wary or overly cautious behavior
- Licking, scratching, chewing on body part, or self-mutilation

Appearance
- Porphyrin staining around eyes and nares—rats

Movement
- Gait irregularities, non-weight-bearing movements

Physical signs
- Rapid or labored respiration
- Excessive salivation
- Changes in posture/hunched posture
- Piloerection, unkempt appearance
- Reduced food/water consumption (loss of body weight or evidence of dehydration)

[a] Individual signs may result from physiological/pharmacological mechanisms not associated with pain. The animal should be assessed in context with the study, design, and procedures performed on the animal.

Source: Hawkins, P. (2002), OECD (2000).

Table 4 Signs of Moribundity[a] as Criteria for Humane Sacrifice[b]

- Prolonged impairment of locomotion, preventing access to food and water
- Sustained 10% decrease in body temperature
- Continued severe diarrhea
- Excessive weight loss/emaciation (>25% over 7 days or more)
- Eyes fixed or sunken
- Severe dehydration
- Significant blood loss from any orifice
- Evidence of irreversible major organ failure
- Prolonged absence of voluntary responses to external stimuli
- Prolonged inability to remain upright
- Persistent convulsions
- Continued difficult, labored breathing
- Self-mutilation

[a] State of dying or inability to survive.

[b] This list is not all-encompassing. A decision to sacrifice an animal may rely on the assessment of the general condition of the animal by a trained professional.

Source: Adapted from OECD (2000).

Table 5 General Information Sources for the Care and Use of Research Animals

1. *Public Health Service Policy on Humane Care and Use of Laboratory Animals.* PHS (Public Health Service), 1996, U.S. Department of Health and Human Services, Washington, D.C. 22 pp. [PL 99-158. Health Research Extension Act, 1985].
2. The Animal Welfare Act of 1966 (P.L. 89-544) as amended by the Animal Welfare Act of 1970 (P.L. 91-579); 1976 Amendments to the Animal Welfare Act (P.L. 94-279); the Food Security Act of 1985 (P.L. 99-198), Subtitle F (Animal Welfare File Name: PL99198); and the Food and Agriculture Conservation and Trade Act of 1990 (P.L. 101-624), Section 2503, Protection of Pets (File Name: PL 101624). Rules and regulations pertaining to implementation are published in the Code of Federal Regulations, Title 9 (Animals and Animal Products), Chapter 1, Subchapter A (Animal Welfare). Available from Regulatory Enforcement and Animal Care, APHIS, USDA, Unit 85, 4700 River Road, Riverdale, MD 20737-1234, File Name 9CFR93. www.nal.usda.gov/awic/legislat/awicregs.html
3. *Guide for the Care and Use of Laboratory Animals.* Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, National Academy Press, Washington, D.C., 1996 or succeeding revised editions. www.nap.edu/readingroom/books/labrats
4. *International Guiding Principles for Biomedical Research Involving Animals.* Council for International Organizations of Medical Sciences (CIOMS), Geneva, 1985.
5. *Interdisciplinary Principles and Guidelines for the Use of Animals in Research, Testing, and Education.* Ad Hoc Animal Research Committee, New York Academy of Sciences, 1988.
6. *Recognition and Alleviation of Pain and Distress in Laboratory Animals. A Report of the Institute of Laboratory Animal Resources Committee on Pain and Distress in Laboratory Animals.* NCR (National Research Council). Washington, D.C.: National Academy Press, 1992.
7. *Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs.* AVMA (American Veterinary Medical Association). Report of the AVMA panel on euthanasia. J. Am. Vet. Med. Assoc. 218(5), 669–696, 2001.
8. *Guide to the Care and Use of Experimental Animals.* CCAC (Canadian Council on Animal Care) Vol. 1, 2nd ed. Edited by E. D. Olfert, B. M. Cross, and A. A. McWilliam. Ontario, Canada: Canadian Council on Animal Care, 1993. 211 pp.

Source: Compiled by the Society of Toxicology.

Table 6 Approximate Daily Food and Water Requirements for Various Species

Species	Daily Food Requirement	Daily Water Requirement
Mouse	3–6 g	3–7 mL
Rat	10–20 g	20–30 mL
Hamster	7–15 g	7–15 mL
Guinea pig[a]	20–30 g	12–15 mL/100 g
Rabbit	75–100 g	80–100 mL/kg
Cat	100–225 g	100–200 mL
Dog	250–1200 g	100–400 mL/day
Primate[a]	40 g/kg	350–1000 mL

[a] Like humans, guinea pigs and nonhuman primates require a continuous supply of vitamin C (ascorbic acid) in the diet.

Table 7 Common Strains of Laboratory Mice

Strain	Description
CD-1 mice	Outbred albino strain descended from "Swiss" mice
CF-1 mice	Outbred albino strain not descended from "Swiss" mice
Swiss-Webster mice	Outbred albino strain from selective inbreeding of Swiss mice by Dr. Leslie Webster
SKH1 (Hairless) mice	Outbred strain that originated from an uncharacterized strain
BALB/c mice	Inbred albino strain developed originally by H.J. Bagg (Bagg albino)
C3H mice	Inbred agouti strain developed originally from "Bagg albino" female and DBA male
C57BL/6 mice	Inbred black strain developed originally by C.C. Little
DBA/2 mice	Inbred non-agouti, dilute brown strain developed originally by C.C. Little; oldest of all inbred mouse strains
FVB mice	Inbred albino strain derived originally from outbred Swiss colony
AKR mice	Inbred albino strain originally developed by Furth as a high-leukemia strain
B6C3F1 mice	Hybrid agouti strain from female C57BL/6N × male C3H/He
DBF1 mice	Hybrid black strain from female C57BL/6N × male DBA/2N
CAF1 mice	Hybrid albino strain from female BALB/cAn × male A/HeN
CDF1 mice	Hybrid brown strain from female BALB/cAnN × male DBA/2N
CB6F1 mice	Hybrid black strain from female BALB/cAnN × male C57BL/6N
Nude CD-1 mice	Outbred hairless albino strain that is athymic and thus immunodeficient (unable to produce T-cells)
Nude BALB/cAnN mice	Inbred hairless albino strain that is athymic and thus immunodeficient (unable to produce T-cells)

Table 8 Common Strains of Laboratory Rats

Strain	Description
Sprague-Dawley rats	Outbred albino strain originated by R.W. Dawley from a hybrid hooded male and female Wistar rat
Wistar rats	Outbred albino strain originated at the Wistar Institute
Long-Evans rats	Outbred white with black or occasional brown hood; originated by Drs. Long and Evans by cross of white Wistar females with wild gray male
Zucker rats	Outbred obese strain with four principal coat colors (predominately brown; brown + white; predominately black; or black + white)
Fischer 344 (F-344) rats	Inbred albino strain originated from mating #344 of rats obtained from local breeder (Fischer)
Lewis rats	Inbred albino strain originally developed by Dr. Lewis from Wistar stock
Wistar Kyoto (WKY) rats	Inbred albino strain originated from outbred Wistar stock from Kyoto School of Medicine
Brown Norway rats	Inbred non-agouti brown strain originated from a brown mutation in a stock of rats trapped from the wild at the Wistar Institute in 1930
Spontaneously hypertensive (SHR) rats	Inbred albino strain developed from Wistar Kyoto rats with spontaneous hypertension

Table 9 Physical and Physiological Parameters of Mice

Life span	1–2 yr
Male adult weight	20–35 g
Female adult weight	20–35 g
Birth weight	1.0–1.5 g
Adult food consumption	3–6 g/day
Adult water consumption	3–7 mL/day
Male breeding age/weight	6–8 wk/20–35 g
Female breeding age/weight	6–8 wk/20–30 g
Placentation	Discoidal endotheliochorial
Estrus cycle	4–5 days (polyestrous)
Gestation period	19–21 days
Weaning age/weight	21 days/8–12 g
Average litter size	10–12 pups
Mating systems	1:1 or 1 male to multiple females
Adult blood volume	6–7% of body weight
Maximum safe bleed	7–8 mL/kg
Red cell count	$7–12 \times 10^6/mm^3$
White cell count	$3–12 \times 10^3/mm^3$
Hemoglobin	13–17 g/dL
Hematocrit	40–54%
Mean corpuscular volume	43–54
Mean corpuscular hemoglobin	13–18
Mean corpuscular hemoglobin concentration	31–34
Platelet count	$1000–1600 \times 10^3/mm^3$
Heart rate	300–600 beats/min
Respiration rate	90–180 breaths/min
Rectal temperature	37.5°C
Urine pH	6.0–7.5
Urine volume	1–3 mL/day
Chromosome number	$2n = 40$

Source: Evans, I.E. and Maltby, C.J. (1989), Williams, C.S.F. (1976), LAMA (1988).

Table 10 Physical and Physiological Parameters of Rats

Life span	2–3 yr
Male adult weight	350–400 g
Female adult weight	180–200 g
Birth weight	5–6 g
Adult food consumption	10–20 g/day
Adult water consumption	20–30 mL/day
Male breeding age/weight	10–12 wk/300–350 g
Female breeding age/weight	8–10 wk/200–300 g
Placentation	Discoidal hemochorial
Estrus cycle	4–5 days (polyestrous)
Gestation	20–22 days
Weaning age/weight	21 days/35–45 g
Average litter size	10–12 pups
Mating systems	1:1 or 1 male to multiple females
Adult blood volume	6–7% of body weight
Maximum safe bleed	5–6 mL/kg
Red cell count	$6–10 \times 10^6/mm^3$
White cell count	$7–14 \times 10^3/mm^3$
Hemoglobin	11–18 g/dL
Hematocrit	34–48%
Mean corpuscular volume	50–65
Mean corpuscular hemoglobin	19–23
Mean corpuscular hemoglobin concentration	32–38
Platelet count	$800–1500 \times 10^3/mm^3$
Heart rate	250–500 beats/min
Respiration rate	80–150 breaths/min
Rectal temperature	37.5°C
Urine pH	6.0–7.5
Urine volume	10–15 mL/day
Chromosome number	$2n = 42$

Source: Evans, I.E. and Maltby, C.J. (1989), Williams, C.S.F. (1976), LAMA (1988).

Table 11 Physical and Physiological Parameters of Dogs

Life span	12–14 yr
Male adult weight	6–25 kg
Female adult weight	6–25 kg
Birth weight	300–500 g
Adult food consumption	250–1200 g/day
Adult water consumption	100–400 mL/day
Breeding age (males)	9–12 mo
Breeding age (females)	10–12 mo
Estrus cycle	Biannual, monestrus
Gestation	56–58 days
Weaning age	6–8 wk
Litter size	4–8
Mating	Pairs, 1 male to multiple females
Adult blood volume	8–9%, 75–110 mL/kg
Maximum safe bleed	8–10 mL/kg
Red cell count	$5.5–8.5 \times 10^6/mm^3$
White cell count	$6–14 \times 10^3/mm^3$
Hemoglobin	13–18 g/dL
Hematocrit	38–52%
Platelet count	$200–600 \times 10^3/mm^3$
Heart rate	80–140 beats/min
Respiration rate	10–30 breaths/min
Rectal temperature	38.5°C
Urine pH	7.0–7.8
Urine volume	25–45 mL/kg
Chromosome number	$2n = 78$

Source: Evans, I.E. and Maltby, C.J. (1989), LAMA (1988).

Table 12 Physical and Physiological Parameters of Rabbits

Life span	5–7 yr
Male adult weight	4.0–5.5 kg
Female adult weight	4.5–5.5 kg
Birth weight	90–110 g
Adult food consumption	75–100 g
Adult water consumption	80–100 mL/kg body weight
Dietary peculiarities	Pelleted diet
Male breeding age/weight	6–7 mo/3.5–4.0 kg
Female breeding age/weight	5–6 mo/4.0–4.5 kg
Placentation	Discoidal hemoendothelial
Estrus cycle	Polyestrous, induced
Gestation	30–32 days
Weaning age/weight	6–7 wk/1.0–1.5 kg
Litter size	4–12
Mating systems	1:1 or via artificial insemination
Adult blood volume	6% of body weight
Maximum safe bleed	6.5–7.5 mL/kg
Red cell count	$4.5–7.0 \times 10^6/mm^3$
White cell count	$5–12 \times 10^3/mm^3$
Hemoglobin	11–14 g/dL
Hematocrit	32–48%
Mean corpuscular volume	58–72
Mean corpuscular hemoglobin	18–24
Mean corpuscular hemoglobin concentration	30–35
Platelet count	$250–750 \times 10^3/mm^3$
Heart rate	250–300 beats/min
Respiration rate	35–55 breaths/min
Rectal temperature	39.5°C
Urine pH	8.2
Urine volume	50–130 mL/kg
Chromosome number	$2n = 44$

Source: Evans, I.E. and Maltby, C.J. (1989), Williams, C.S.F. (1976), LAMA (1988).

Table 13 Physical and Physiological Parameters of Guinea Pigs

Life span	4–6 yr
Male adult weight	1000–1200 g
Female adult weight	850–900 g
Birth weight	90–120 g
Adult food consumption	20–30 g/day
Adult water consumption	12–15 m1/100 g
Dietary peculiarities	Vitamin C required to avoid scurvy
Male breeding age/weight	11–12 wk/600–700 g
Female breeding age/weight	7–8 wk/350–450 g
Placentation	Discoidal hemochorial
Estrus cycle	16–18 days
Gestation	65–70 days
Weaning age/weight	7–14 days/150–200 g
Litter size	2–5
Mating	1M:1F or 1M:10F
Adult blood volume	6–7% body weight
Maximum safe bleed	7–8 mL/kg
Red cell count	$4.5–7 \times 10^6/mm^3$
White cell count	$5–15 \times 10^3/mm^3$
Hemoglobin	11–17 g/dL
Hematocrit	39–47%
Platelet count	$250–750 \times 10^3/mm^3$
Heart rate	230–300 beats/min
Respiration rate	60–110 breaths/min
Rectal temperature	39.5°C
Urine pH	8.0–9.0
Urine volume	15–75 mL/day
Chromosome number	$2n = 64$

Source: Evans, I.E. and Maltby, C.J. (1989), Williams, C.S.F. (1976), LAMA (1988).

Table 14 Body Weight and Food Consumption—CD-1 Mice[a]

Week	Males		Females	
	Body Weight (g)	Food Consumption (g/kg/day)	Body Weight (g)	Food Consumption (g/kg/day)
-1	23.64	—	19.24	—
0	27.46	235.55	21.62	293.20
1	28.82	212.60	22.66	267.00
2	30.00	198.36	24.24	262.42
3	31.02	196.14	24.80	273.80
4	31.92	196.60	25.92	252.74
5	32.46	182.76	26.32	269.70
6	33.36	181.46	27.06	245.48
7	34.44	170.20	27.80	247.56
8	34.40	180.72	27.96	240.86
9	34.88	169.70	28.50	222.38
10	35.08	166.00	28.90	216.24
11	35.36	166.90	29.26	211.50
12	36.14	153.94	29.34	209.74
13–14	36.30	166.34	29.80	218.14
17–18	37.62	146.16	30.98	209.00
21–22	38.00	152.86	31.54	204.54
25–26	38.24	153.40	32.28	190.88
27–30	38.40	149.40	32.30	190.95
31–34	39.40	134.50	33.12	177.30
35–38	39.66	135.48	33.48	166.90
39–42	40.26	136.42	33.28	180.42
43–46	40.03	131.80	34.10	165.70
47–50	40.40	126.46	34.34	156.52
51–54	39.90	128.72	35.10	149.16
55–58	40.16	135.80	34.46	173.96
59–62	39.80	137.88	35.20	158.84
63–66	40.46	133.70	34.76	172.72
67–70	40.24	133.18	34.78	161.12
71–74	39.88	142.22	35.14	167.62
75–79	40.56	142.66	35.48	171.02

[a] Typical chronic study, age at -1 week is approximately 5 weeks.

Table 15 Body Weight and Food Consumption—Sprague-Dawley Rats[a]

Week	Males		Females	
	Body Weight (g)	Food Consumption (g/kg/day)	Body Weight (g)	Food Consumption (g/kg/day)
-1	132.46	—	103.82	—
0	188.64	146.00	139.14	122.30
1	236.12	115.98	161.56	122.58
2	286.94	101.12	182.80	111.00
3	327.78	90.28	203.46	104.30
4	362.78	82.02	222.10	94.04
5	393.70	75.12	232.70	87.44
6	417.26	68.98	243.04	84.82
7	432.70	63.32	250.68	77.12
8	446.16	62.08	255.40	76.44
9	457.80	58.44	261.36	73.40
10	475.74	60.96	268.62	75.84
11	481.42	57.14	274.52	73.34
12	497.12	59.78	278.24	73.26
13	508.12	56.14	282.46	70.68
17–18	549.84	50.30	299.70	67.42
21–22	577.62	47.62	311.82	63.30
25–26	603.22	45.04	327.22	62.18
29–30	616.76	44.36	334.22	61.84
33–34	635.46	43.94	348.96	61.74
37–38	651.96	42.60	363.38	58.44
41–42	660.34	41.12	374.96	56.40
45–46	678.16	40.12	389.65	52.63
49–50	695.72	39.24	409.40	52.34
53–54	703.72	39.20	412.76	51.28
57–58	720.88	37.70	430.90	49.16
61–62	728.74	37.56	441.18	48.82
65–66	735.76	38.00	455.06	48.26
69–70	735.04	38.46	460.24	48.24
72–74	737.54	37.80	465.70	47.78
77–78	736.58	39.34	467.70	46.78
81–82	738.04	38.48	471.72	47.74
85–86	733.70	39.22	473.98	47.38
89–90	725.80	38.52	479.42	47.82
93–94	723.62	37.92	490.06	45.68
97–98	721.50	37.48	494.10	45.04
101–102	703.84	35.60	498.56	44.10

[a] Typical chronic study, age at -1 week is approximately 5 weeks.

Table 16 Body Weight and Food Consumption—Fischer 344 Rats[a]

Week	Males		Females	
	Body Weight (g)	Food Consumption (g/kg/day)	Body Weight (g)	Food Consumption (g/kg/day)
-1	86.03	—	68.43	—
0	118.27	137.73	89.90	146.93
1	151.50	112.73	108.07	124.63
2	183.60	99.33	123.70	107.00
3	211.07	85.73	135.70	96.43
4	228.17	77.73	142.80	90.93
5	244.10	75.07	150.60	89.03
6	256.27	67.13	155.77	80.47
7	263.53	63.07	162.07	72.73
8	275.23	60.40	164.40	69.67
9	281.90	56.17	166.47	68.20
10	290.47	54.20	170.20	66.27
11	296.60	55.63	172.23	67.40
12	300.23	54.40	173.07	69.10
13	301.10	54.25	174.75	64.10
16	319.07	51.10	181.53	65.63
20	331.67	48.17	186.87	62.63
24	343.40	47.97	193.67	62.07
28–30	355.70	46.67	201.90	59.87
32–34	366.23	45.33	206.70	60.00
36–38	374.67	44.23	211.37	61.10
40–42	382.90	44.07	215.40	58.27
44–46	384.13	42.63	218.90	56.00
48–50	385.90	38.17	223.53	57.07
52–54	396.23	44.17	228.47	57.37
56–59	400.87	43.57	236.17	55.23
60–62	401.90	40.97	241.47	50.63
64–66	404.87	43.77	246.37	53.43
68–70	406.57	44.37	253.80	54.60
72–74	410.20	43.67	259.53	54.57
76–78	404.93	46.00	265.07	54.77
80–82	394.77	43.60	262.80	51.50
84–86	393.60	43.37	264.47	50.37
88–90	397.07	43.73	270.70	51.50
92–94	391.43	42.93	275.13	50.83
96–98	388.77	42.47	277.17	49.63
100–102	388.03	43.33	277.70	51.57

[a] Typical chronic study, age at -1 week is approximately 5 weeks.

Table 17 Typical Routes and Dosages of Several Sedative, Analgesic, and Anesthetic Agents

	Dosage and Route in Species						
Agents	**Mouse**	**Rat**	**Hamster**	**Guinea Pig**	**Rabbit**	**Dog**	**Primate**
Chlorpromazine (mg/kg)	3–35 (IM)6 (IP)	1–20 (IM) 4–8 (IP)	0.05 (IM)	5–10 (IM)	10–25 (IM)	1–6 (IM) 0.5–8 (PO)	1–6 (IM)
Promazine (mg/kg)	0.5 (IM)	0.5–1 (IM)	0.5–1 (IM)	0.5–1 (IM)	1–2 (IM)	2–4 (IM)	2–4 (IM)
Acepromazine (mg/kg)	—	—	—	—	1 (IM)	0.5–1 (IM) 1–3 (PO)	0.5–1 (IM)
Meperidine (mg/kg)	60 (IM)40 (IP)	44 (IM)50 (IP) 25 (IV)	2 (IM)	1 (IP) 2 (IM)	10 (IV)	0.4–10 (IM)	3–11 (IM)
Innovar-Vet (mL/kg)	0.05 (IM)	0.13–0.16 (IM)	—	0.08–0.66 (IM)	0.2–0.3 (IM)	0.13–0.15 (IM)	0.05 (IM)
Ketamine (mg/kg)	25 (IV)25–50 (IP) 22 (IM)	25 (IV)50 (IP) 22 (IM)	40 (IM) 100 (IP)	22–64 (IM)	22–44 (IM)	—	5–15 (IM)
Pentobarbital (mg/kg)	35 (IV)40–70 (IP)	25 (IV)40–50 (IP)	50–90 (IP)	24 (IV) 30 (IP)	25 (IV) 40 (IP)	30 (IV)	25–35 (IV)
Thiopental (mg/kg)	25–50 (IV)	40 (IM) 25–48 (IP)	—	55 (IM) 20 (IP)	25–50 (IV)	16 (IV)	25 (IV)

Note: Drugs and dosages presented are to serve only as guidelines. Selection and administration of specific agents and dosages should be supervised by a qualified veterinarian. See Chapter 1, *CRC Handbook of Toxicology*, 2nd edition, Derelanko, M.J. and Hollinger, M.A., Eds., CRC Press, Boca Raton, 2002, for additional information on anesthetics.

Table 18 Guiding Principles for Animal Euthanasia

- Whenever an animal's life is to be taken, it should be treated with the highest respect.
- Euthanasia should place emphasis on making the animal's death painless and distress free.
- Euthanasia techniques should result in rapid loss of consciousness, followed by cardiac or respiratory arrest and ultimate loss of brain function.
- Techniques should require minimum restraint of the animal and should minimize distress and anxiety experienced by the animal before loss of consciousness.
- Techniques should be appropriate for the species, age, and health of the animal.
- Death must be verified following euthanasia and before disposal of the animal.
- Personnel responsible for carrying out the euthanasia techniques should be trained (1) to carry out euthanasia in the most effective and humane manner; (2) to recognize signs of pain, fear, and distress in relevant species; and (3) to recognize and confirm death in relevant species.
- Human psychological responses to euthanasia should be taken into account when selecting the method of euthanasia, but should not take precedence over animal welfare considerations.
- Ethics committees should be responsible for approval of the method of euthanasia (in line with any relevant legislation). This should include euthanasia as part of the experimental protocol, as well as euthanasia for animals experiencing unanticipated pain and distress.
- A veterinarian experienced with the species in question should be consulted when selecting the method of euthanasia, particularly when little species-specific euthanasia research has been done.

Source: Demers, G. et al. (2006). With permission.

Table 19 Acceptable and Conditionally Acceptable Agents and Methods of Euthanasia

Method	Rodents	Rabbits	Dogs	Swine	Primates
CO_2 (bottled gas only)	A	A	A	A	C
CO (bottled gas only)	A	A	A	C	C
N_2 or Argon (only if <2% O_2 is achieved rapidly and animals are heavily sedated or anesthetized)	C	C	C		C
Inhalant anesthetics (halothane preferred)	A	A	A	C	C
Methoxyflurane (slow action, may be accompanied by agitation)	C				
Ether (irritating to eyes and nose, may cause stress, hazardous)	C				
Barbiturates (IV; IP acceptable only for small animals and in special situations) (preferred method for dogs)	A	A	A	A	A
Potassium chloride (in conjunction with general anesthesia)	A	A	A	A	
Chloral hydrate (IV after sedation)				C	
Cervical dislocation (requires training; rats < 200 g and rabbits <1 kg)	C	C			
Decapitation (with trained operator, sharp, well-maintained device) (only for small rabbits).	C	C			
Blow to the head (requires training, swine < 3 wk of age)				C	
Penetrating captive bolt (not preferred method for dogs)		C	C	A	
Gunshot				C	
Microwave irradiation (brain) (rats and mice only. Requires specialized, high-power euthanasia microwave device)	A				
Electrocution (only with animal rendered unconscious)			C	C	
Exsanguination (only with highly sedated or anesthetized animals).					

A = Acceptable method. Consistently produces death when used as the sole means of euthanasia.

C = Conditionally acceptable method. By nature of the technique or because of greater potential for operator error, might not consistently produce humane death; are safety hazards; or are methods not well documented in the scientific literature.

Source: Adapted from AVMA (2001).

Table 20 Summary of the Characteristics of Several Euthanasia Methods

Euthanasia Method	Mechanism of Action	Effectiveness	Personnel Safety
Inhalant anesthetics	Hypoxia due to depression of vital centers	Moderately rapid onset of anesthesia; initial excitation may occur	Minimize exposure to personnel by scavenging or venting
Carbon dioxide	Hypoxia due to depression of vital centers	Effective in adult animals; may be prolonged in immature and neonatal animals	Minimal hazard
Carbon monoxide	Hypoxia due to inhibition of O_2–carrying capacity of hemoglobin	Effective and acceptable with proper equipment and operation	Extremely hazardous, difficult to detect
Barbiturates	Hypoxic due to depression of vital centers	Highly effective when administered appropriately	Safe, except human abuse potential of controlled substances
Inert gases (N_2, Ar)	Hypoxic hypoxemia	Effective, but other methods are preferable; acceptable only if animal is heavily sedated or anesthetized	Safe to use in ventilated area
Cervical dislocation	Hypoxia due to disruption of vital centers, direct depression of brain	Effective and irreversible; requires training, skill, and IACUC approval; aesthetically displeasing	Safe
Decapitation	Hypoxia due to disruption of vital centers, direct depression of brain	Effective and irreversible; requires training, skill, and IACUC approval; aesthetically displeasing	Potential injury due to guillotine

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Section 2
General Toxicology

Table 21 Minimum Requirements for an Acceptable Toxicology Study

1. The study should be conducted at a laboratory recognized by accreditation and/or reputation as having the scientific capability, expertise, and experience to conduct the study of interest.
2. The study should be conducted according to Good Laboratory Practices (GLP).
3. The objectives and design of the study should be specified in a study-specific protocol approved by the study director and the sponsor (if applicable).
4. The chemical nature of the tested material should be precisely defined and documented including chemical identity, stability, and degree of purity with any impurities clearly defined.
5. The specificity of any methodology used should be adequate for the degree of detection of the endpoints to be evaluated. Such methods must be validated. Positive controls and standards should be used as necessary.
6. The number of test and control animals should be sufficient to allow the detection of biological variability in response to exposure, to allow trends to be appreciated, and to be sufficient for statistical analyses.
7. Ideally, doses or exposure levels should be sufficient to detect toxicity, define thresholds, and establish no-effect levels.
8. Statistical procedures used should be appropriate for the type of data analyzed.
9. The study should be reported in a clear and unambiguous manner with all necessary detail to allow the reader to understand the study design, interpret the results, and draw conclusions. All deviations from the protocol that have occurred should be clearly stated and the potential impact on the study assessed.
10. The report should be signed by the study director to indicate agreement with the results and conclusions. In addition, the study director should sign the GLP compliance statement which states whether the study was conducted in full GLP compliance and if not, the areas of noncompliance. The report should also contain the signed Quality Assurance Statement providing dates of inspection and reporting to management.

Table 22 Typical Contents of a GLP Protocol

Minimum Required

- A descriptive title and statement of the purpose of the study
- Identification of the test article by name and/or code number
- The name of the sponsor of the study
- The name and address of the testing facility
- The number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system (animals)
- The procedure to be used for identification of the test system
- A description and/or identification of the diet used in the study to include a statement of contaminants
- A description of the experimental design, including the methods for the control of bias
- A description and/or identification of solvents, emulsifiers, and/or other materials used to solubilize or suspend the test article
- Dose levels in appropriate units, and method and frequency of administration
- The type and frequency of tests, analyses, and measurements to be conducted
- A statement of the proposed statistical methods to be used
- The records to be maintained
- Date of approval by the sponsor and dated signature of the study director

Additional Information Frequently Provided

- Contact information for study director, principal investigators, and other key personnel
- Proposed experimental start and termination dates
- Statement of regulatory guideline compliance
- Storage conditions for test and control articles
- Reserve archive samples to be taken
- Justification for selection of the test system
- Animal care and use statement
- Animal husbandry practices
- Justification of dose and route of administration
- Test article disposition
- Computer systems utilized
- Proposed content of study report

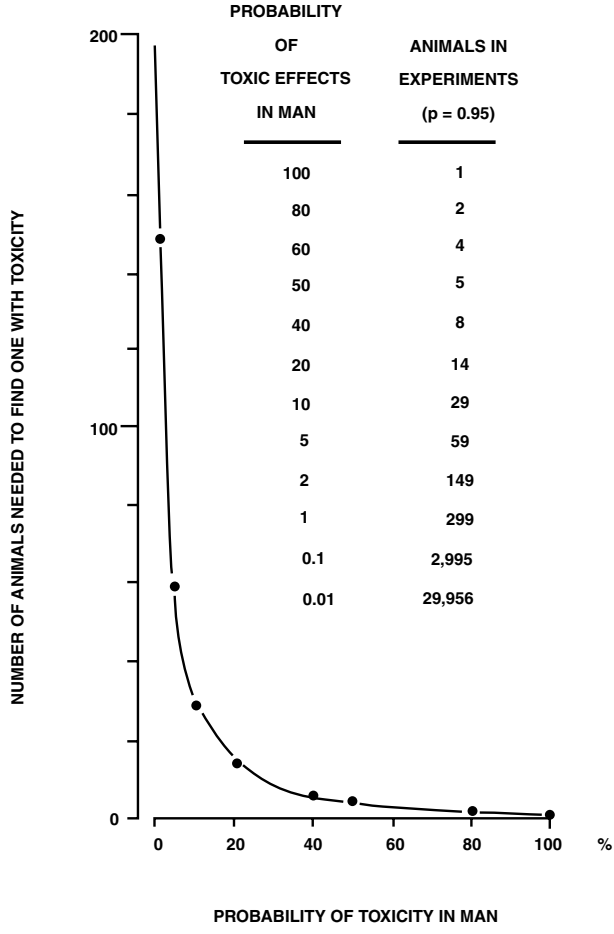

Figure 1 Animal number and predictive probability. Data derived from Zbinden, G. (1973) and Ecobichon, D.J. (1992). With permission.

Table 23 Suggested Dose Volumes (mL/kg) for Test Material Administration

	Route											
	Gavage		Dermal		IV		IP		SC		IM	
Species	Ideal	Limit	Ideal	Limit	Ideal	Limit	Ideal	Limit	Ideal	Limit	Ideal	Limit
Mouse	10	20–50	—	—	5	15–25	5–10	30–50	1–5	10–20	0.1	0.5–1
Rat	10	20–50	2	6	1–5	10–20	5–10	10–20	1	10–20	0.1–1	1–10
Rabbit	10	10–20	2	8	1–3	5–10	—	—	1–2.5	5–10	0.1–0.5	1
Dog	10	10–20	—	—	1	5–10	3	5	0.5	1–2	0.1–0.2	1
Monkey	10	10	—	—	1	5–10	3	5	0.5	1–2	0.1–0.5	1

Source: Adapted from *SYNAPSE* (1991). Some adaptations have been made based on experience.

Table 24 Suggested Dosing Apparatus/Needle Sizes (Gauge) for Test Material Administration

	Route								
	Gavage	IV		Ip		SC		Im	
Species	Recommended	Ideal	Range	Ideal	Range	Ideal	Range	Ideal	Range
Mouse	Premature infant feeding tube cut to 70 mm, marked at 38 mm	25 or 27	25–30	25 or 27	22–30	25 or 27	22–30	25 or 27	22–30
Rat	3-in. ball-tipped intubation needle	25	25–30	25	22–30	25	25–30	25	22–30
Rabbit	No. 18 French catheter, cut to 15 in., marked at 12 in.	21	22–30	21	18–23	25	22–25	25	22–30
Dog	Kaslow stomach tube 12Fr ≥ 24 in.; Davol 32Fr intubation tube	21	21–22	—	—	22	20–23	21 or 25	20–25
Monkey	No. 8 French tube (nasogastric gavage)	25	21–22	—	—	22	22–25	25	22–25

Note: Recommended gavage equipment and ideal needle sizes are based on laboratory experience. Suggested ranges of needle sizes are from *Laboratory Manual for Basic Biomethodology of Laboratory Animals*, MTM Associates Inc.

Table 25 Body Weight: Surface Area Conversion

Species	Representative Body Weight to Surface Area[a]		
	Body Weight (kg)	Surface Area (m^2)	Conversion Factor (km)
Mouse	0.02	0.0066	3
Rat	0.15	0.025	5.9
Monkey	3	0.24	12
Dog	8	0.4	20
Human			
Child	20	0.8	25
Adult	60	1.6	37

[a] Example: To express a mg/kg dose in any given species as the equivalent mg/m^2 dose, multiply the dose by the appropriate km. In human adults, 100 mg/kg is equivalent to 100 mg/kg × 37 kg/m^2 = 3700 mg/m^2.

Source: Adapted from Freireich, E.J. et al. (1966).

Table 26 Equivalent Surface Area Dosage Conversion Factors

		TO				
		Mouse (20 g)	Rat (150 g)	Monkey (3 kg)	Dog(8 kg)	Human (60 kg)
	Mouse	1	1/2	1/4	1/6	1/12
F	Rat	2	1	1/2	1/3	1/6
R	Monkey	4	2	1	3/5	1/3
O	Dog	6	4	3/2	1	1/2
M	Human	12	7	3	2	1

Example: To convert a dose of 50 mg/kg in the mouse to an equivalent dose in the monkey, assuming equivalency on the basis of mg/m^2; multiply 50 mg/kg × 1/4 = 13 mg/kg.

Note: This table gives approximate factors for converting doses expressed in terms of mg/kg from one species to an equivalent surface area dose expressed as mg/kg in the other species tabulated.

Source: Adapted from Freireich, E.J. et al. (1966).

Table 27 Comparison of Dosage by Weight and Surface Area

Species	Weight (g)	Dosage (mg/kg)	Dose (mg/animal)	Surface Area (cm^2)	Dosage (mg/cm^2)
Mouse	20	100	2	46	0.043
Rat	200	100	20	325	0.061
Guinea pig	400	100	40	565	0.071
Rabbit	1,500	100	150	1,270	0.118
Cat	2,000	100	200	1,380	0.145
Monkey	4,000	100	400	2,980	0.134
Dog	12,000	100	1,200	5,770	0.207
Human	70,000	100	7,000	18,000	0.388

Source: From Amdur, M.O. et al., Eds. (1991), *Casarett and Doull's Toxicology,* 4th ed., Pergamon Press, New York. With permission.

Table 28 Approximate Diet Conversion Factors (ppm to mg/kg)

Species	Age	Conversion Factor (divide ppm by)
Mice	Young (1–12 wk of study)	5
	Older (13–78 wk of study)	6–7
Rats	Young (1–12 wk of study)	10
	Older (13–104 wk of study)	20
Dogs		40

Note: To estimate the approximate test material of rats receiving a 1000-ppm dietary concentration during a 4-wk study: 1000 ppm ÷ 10 = 100 mg/kg b.w./day.

Table 29 Clinical Signs of Toxicity

	Clinical Observation		Observed Signs	Organs, Tissues, of Systems Most Likely to be Involved
I.	Respiratory: blockage in the nostrils, changes in rate and depth of breathing, changes in color of body surfaces	A.	Dyspnea: difficult or labored breathing, essentially gasping for air, respiration rate usually slow	
			1. Abdominal breathing: breathing by diaphragm, greater deflection of abdomen upon inspiration	CNS respiratory center, paralysis of costal muscles, cholinergic
			2. Gasping: deep labored inspiration, accompanied by a wheezing sound	CNS respiratory center, pulmonary edema, secretion accumulation in airways (increased cholinergic)
		B.	Apnea: a transient cessation of breathing following a forced respiration	CNS respiratory center, pulmonary–cardiac insufficiency
		C.	Cyanosis: bluish appearance of tail, mouth, footpads	Pulmonary–cardiac insufficiency, pulmonary edema
		D.	Tachypnea: quick and usually shallow respiration	Stimulation of respiratory center, pulmonary–cardiac insufficiency
		E.	Nostril discharges: red or colorless	Pulmonary edema, hemorrhage
II.	Motor activities: changes in frequency and nature of movements	A.	Decrease or increase in spontaneous motor activities, curiosity, preening, or locomotion	Somatomotor, CNS

Table 29 Clinical Signs of Toxicity (Continued)

Clinical Observation	Observed Signs	Organs, Tissues, of Systems Most Likely to be Involved
	B. Somnolence: animal appears drowsy, but can be aroused by prodding and resumes normal activities	CNS sleep center
	C. Loss of righting reflex: loss of reflex to maintain normal upright posture when placed on the back	CNS, sensory, neuromuscular
	D. Anesthesia: loss of righting reflex and pain response (animal will not respond to tail and toe pinch)	CNS, sensory
	E. Catalepsy: animal tends to remain in any position in which it is placed	CNS, sensory, neuromuscular, autonomic
	F. Ataxia: inability to control and coordinate movement while animal is walking, with no spasticity, epraxia, paresis, or rigidity	CNS, sensory, autonomic
	G. Unusual locomotion: spastic, toe walking, pedaling, hopping, and low body posture	CNS, sensory, neuromuscular
	H. Prostration: immobile and rests on belly	CNS, sensory, neuromuscular
	I. Tremors: involving trembling and quivering of the limbs or entire body	Neuromuscular, CNS
	J. Fasciculation: involving movements of muscles, seen on the back, shoulders, hind limbs, and digits of the paws	Neuromuscular, CNS, autonomic

Table 29 Clinical Signs of Toxicity (Continued)

	Clinical Observation		Observed Signs	Organs, Tissues, of Systems Most Likely to be Involved
III.	Convulsion (seizure): marked involuntary contraction or seizures of contraction of voluntary muscle	A.	Clonic convulsion: convulsive alternating contraction and relaxation of muscles	CNS, respiratory failure, neuromuscular, autonomic
		B.	Tonic convulsion: persistent contraction of muscles, attended by rigid extension of hind limbs	CNS, respiratory failure, neuromuscular, autonomic
		C.	Tonic–clonic convulsion: both types may appear consecutively	CNS, respiratory failure, neuromuscular, autonomic
		D.	Asphyxial convulsion: usually of clonic type, but accompanied by gasping and cyanosis	CNS, respiratory failure, neuromuscular, autonomic
		E.	Opisthotonos: tetanic spasm in which the back is arched and the head is pulled toward the dorsal position	CNS, respiratory failure, neuromuscular, autonomic
IV.	Reflexes	A.	Corneal (eyelid closure): touching of the cornea causes eyelids to close	Sensory, neuromuscular
		B.	Pinnal: twitch of external ear elicited by light stroking of inside surface of ear	Sensory, neuromuscular, autonomic
		C.	Righting: ability of animal to recover when placed dorsal side down	CNS, sensory, neuromuscular
		D.	Myotact: ability of animal to retract its hind limb when limb is pulled down over the edge of a surface	Sensory, neuromuscular

Table 29 Clinical Signs of Toxicity (Continued)

	Clinical Observation		Observed Signs	Organs, Tissues, of Systems Most Likely to be Involved
		E.	Light (pupillary): constriction of pupil in the presence of light	Sensory, neuromuscular, autonomic
		F.	Startle reflex: response to external stimuli such as touch, noise	Sensory, neuromuscular
V.	Ocular signs	A.	Lacrimation: excessive tearing, clear or colored	Autonomic
		B.	Miosis: constriction of pupil regardless of the presence or absence of light	Autonomic
		C.	Mydriasis: dilation of pupils regardless of the presence or absence of light	Autonomic
		D.	Exophthalmos: abnormal protrusion of eye from orbit	Autonomic
		E.	Ptosis: dropping of upper eyelids, not reversed by prodding animal	Autonomic
		F.	Chromodacryorrhea (red lacrimation)	Autonomic, hemorrhage, infection
		G.	Relaxation of nictitating membrane	Autonomic
		H.	Corneal opacity, iritis, conjunctivitis	Irritation of the eye
VI.	Cardiovascular signs	A.	Bradycardia: decreased heart rate	Autonomic, pulmonary–cardiac insufficiency
		B.	Tachycardia: increased heart rate	Autonomic, pulmonary–cardiac insufficiency
		C.	Vasodilation: redness of skin, tail, tongue, ear, foot pad, conjunctivae, and warm body	Autonomic, CNS, increased cardiac output, hot environment
		D.	Vasoconstriction: blanching or whitening of skin, cold body	Autonomic, CNS, cold environment, cardiac output decrease

Table 29 Clinical Signs of Toxicity (Continued)

Clinical Observation		Observed Signs		Organs, Tissues, of Systems Most Likely to be Involved
		E.	Arrhythmia: abnormal cardiac rhythm	CNS, autonomic, cardiac–pulmonary insufficiency, myocardial infarction
VII.	Salivation	A.	Excessive secretion of saliva: hair around mouth becomes wet	Autonomic
VIII.	Piloerection	A.	Contraction of erectile tissue of hair follicles resulting in rough hair	Autonomic
IX.	Analgesia	A.	Decrease in reaction to induced pain (e.g., hot plate)	Sensory, CNS
X.	Muscle tone	A.	Hypotonia: generalized decrease in muscle tone	Autonomic
		B.	Hypertonia: generalized increase in muscle tension	Autonomic
XI.	Gastrointestinal signs: dropping (feces)	A.	Solid, dried, and scant	Autonomic, constipation, GI motility
		B.	Loss of fluid, watery stool	Autonomic, diarrhea, GI motility
	Emesis	A.	Vomiting and retching	Sensory, CNS, autonomic (in rat, emesis is absent)
	Diuresis	A.	Red urine (hematuria)	Damage in kidney
		B.	Involuntary urination	Autonomic, sensory
XII.	Skin	A.	Edema: swelling of tissue filled with fluid	Irritation, renal failure, tissue damage, long-term immobility
		B.	Erythema: redness of skin	Irritation, inflammation, sensitization

Source: From Chan, P.K. and Hayes, A.W. (1989). With permission.

Table 30 Autonomic Signs

Sympathomimetic	Piloerection
	Partial mydriasis
Sympathetic block	Ptosis
	Diagnostic if associated with sedation
Parasympathomimetic	Salivation (examined by holding blotting paper)
	Miosis
	Diarrhea
	Chromodacryorrhea in rats
Parasympathomimetic block	Mydriasis (maximal)
	Excessive dryness of mouth (detect with blotting paper)

Source: From Chan, P.K. and Hayes, A.W. (1989). With permission.

Table 31 Clinical Chemistry Parameters of Subchronic and Chronic Studies—Standard Study Guidelines

Parameter	Guidelines[a]					
	OECD	JMHW	RDBK	OPPTS	JMAFF	MITI
Alkaline phosphatase		×		×	×	×
Alanine aminotransferase (ALT)	×	×	×	×	×	×
Aspartate aminotransferase (AST)	×	×	×	×	×	×
γ-glutamyltransferase (GGT)	×		×	×		×
Glucose	×	×	×	×	×	×
Bilirubin: total	×	×	×	×[c]		
Creatinine	×	×	×	×		×
Urea (BUN)	×	×	×	×	×	×
Total protein	×	×	×	×	×	×
Albumin	×	×	×	×	×	
Albumin/globulin ratio		×				
Electrolytes (Na, K, Cl, Ca, P)	×	×	×	×	×	×
Cholesterol		×		×		×
Triglycerides		×		×		×
Ornithine decarboxylase (ODC)	[b]	[b]				[b]
Protein-electrophoretogram			×			
Lactate dehydrogenase						[c]
Creatine kinase						[c]
Phosphotipids						[c]
Uric acid						[c]

[a] OECD = Organization for Economic Cooperation and Development; JMHW = Japanese Ministry of Health and Welfare; RDBK = FDA Redbook; OPPTS = Office of Prevention, Pesticides and Toxic Substances (Environmental Protection Agency); JMAFF = Japanese Ministry of Agriculture, Forestry and Fisheries; MITI = Ministry of International Trade and Industry (Japan).

[b] Ornithine decarboxylase is a tissue enzyme; no acceptable analytical procedure for blood exists.

[c] Chronic studies only.

Table 32 Hematology Parameters of Subchronic and Chronic Studies—Standard Study Guidelines[a]

Hematology	
All Guidelines	
Erythrocyte count	
Hematocrit	
Hemoglobin concentration	
Leukocyte count (total and differential)	
Some measures of clotting function	
Suggestions:	Clotting time
	Platelet count
	Prothrombin time (PT)
	Activated partial thromboplastin time (APTT)
Exceptions/Additions	
OPPTS: MCV, MCH, MCHC	
MHW: in addition, reticulocyte count, PT, APTT	
JMAFF: specifies platelet count	
MITI chronic studies: in addition, reticulocyte count; specifies platelet count	
EC: Guidelines do not specify parameters	

[a] OPPTS = Office of Prevention, Pesticides and Toxic Substances (EPA); MHW = Ministry of Health and Welfare (Japan); JMAFF = Japanese Ministry of Agriculture, Forestry and Fisheries; MITI = Ministry of International Trade and Industry (Japan); EC = European Community.

Table 33 Urinalysis Parameters of Subchronic and Chronic Studies—Standard Study Guidelines

Parameter	Guideline[a]				
	OECD	MHW	OPPTS	JMAFF	MITI (chronic)
Appearance	×		×	×	
Volume	×	×	×	×	×
Specific gravity	×	×	×	×	
Protein	×	×	×	×	×
Glucose	×	×	×	×	×
Ketones		×		×	×
Occult blood[b]	×	×	×	×	×
Sediment microscopy[b]		×	×	×	[c]
pH	×	×	×		×
Bilirubin		×	×		×
Urobilinogen		×			×
Electrolytes (Na, K, etc.)		×			

[a] OECD = Organization for Economic Cooperation and Development; JMHW = Japanese Ministry of Health and Welfare; RDBK = FDA Redbook; OPPTS = Office of Prevention, Pesticides and Toxic Substances (Environmental Protection Agency); JMAFF = Japanese Ministry of Agriculture, Forestry and Fisheries; MITI = Ministry of International Trade and Industry (Japan).

[b] Semiquantitative evaluation.

[c] When necessary.

Table 34 Organ Weight Requirements—Standard Study Guidelines

Organ to be Weighed	Guideline[a]					
	OECD	JMHW	RDBK	OPPTS	JMAFF	MITI
Adrenal glands	×	×	×	×	×	×
Kidneys	×	×	×	×	×	×
Liver	×	×	×	×	×	×
Testes	×	×	×	×	×	×
Epididymides	×					
Ovaries	×	×		×		×
Thyroid/ Parathyroids	NR	[b]	NR	NR	NR	
Brain	×	×		×	Chronic	Chronic
Heart	×	×		×		Chronic
Lungs		[b]				Chronic
Spleen	×	×		×		Chronic
Pituitary		×				Chronic
Salivary gland		[b]				
Seminal vesicles		[b]				
Thymus	×	[b]		×		
Uterus	×	[b]		×		

[a] OECD = Organization for Economic Cooperation and Development; JMHW = Japanese Ministry of Health and Welfare; RDBK = FDA Redbook; OPPTS = Office of Prevention, Pesticides and Toxic Substances (Environmental Protection Agency); JMAFF = Japanese Ministry of Agriculture, Forestry and Fisheries; MITI = Ministry of International Trade and Industry (Japan).

[b] Guidelines state that these organs are "often weighed."

Table 35 Microscopic Pathology Requirements—Standard Study Guidelines—Tissues Most Often Recommended for Chronic Studies[a]

Tissues	OECD	EC	JMHW	RDBK	OPPTS	JMAFF	MITI
Adrenal glands	×	×	×	×	×	×	×
Bone (sternum/femur/vertebrae)	S, F	S, F, or V	S, F	S	×	S, F	S, F, or V
Bone marrow (sternum/femur/vertebrae)	S	S, F, or V	S, F	S	×	S, F	S
Brain (medulla/pons, cerebrum, cerebellum)	×	×	×	×	×	×	×
Esophagus	×	×	×	×	×	×	×
Heart	×	×	×	×	×	×	×
Kidney	×	×	×	×	×	×	×
Large intestine (cecum, colon, rectum)	×	Colon	×	×	×	×	×
Liver	×	×	×	×	×	×	×
Lung (with mainstem bronchi)	×	×	×	×	×	×	×
Lymph node (representative)	×	×	×	×	×	×	×
Mammary gland	♀	×	×	×	♀	♀	♀
Ovaries	×	×	×	×		×	×
Pancreas	×	×	×	×	×	×	×
Pituitary	×	×	×	×	×	×	×
Prostate	×	×	×	×	×	×	×
Salivary glands	×	×	×	×	×	×	×
Small intestine (duodenum, ileum, jejunum)	×	×	×	×	×	×	×
Spleen	×	×	×	×	×	×	×
Stomach	×	×	×	×	×	×	×
Testes (with epididymides)	×	×	×	×	×	×	×
Thymus	×	×	×	×	×	×	×
Thyroid (with parathyroids)	×	×	×	×	×	×	×
Trachea	×	×	×	×	×	×	×
Urinary bladder	×	×	×	×	×	×	×
Uterus	×	×	×	×	×	×	×
Gross lesions/masses/target organs	×	×	×	×	×	×	×

[a] OECD = Organization for Economic Cooperation and Development; EC = European Community; JMHW = Japanese Ministry of Health and Welfare; RDBK = FDA Redbook; OPPTS = Office of Prevention, Pesticides and Toxic Substances (Environmental Protection Agency); JMAFF = Japanese Ministry of Agriculture, Forestry and Fisheries; MITI = Ministry of International Trade and Industry (Japan).

Table 36 Microscopic Pathology Requirements—Tissues Occasionally Recommended for Chronic Studies—Standard Study Guidelines[a]

Tissue	OECD	EC	JMHW	RDBK	JMAFF	OPPTS	MITI
Aorta	×			×	×	×	
Eyes	×	×	×	×		×	×
Gallbladder (not present in rats)		×	×	×	×	×	
Lacrimal gland (rodent only)			×				
Larynx						×	
Fallopian tubes				×			
Muscle (skeletal, usually biceps femoris)	×			×	×		
Nerve (peripheral/sciatic)	×			×	×	×	×
Nose						×	
Pharynx						×	
Seminal vesicles (not present in dogs)	×		×	×	×	×	×
Skin	×		×		×	×	×
Smooth muscle				×			
Spinal cord (number of sections; total number indicated)	3	×	×	2	×	3	×
Tongue			×				×
Vagina			×				

[a] OECD = Organization for Economic Cooperation and Development; EC = European Community; JMHW = Japanese Ministry of Health and Welfare; RDBK = FDA Redbook; OPPTS = Office of Prevention, Pesticides and Toxic Substances (Environmental Protection Agency); JMAFF = Japanese Ministry of Agriculture, Forestry and Fisheries; MITI = Ministry of International Trade and Industry (Japan).

Note: Additional tissues sometimes taken—Harderian gland, clitoral gland, preputial gland, zymbal gland, and nasal turbinates.

Table 37 Effect of Decreased Body Weights on Relative Organ Weights of Rats

Decrease	No Change	Increase
Liver (?)	Heart	Adrenal glands (?)
	Kidneys	Brain
	Prostate	Epididymides
	Spleen	Pituitary
	Ovaries	Testes
		Thyroid (?)
		Uterus

Note 1: (?) = Differences slight or inconsistent.

Note 2: Relative weights = organ/body weight ratios.

Note 3: For absolute weights, all except thyroids decrease. Summary of results reported in Schwartz, E. et al. (1973), Scharer, K. (1977).

Table 38 Common Abbreviations and Codes Used in Histopathology

Code	Finding or Observation
+ (1)	= Minimal grade lesion
++ (2)	= Mild or slight grade lesion
+++ (3)	= Moderate grade lesion
++++ (4)	= Marked or severe grade lesion
+++++ (5)	= Very severe or massive grade lesion
(No Entry)	= Lesion not present or organ/tissue not examined
+	= Tissue examined microscopically
–	= Organ/tissue present, no lesion in section
A	= Autolysis precludes examination
B	= Primary benign tumor
I	= Incomplete section of organ/tissue or insufficient tissue for evaluation
M	= Primary malignant tumor
M	= Organ/tissue missing, not present in section
N	= No section of organ/tissue
N	= Normal, organ/tissue within normal limits
NCL	= No corresponding lesion for gross finding
NE	= Organ/tissue not examined
NRL	= No remarkable lesion, organ/tissue within normal limits
NSL	= No significant lesion, organ/tissue within normal limits
P	= Lesion present, not graded (for example, cyst, anomaly)
R	= Recut of section with organ/tissue
U	= Unremarkable organ/tissue, within normal limits
WNL	= Organ/tissues within normal limits
X	= Not remarkable organ/tissue, normal
X	= Incidence of listed morphology, lesion present

Table 39 Examples of Frequently Used Grading Schemes[a] for Histopathology Findings

A1	A2	B	C	D	E
(1) Minimal <1–25%	(1) Minimal <1–15%	(1) Minimal <1%	(1) Slight 1–25%	(1) Minimal <1%	1 = 1–4 foci
(2) Mild 26–50%	(2) Mild 16–35%	(2) Slight 1–25%	(2) Mild 26–50%	(2) Mild 1–30%	2 = 5–8 foci
(3) Moderate 51–75%	(3) Moderate 36–60%	(3) Moderate 26–50%	(3) Moderate 51–75%	(3) Moderate 31–60%	3 = 9–12 foci
(4) Marked 76–100%	(4) Marked 61–100%	(4) Moderately severe 51–75%	(4) Severe 76–100%	(4) Severe 61–90%	4 = >12 foci
		(5) Severe 76–100%		5) Very severe or massive 91–100%	

[a] A1 and A2 are examples of four-severity grade schemes commonly used by pathologists in the National Toxicology Program, B and D are examples of five-severity grade schemes that have been used by other researchers, often for pharmaceutical companies, C is another four-severity grade scheme similar to A1 using different terminology, and E is an example of grading of a quantifiable lesion.

The relative proportion of an affected organ associated with specific severity term: *Minimal* is a very small amount; *Slight* is a very small to small amount; *Mild* is a small amount; *Moderate* is a middle or median amount; *Marked* is a large amount; *Moderately severe* is also a large amount; *Severe* is a very large amount; and *Very severe* or massive is also a very large amount.

Source: Adapted by Dr. John Peckham from Hardisty, J.F. and Eustis, S.L. (1990), World Health Organization (1978).

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Section 3
Inhalation Toxicology

Table 40 Body Weight and Lung Volumes in Fischer-344 Rats at Various Ages

Parameter	3 mo	18 mo	27 mo
Body weight (g)	222 ± 61	334 ± 106	332 ± 71
Total lung capacity (TLC) (mL)	11.9 ± 1.7	13.9 ± 2.2	14.4 ± 1.9
TLC/body weight (mL/kg)	56 ± 8	42 ± 7	43 ± 6
Vital capacity (mL)	11.0 ± 1.8	13.4 ± 2.3	13.4 ± 1.7
Functional residual capacity (mL)	2.1 ± 0.3	1.7 ± 0.3	2.7 ± 0.4
Residual volume (RV) (mL)	1.0 ± 0.3	0.6 ± 0.2	1.1 ± 0.5
RV/TLC (mL/mL)	0.08 ± 0.03	0.04 ± 0.01	0.07 ± 0.03

Note: Values are means ± SD.

Source: Adapted from Mauderly, J.L. (1982). From Sahebjami, H. (1992).

Table 41 Body Weight and Lung Volumes in Adult and Older Hamsters

Parameter	15 wk	65 wk	*p Value*
Body weight (g)	126 ± 12	125 ± 7	>0.20
Total lung capacity (mL)	9.6 ± 1.3	11.1 ± 1.0	<0.02
Vital capacity (mL)	6.9 ± 1.0	7.8 ± 0.9	<0.10
Functional residual capacity (mL)	3.5 ± 0.5	4.3 ± 0.3	<0.05
Residual volume (RV) (mL)	2.7 ± 0.6	3.3 ± 0.3	<0.05
RV/TLC (%)	28 ± 5	30 ± 5	>0.20

Note: Values are means ± SD.

Source: Adapted from Mauderly, J.L. (1979). From Sahebjami, H. (1992).

Table 42 Ventilatory Parameters in Fischer-344 Rats at Various Ages

Parameter	3 mo	18 mo	27 mo
Respiratory frequency (breath/min)	48 ± 6	54 ± 7	54 ± 6
Tidal volume (mL)	1.1 ± 0.3	1.5 ± 0.3	1.5 ± 0.3
Minute ventilation ($\dot{V}_\varepsilon$) (mL/min)	54 ± 14	82 ± 23	82 ± 18
$\dot{V}_\varepsilon$ *body weight (mL/min/kg)*	254 ± 48	251 ± 45	252 ± 52

Note: Values are means ± SD.

Source: Adapted from Mauderly, J.L. (1982). From Sahebjami, H. (1992).

Table 43 Ventilatory Parameters in Hamsters at Various Ages

Parameter	15 wk	65 wk
Respiratory frequency (breath/min)	24 ± 2.7	25 ± 3.9
Tidal volume (mL)	1.2 ± 0.2	1.1 ± 0.2
Minute volume (mL/min)	27.8 ± 3.3	28.1 ± 4.0

Note: Values are means ± SD.

Source: Adapted from Mauderly, J.L. (1979). From Sahebjami, H. (1992).

Table 44 Morphometric Values in Sprague-Dawley Rats at Various Ages

Parameter	4 mo	8 mo	18 mo
V_L body weight (mL/kg)[a]	21.7 ± 1.0	30.9 ± 1.5	38.4 ± 2.8
Lm (μm)	54 ± 2	71 ± 2	87 ± 7
ISA (cm^2)	5.571 ± 445	7.979 ± 318	8.733 ± 721

Note: Values are means ± SEM. V_L, postfixation lung volume; Lm, mean chord length; ISA, internal surface area.

Source: Adapted from Johanson, W.G., Jr. and Pierce, A.K. (1973); Sahebjami, H. (1992).

Table 45 Normal Cytology of BALF (Percentage of Total Cells)

Animal	Macrophages	Neutrophil	EOS	Lymph
Rat, mouse, rabbit, Syrian hamster	95	<1	<1	<1
Guinea pig	90	—	10	—
Rabbit	95	<1	<1	4
Dog	85	5	5	5
Sheep	70	5	5	15
Horse	83	5	<1	10
Monkey	89	—	—	10
Human (nonsmoker)	88	<1	<1	10

Note: Abbreviations: BALF = bronchoalveolar lavage fluid; EOS = eosinophils; Lymph = lymphocytes.

Source: From Henderson, R.F. (1989). With permission.

Table 46 Normal Biochemical Content of BALF, $\bar{X}$ (SE)

Animal	*n*	LDH (mLU/mL)	Alkaline Phosphatase (mLU/mL)	Acid Phosphatase (mLU/mL)	β-Glucuronidase (mLU/mL)	Protein (mg/mL)
Rat	240–280	109 (2)	53 (1)	2.4 (0.1)	0.34 (0.02)	0.39 (0.02)
Mouse	45–95	233 (23)	2.5 (0.2)	7.5 (0.8)	0.53 (0.08)	0.82 (0.07)
Guinea pig	6	69 (26)	5.7 (1.6)	2.5 (0.2)	0.65 (0.12)	0.13 (0.03)
Syrian hamster	6	72 (7)	3.6 (1.0)	2.0 (0.1)	0.57 (0.09)	0.37 (0.03)
Rabbit	6	27 (6)	8.5 (4.4)	5.3 (0.5)	0.37 (0.02)	0.44 (0.10)
Dog	4–12	134 (25)	22 (5)	1.4 (0.1)	0.30 (0.04)	0.35 (0.18)
Chimp-anzee	5	51 (12)	53 (3)	—	—	0.01 (9.01)

Note: Values are normalized per milliliter of lung volume washed.

Source: From Henderson, R.F. (1989). With permission.

Table 47 Tracheal Mucociliary Clearance

Species	Mucous Velocity[a] (mm/min)
Mouse	+
Rat	1.9 ± 0.7
	5.1 ± 3.0
	5.9 ± 2.5
Ferret	+
	18.2 ± 5.1
	10.7 ± 3.7
Guinea pig	2.7 ± 1.4
Rabbit	3.2 ± 1.1
	+
Chicken	*
Cat	2.5 ± 0.8
Dog	21.6 ± 5.0
	9.8 ± 2.1
	19.2 ± 1.6
	7.5 ± 3.7
	14.5 ± 6.3
Baboon	+
Sheep	17.3 ± 6.2
	10.5 ± 2.9
Pig	*
Cow	*
Donkey	14.7 ± 3.8
Horse	16.6 ± 2.4
	17.8 ± 5.1
Human	3.6 ± 1.5
	5.5 ± 0.4
	5.1 ± 2.9
	11.5 ± 4.7
	10.1 ± 3.5
	21.5 ± 5.5
	15.5 ± 1.7

Note: *, transport studied but no velocity given; +, inhalation study, clearance measured but no tracheal velocities given.

[a] Mean ± SD.

Source: From Wolff, R.K. (1992). With permission.

Table 48 Nasal Mucociliary Clearance

Species	Velocity[a] (mm/min)
Rat	2.3 ± 0.8
Dog	3.7 ± 0.9
Human	5.2 ± 2.3
	5.5 ± 3.2
	5.3 (0.5–23.6)
	8.4 ± 4.8
	6.8 ± 5.1
	7 ± 4

[a] Mean ± SD.

Source: From Wolff, R.K. (1992). With permission.

Table 49 Ammonia Concentrations in an Inhalation Chamber

Animal Loading (%)	Chamber Air Flow (L/min)	Number of Air Changes per Hour	Hour of Sample (ppm NH_3 ± SE)		
			2	4	6
1	13	8	0.38 ± 0.08	0.48 ± 0.07	0.46 ± 0.13
1	26	16	0.20 ± 0.01	0.24 ± 0.02	0.45 ± 0.06
1	40	24	0.19 ± 0.04	0.24 ± 0.05	0.22 ± 0.03
3.1	13	8	0.84 ± 0.14	1.13 ± 0.14	1.11 ± 0.27
3.1	26	16	0.60 ± 0.09	1.04 ± 0.23	1.60 ± 0.22
3.1	40	24	0.19 ± 0.02	0.33 ± 0.05	0.39 ± 0.05
5.1	13	8	1.23 ± 0.18	1.51 ± 0.16	2.42 ± 0.38
5.2	26	16	0.66 ± 0.06	1.23 ± 0.20	2.05 ± 0.41
5.2	40	24	0.46 ± 0.08	1.02 ± 0.11	1.30 ± 0.27

Source: From Phalen, R.F. (1984). With permission.

Table 50 Conversion Table for Gases and Vapors (1 mg/L → ppm, and 1 ppm → mg/L)[a]

Molecular Weight	1 mg/L ppm	1 ppm mg/L	Molecular Weight	1 mg/L ppm	1 ppm mg/L	Molecular Weight	1 mg/L ppm	1 ppm mg/L
1	24,450	0.0000409	26	940	0.001063	51	479	0.002086
2	12,230	0.0000818	27	906	0.001104	52	470	0.002127
3	8,150	0.0001227	28	873	0.001145	53	461	0.002168
4	6,113	0.0001636	29	843	0.001186	54	453	0.002209
5	4,890	0.0002045	30	815	0.001227	55	445	0.002250
6	4,075	0.0002454	31	789	0.001268	56	437	0.002290
7	3,493	0.0002863	32	764	0.001309	57	429	0.002331
8	3,056	0.000327	33	741	0.001350	58	422	0.002372
9	2,717	0.000368	34	719	0.001391	59	414	0.002413
10	2,445	0.000409	35	699	0.001432	60	408	0.002554
11	2,223	0.000450	36	679	0.001472	61	401	0.002495
12	2,038	0.000491	37	661	0.001513	62	394	0.00254
13	1,881	0.000532	38	643	0.001554	63	388	0.00258
14	1,746	0.000573	39	627	0.001595	64	382	0.00262
15	1,630	0.000614	40	611	0.001636	65	376	0.00266
16	1,528	0.000654	41	596	0.001677	66	370	0.00270
17	1,438	0.000695	42	582	0.001718	67	365	0.00274
18	1,358	0.000736	43	569	0.001759	68	360	0.00278
19	1,287	0.000777	44	556	0.001800	69	354	0.00282
20	1,223	0.000818	45	543	0.001840	70	349	0.00286
21	1,164	0.000859	46	532	0.001881	71	344	0.00290
22	1,111	0.000900	47	520	0.001922	72	340	0.00294
23	1,063	0.000941	48	509	0.001963	73	335	0.00299
24	1,019	0.000982	49	499	0.002004	74	330	0.00303
25	987	0.001022	50	489	0.002045	75	326	0.00307

76	322	0.00311	106	230.7	0.00434	136	179.8	0.00556
77	318	0.00315	107	228.5	0.00438	137	178.5	0.00560
78	313	0.00319	108	226.4	0.00442	138	177.2	0.00564
79	309	0.00323	109	224.3	0.00446	139	175.9	0.00569
80	306	0.00327	110	222.3	0.00450	140	174.6	0.00573
81	302	0.00331	111	220.3	0.00454	141	173.4	0.00577
82	298	0.00335	112	218.3	0.00458	142	172.2	0.00581
83	295	0.00339	113	216.4	0.00462	143	171.0	0.00585
84	291	0.00344	114	214.5	0.00466	144	169.8	0.00589
85	288	0.00348	115	212.6	0.00470	145	168.6	0.00593
86	284	0.00352	116	210.8	0.00474	146	167.5	0.00597
87	281	0.00356	117	209.0	0.00479	147	166.3	0.00601
88	278	0.00360	118	207.2	0.00483	148	165.2	0.00605
89	275	0.00364	119	205.5	0.00487	149	164.1	0.00609
90	272	0.00368	120	203.8	0.00491	150	163.0	0.00613
91	269	0.00372	121	202.1	0.00495	151	161.9	0.00618
92	266	0.00376	122	200.4	0.00499	152	160.9	0.00622
93	263	0.00380	123	198.8	0.00503	153	159.8	0.00626
94	260	0.00384	124	197.2	0.00507	154	158.8	0.00630
95	257	0.00389	125	195.6	0.00511	155	157.7	0.00634
96	255	0.00393	126	194.0	0.00515	156	156.7	0.00638
97	252	0.00397	127	192.5	0.00519	157	153.7	0.00642
98	249.5	0.00401	128	191.0	0.00524	158	154.7	0.00646
99	247.0	0.00405	129	189.5	0.00528	159	153.7	0.00650
100	244.5	0.00409	130	188.1	0.00532	160	152.8	0.00654
101	242.1	0.00413	131	186.6	0.00536	161	151.9	0.00658
102	239.7	0.00417	132	185.2	0.00540	162	150.9	0.00663
103	237.4	0.00421	133	183.8	0.00544	163	150.0	0.00667
104	235.1	0.00425	134	182.5	0.00548	164	149.1	0.00671
105	232.9	0.00429	135	181.1	0.00552	165	148.2	0.00675

(Continued)

Table 50 Conversion Table for Gases and Vapors (1 mg/L → ppm, and 1 ppm → mg/L)[a] (Continued)

Molecular Weight	1 mg/L ppm	1 ppm mg/L	Molecular Weight	1 mg/L ppm	1 ppm mg/L	Molecular Weight	1 mg/l ppm	1 ppm mg/L
166	147.3	0.00679	191	128.0	0.00781	216	113.2	0.00883
167	146.4	0.00683	192	127.3	0.00785	217	112.7	0.00888
168	145.5	0.00687	193	126.7	0.00789	218	112.2	0.00892
169	144.7	0.00691	194	126.0	0.00793	219	111.6	0.00896
170	143.8	0.00695	195	125.4	0.00798	220	111.1	0.00900
171	143.0	0.00699	196	124.7	0.00802	221	110.6	0.00904
172	142.2	0.00703	197	124.1	0.00806	222	110.1	0.00908
173	141.3	0.00708	198	123.5	0.00810	223	109.6	0.00912
174	140.5	0.00712	199	122.9	0.00814	224	109.2	0.00916
175	139.7	0.00716	200	122.3	0.00818	225	108.7	0.00920
176	138.9	0.00720	201	121.6	0.00822	226	108.2	0.00924
177	138.1	0.00724	202	121.0	0.00826	227	107.7	0.00928
178	137.4	0.00728	203	120.4	0.00830	228	107.2	0.00933
179	136.6	0.00732	204	119.9	0.00834	229	106.8	0.00937
180	135.8	0.00736	205	119.3	0.00838	230	106.3	0.00941
181	135.1	0.00740	206	118.7	0.00843	231	105.8	0.00945
182	134.3	0.00744	207	118.1	0.00847	232	105.4	0.00949
183	133.6	0.00748	208	117.5	0.00851	233	104.9	0.00953
184	132.9	0.00753	209	117.0	0.00855	234	104.5	0.00957
185	132.2	0.00757	210	116.4	0.00859	235	104.0	0.00961
186	131.5	0.00761	211	115.9	0.00863	236	103.6	0.00965
187	130.7	0.00765	212	115.3	0.00867	237	103.2	0.00969
188	130.1	0.00769	213	114.8	0.00871	238	102.7	0.00973
189	129.4	0.00773	214	114.3	0.00875	239	102.3	0.00978
190	128.7	0.00777	215	113.7	0.00879	240	101.9	0.00982

241	101.5	0.00986	261	93.7	0.01067	281	87.0	0.01149
242	101.0	0.00990	262	93.3	0.01072	282	86.7	0.01153
243	100.6	0.00994	263	93.0	0.01076	283	86.4	0.01157
244	100.2	0.00998	264	92.6	0.01080	284	86.1	0.01162
245	99.8	0.01002	265	92.3	0.01084	285	85.8	0.01166
246	99.4	0.01006	266	91.9	0.01088	286	85.5	0.01170
247	99.0	0.01010	267	91.6	0.01092	287	85.2	0.01174
248	98.6	0.01014	268	91.2	0.01096	288	84.9	0.01178
249	98.2	0.01018	269	90.9	0.01100	289	84.6	0.01182
250	97.8	0.01022	270	90.6	0.01104	290	84.3	0.01186
251	97.4	0.01027	271	90.2	0.01108	291	84.0	0.01190
252	97.0	0.01031	272	89.9	0.01112	292	83.7	0.01194
253	96.6	0.01035	273	89.6	0.01117	293	83.4	0.01198
254	96.3	0.01039	274	89.2	0.01121	294	83.2	0.01202
255	95.9	0.01043	275	88.9	0.01125	295	82.9	0.01207
256	95.5	0.01047	276	88.6	0.01129	296	82.6	0.01211
257	95.1	0.01051	277	88.3	0.01133	297	82.3	0.01215
258	94.8	0.01055	278	87.9	0.01137	298	82.0	0.01219
259	94.4	0.01059	279	87.6	0.01141	299	81.8	0.01223
260	94.0	0.01063	280	87.3	0.01145	300	81.5	0.01227

[a] at 25° and 760 mm Hg

Source: From Fieldner, A.C. et al. (1921); Clayton, G.D. and Clayton, F.E., Eds. (1991). With permission.

Table 51 Calculations Used in Inhalation Toxicology

- ***Chamber air change time***

  Air change (min) = V/F

  where V = volume of the chamber (L)
  F = flow rate through the chamber (L/min)

- ***Time to chamber equilibration (T_x)***

  T_x (min) = K × V/F

  where V = volume of chamber (L)
  F = flow rate through the chamber (L/min)
  K = exponential constant = 4.6 (99% equilibration)
  = 2.3 (90% equilibration)

- ***Minimum flow rate for nose only chamber (Q)***

  Q(L/min) = number of animals × minute volume

- ***Volume-to-volume concentration of gas or vapor in air***

  Concentration (ppm) = volume of vapor or gas (μL)/volume of air (L)

- ***Weight-to-volume/ppm conversion***

  Concentration (mg/m^3) = concentration (ppm) × MW/24.5

  where MW = molecular weight
  24.5 = universal gas constant at 25°C and 760 mmHg

- ***Concentration of pure gas metered into a chamber***

  Concentration (ppm) = flow rate of gas(L/min)/flow rate of chamber(L/min) × 10^6 μL/L

- ***Maximum attainable concentration in air for a volatile liquid***

  Concentration (ppm) = vapor pressure (mmHg)/atmospheric pressure(mmHg) × 10^6 μL/L

  where atmospheric pressure = 760 mm/Hg at sea level

- ***Haber's rule***

  Response = C × T

  where C = exposure concentration
  T = time of exposure

Table 51 Calculations Used in Inhalation Toxicology (Continued)

- ***Nominal concentration***

$$\text{Nominal concentration (mg/m}^3\text{)} = \text{W/V} \times 1000\ \text{L/m}^3$$

where W = quantity (mg) of test material consumed during the exposure
V = volume of air (L) through the chamber during the exposure

- ***Theoretical resting ventilation rate for mammals (V_m)***

$$V_m\ \text{(mL/min)} = 2.18\ M^{3/4}$$

where M = mass of the animal (g)

- ***Theoretical dose from an inhalation exposure***

$$\text{Dose (mg/kg)} = C \times MV \times T \times D/BW$$

where C = concentration of test material in air (mg/L)
MV = minute volume of animal (L/min)
T = time of exposure duration (min)
D = deposition fraction into the respiratory tract
BW = body weight of animal (kg)

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Section 4
Dermal Toxicology

Table 52 Relative Ranking of Skin Permeability in Different Animal Species

Mouse > Guinea Pig > Rabbit > Dog > Monkey > Pig > Human > Chimpanzee
Most permeable → Least permeable

Source: Leung, H-W. and Paustenbach, D.J. (1999).

Table 53 Common Materials Used as Positive Controls

Material	CAS No.	Suggested Concentrations	Category
Sodium lauryl sulfate	151-21-3	1.0%	Irritant
Hexyl cinnamic aldehyde	101-86-0	—	Mild to moderate sensitizer
Mercaptobenzothiazole	149-30-4	—	Mild to moderate sensitizer
Benzocaine	94-09-7	—	Mild to moderate sensitizer
p-Phenylenediamine	106-50-3	—	Sensitizer
2,4-Dinitrochlrobenzene (DNCB)	97-00-7	Induction: 0.1% to 0.5%, 0.25% w/v in ethanol/acetone Challenge: 0.1% to 0.3%, w/v in ethanol/acetone	Sensitizer
Potassium dichromate	7778-50-9	—	Sensitizer
Neomycin sulfate	1405-10-3	—	Sensitizer
Nickel sulfate	7786-81-4	—	Sensitizer
8-Methoxypsoralen (Oxsoralen lotion©)	298-81-7	1.0%	Photoirritant

Table 53 Common Materials Used as Positive Controls (Continued)

Material	CAS No.	Suggested Concentrations	Category
5-Methoxypsoralen (Bergapten)	298-81-7	1.0%	Photoirritant
2,4-Dinitro-3-methyl-6-tertiary-butylanisole (musk ambrette)	83-66-9	Induction: 10.0% w/v in ethanol/acetone Challenge: 0.5% w/v in ethanol/acetone	Photosensitizer
2-Chloro-10-[3-dimethyl-aminopropyl] phenothiazine hydrochloride (chlorpromazine)	50-S3-3	Induction: 1.0% w/v in methanol Challenge: 0.1 % w/v in methanol	Photosensitizer
3,3,4,5-Tetrachlorosalicylanide (TCSA)	11S4-S9-2	Induction: 1.0% w/v in acetone Challenge: 1.0% w/v in acetone	Photosensitizer (in mice and guinea pigs), possible sensitizer in guinea pigs

Source: From Organization for Economic Cooperation and Development (1992), The Commission of the European Communities (1992b), Springborn Laboratories, Inc. (1994a, 1994b, 1994c, 1994d), Hawkins, R.E. et al. (1961), Siglin, J.C. et al. (1991), Ichikawa,H. et al. (1981).

Table 54 Draize Dermal Irritation Scoring System

Erythema and Eschar Formation	Value	Edema Formation	Value
No erythema	0	No edema	0
Very slight erythema (barely perceptible)	1	Very slight edema (barely perceptible)	1
Well-defined erythema	2	Slight edema (edges of area well defined by definite raising)	2
Moderate to severe erythema	3	Moderate edema (raised approximately 1 mm)	3
Severe erythema (beet-redness) to slight, eschar formation (injuries in depth)	4	Severe edema (raised more than 1 mm and extending beyond the area of exposure)	4

Source: From Draize, J.H. (1959).

Table 55 Human Patch Test Dermal Irritation Scoring System

Skin Reaction	Value
No sign of inflammation; normal skin	0
Glazed appearance of the sites, or barely perceptible erythema	±(0.5)
Slight erythema	1
Moderate erythema, possible with barely perceptible edema at the margin, papules may be present	2
Moderate erythema, with generalized edema	3
Severe erythema with severe edema, with or without vesicles	4
Severe reaction spread beyond the area of the patch	5

Source: From Patrick, E. and Maibach, H.I. (1989).

Table 56 Chamber Scarification Dermal Irritation Scoring System

Skin Reaction	Value
Scratch marks barely visible	0
Erythema confined to scratches; perceptible erythema	1
Broader bands of increased erythema, with or without rows of vesicles, pustules, or erosions	2
Severe erythema with partial confluency, with or without other lesions	3
Confluent, severe erythema sometimes associated with edema, necrosis, or bullae	4

Source: From Patrick, E. and Maibach, H.I. (1989).

Table 57 Magnusson Sensitization Scoring System

Skin Reaction	Value
No reaction	0
Scattered reaction	1
Moderate and diffuse reaction	2
Intense reddening and swelling	3

Source: From Magnusson, B. and Kligman, A. (1970).

Table 58 Split Adjuvant Sensitization Scoring System

Skin Reaction	Value
Normal skin	0
Very faint, nonconfluent pink	±
Faint pink	+
Pale pink to pink, slight edema	++
Pink, moderate edema	+++
Pink and thickened	++++
Bright pink, markedly thickened	+++++

Source: From Klecak, G. (1983).

Table 59 Buehler Sensitization Scoring System

Skin Reaction	Value
No reaction	0
Very faint erythema, usually confluent	±(0.5)
Faint erythema, usually confluent	1
Moderate erythema	2
Strong erythema, with or without edema	3

Source: From Buehler, E.V. and Griffin, F. (1975).

Table 60 Contact Photosensitization Scoring System

Skin Reaction	Value
No erythema	0
Minimal but definite erythema confluent	1
Moderate erythema	2
Considerable erythema	3
Maximal erythema	4

Source: From Harber, L.C. et al. (1993).

Table 61 Human Patch Test Sensitization Scoring System

Skin Reaction	Value
Doubtful reaction; faint erythema only	? or + ?
Weak positive reaction; erythema, infiltration, discrete papules	+
Strong positive reaction; erythema, infiltration, papules, vesicles	++
Extreme positive reaction; intense erythema, infiltration, and coalescing vesicles	+++
Negative reaction	—
Irritant reaction of different types	IR
Not tested	NT

Source: From Fischer, T. and Maibach, H.I. (1991).

Table 62 Environmental Protection Agency (EPA) Method of Calculating the Primary Irritation Index (PII) for Dermal Irritation Studies

Option 1
Separately add up each animal's erythema and edema scores for the 1-, 24-, 48-, and 72-hr scoring intervals. Add all six values together and divide by the (number of test sites × 4 scoring intervals).
Option 2
Add the 1-, 24-, 48-, and 72-hr erythema and edema scores for all animals and divide by the (number of test sites × 4 scoring intervals).

Source: From U.S. Environmental Protection Agency (1984a) and (1992).

Table 63 Federal Hazardous Substances Act (CPSC-FHSA) Method of Calculating the Primary Irritation Index (PII) for Dermal Irritation Studies

Option 1
Separately add up each animal's intact and abraded erythema and edema scores for the 25- and 72-hr scoring intervals. Add all six values together and divide by the (number of test sites × 2 scoring intervals).
Option 2
Add the 25- and 72-hr erythema and edema scores for all animals (intact and abraded sites) and divide by the (number of test sites × 2 scoring intervals).

Source: From U.S. Consumer Products Safety Commission (1993).

Table 64 European Economic Community's (EEC) Method of Calculating the Primary Irritation Index (PII) for Dermal Irritation Studies

1. *Erythema: Add all 24-, 48-, and 72-hr erythema scores for each animal together and divide by the (number of test sites × 3 scoring intervals).*
2. *Edema: Add all 24-, 48-, and 72-hr edema scores for each animal together and divide by the (number of test sites × 3 scoring intervals).*

Source: From the Commission of the European Communities (1992a).

Table 65 Environmental Protection Agency (EPA) Dermal Classification System

Primary Irritation Index	Irritation Rating
0.00	Nonirritant
0.01–1.99	Slight irritant
2.00–5.00	Moderate irritant
5.01–8.00	Severe irritant

Source: From U.S. Environmental Protection Agency (1988).

Table 66 Environmental Protection Agency (EPA) Standard Evaluation Procedure Dermal Classification System

Mean Score (Primary Irritation Index)	Response Category
0–0.4	Negligible
0.5–1.9	Slight
2–4.9	Moderate
5–8.0	Strong (primary irritant)

Source: From U.S. Environmental Protection Agency (1984b).

Table 67 Federal Fungicide, Insecticide, and Rodenticide Act (EPA-FIFRA) Dermal Classification System

Toxicity Category	Warning Label
I	Corrosive. Causes eye and skin damage (or irritation). Do not get in eyes, on skin, or on clothing. Wear goggles or face shield and gloves when handling. Harmful or fatal if swallowed. (Appropriate first aid statement required.)
II	Severe irritation at 72 hr. Causes eye (and skin) irritation. Do not get on skin or on clothing. Harmful if swallowed. (Appropriate first aid statement required.)
III	Moderate irritation at 72 hr. Avoid contact with skin, eyes, or clothing. In case of contact, immediately flush eyes or skin with plenty of water. Get medical attention if irritation persists.
IV	Mild or slight irritation at 72 hr. (No precautionary statements required.)

Source: From U.S. Environmental Protection Agency (1993a).

Table 68 European Economic Community (EEC) Dermal Classification System

Mean Erythema Score	Irritation Rating
0.00–1.99	Nonirritant
≥2.00	Irritant
Mean Edema Score	**Irritation Rating**
0.00–1.99	Nonirritant
≥2.00	Irritant

Source: From The Commission of the European Communities (1983).

Table 69 Federal Hazardous Substances Act (CPSC-FHSA) Dermal Classification System

Primary Irritation Score	Irritation Rating
0.00–4.99	Nonirritant
≥5.00	Irritant

Source: From U.S. Consumer Products Safety Commission (1993).

Table 70 Draize Dermal Classification System

Primary Irritation Index	Irritation Rating
<2	Mildly irritating
2–5	Moderately irritating
>5	Severely irritating

Source: From Patrick, E. and Maibach, H.I. (1989).

Table 71 Department of Transportation (DOT), Occupational Safety and Health Administration (OSHA), and International Maritime Organization (IMO) Packing Group Classification System

Packing Group	Definition
I	Materials that cause full-thickness destruction of intact skin tissue within an observation period of up to 60 min starting after the exposure time of 3 min or less.
II	Materials other than those meeting Packing Group I criteria that cause full-thickness destruction of intact skin tissue within an observation period of up to 14 days starting after the exposure time of more than 3 min but not more than 60 min.
III	Materials other than those meeting Packing Group I or II criteria—1.That cause full-thickness destruction of intact skin tissue within an observation period of up to 14 days starting after the exposure time of more than 60 min but not more than 4 hr; or 2. That do not cause full-thickness tissue destruction of intact skin tissue but exhibit a corrosion rate on steel or aluminum surfaces exceeding 6.25 mm (0.25 in.)/yr at a test temperature of 55°C (130°F).

Source: U.S. Occupational Safety and Health Administration (1991), DOT (1998), International Maritime Dangerous Goods Code (1994).

Table 72 Maximization Sensitization Classification System

Sensitization Rate (%)	Grade	Classification
0	—	Nonsensitizer
>0–8	I	Weak sensitizer
9–28	II	Mild sensitizer
29–64	III	Moderate sensitizer
65–80	IV	Strong sensitizer
81–100	V	Extreme sensitizer

Source: From Magnusson, B. and Kligman, A. (1970).

Table 73 Optimization Sensitization Classification System

Intradermal Positive Animals (%)	Epidermal Positive Animals (%)	Classification
s, >75	and/or s, >50	Strong sensitizer
s, 50–75	and/or s, 30–50	Moderate sensitizer
s, 30–50	n.s., 0–30	Weak sensitizer
n.s., 0–30	n.s., 0	No sensitizer

Note: s, significant; n.s., not significant (using Fisher's Exact Test).

Source: From Patrick, E. and Maibach, H.I. (1989).

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Section 5
Ocular Toxicology

Table 74 Scale of Weighted Scores for Grading the Severity of Ocular Lesions (developed by Draize et al)

In 1994, Draize et al.[1] described an eye irritancy grading system for evaluating drugs and other materials intended for use in or around the eye. Numerical scores were assigned for reactions of cornea, iris, and conjunctiva. The total ocular irritation score was calculated by a formula that gave the greatest weight to corneal changes (total maximum = 80). A total maximum score = 10 for the iris, and 20 for the conjunctiva.

I. Cornea

A. Opacity-Degree of Density (area that is most dense is taken for reading)
- Scattered or diffuse area — details of iris clearly visible 1
- Easily discernible translucent areas, details of iris clearly visible 2
- Opalescent areas, details of iris not visible, size of pupil barely discernible 3
- Opaque, iris invisible 4

B. Area of Cornea Involved
- One-quarter (or less) but not zero 1
- Greater than one–quarter — less than one-half 2
- Greater than one-half — less than three-quarters 3
- Greater than three-quarters — up to whole area 4

Score equals A × B × 5 Total maximum = 80

II. Iris

A. Values

Folds have normal, congestion, swelling, circumcorneal injection (any one or all of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive) 1

No reaction to light, hemorrhage; gross destruction (any one or all of these) 2

Score equals A × 5 Total possible maximum = 10

III. Conjunctivae

A. Redness (refers to palpebral conjunctivae only)
- Vessels definitely injected above normal 1
- More diffuse, deeper crimson red, individual vessels not easily discernible 2
- Diffuse beefy red 3

Table 74 Scale of Weighted Scores for Grading the Severity of Ocular Lesions (developed by Draize et al) (Continued)

B. Chemosis
Any swelling above normal (includes nictitating membrane) 1
Obvious swelling with partial eversion of the lids..... 2
Swelling with lids about half-closed 3
Swelling with lids about half-closed to completely closed..... 4

C. Discharge
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals) 1
Discharge with moistening of the lids and hairs just adjacent to the lids..... 2
Discharge with moistening of the lids and considerable area around the eye 3

Score (A + B + C) × 2 Total maximum = 20

Note: The maximum total score is the sum of all scores obtained for the cornea, iris, and conjunctiva.

Table 75 Grades for Ocular Lesions

The following standardized grading system is used in testing guidelines of several U.S. federal agencies (Consumer Product Safety Commission, Occupational Safety and Health Administration, Food and Drug Administration, Environmental Protection Agency, and Food Safety and Quality Service of the Department of Agriculture) and the Organization for Economic Cooperation and Development (OECD) member countries.

Cornea

Opacity: degree of density (area most dense taken for reading)

No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster, details of iris clearly visible)	1[a]
Easily discernible translucent areas, details of iris slightly obscured	2
Nacreous areas, no details of iris visible, size of pupil barely discernible	3
Opaque cornea, iris not discernible through the opacity	4

Iris

Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperemia, or injection, any of these or any combination thereof, iris still reacting to light (sluggish reaction is positive)	1[a]
No reaction to light, hemorrhage, gross destruction (any or all of these)	2

Conjunctivae

Redness (refers to palpebral and bulbar conjunctivae, excluding cornea and iris)

Blood vessels normal	0
Some blood vessels definitely hyperemic (injected)	1
Diffuse, crimson color, individual vessels not easily discernible	2[a]
Diffuse beefy red	3

Chemosis: lids and/or nictitating membranes

No swelling	0
Any swelling above normal (includes nictitating membranes)	1
Obvious swelling with partial eversion of lids	2[a]
Swelling, with lids about half closed	3
Swelling, with lids more than half closed	4

[a] Readings at these numerical values or greater indicate positive responses.

Table 76 Classification of Compounds Based on Eye Irritation Properties

This classification scheme, developed by Kay and Calandra (1962),[2] utilizes the Draize scoring system to rate the irritating potential of substances.

1. Step 1

Using the Draize eye irritation scoring system, find the maximum mean total score for all three tissues (cornea, iris, and conjunctivae) occurring within the first 96 hr after instillation for which the incidence of this score plus or minus 5 points is at least 40%.

2. Step 2

Choose an initial or "tentative rating" on the basis of the score found in Step 1 as follows:

Score from Step 1	Tentative Eye Irritation Rating	Symbol
0.0–0.5 points	Nonirritating	N
0.5–2.5 points	Practically nonirritating	PN
2.5–15 points	Minimally irritating	M_1
15–25 points	Mildly irritating	M_2
25–50 points	Moderately irritating	M_3
50–80 points	Severely irritating	S
80–100 points	Extremely irritating	E
100–110 points	Maximally irritating	M_x

For borderline scores, choose the higher rating.

3. Step 3

Tentative Rating	Requirement for Maintenance
N	$MTS_{24} = 0$; for $MTS_{24} > 0$, raise one level
PN	As for N
M_1	$MTS_{48} = 0$; for $MTS_{48} > 0$, raise one level
M_2	$MTS_{96} = 0$; for $MTS_{96} > 0$, raise one level
M_3	1. $MTS_f \leq 20$; for $MTS_f > 20$, raise one level 2. $ITS_f \leq 10$ (60%); if not true, then no rabbit may show ITS_f 30; otherwise, raise one level
S	1. As for M_3 except use $MTS_f \leq 40$ 2. As for M_3 except use $ITS_f \leq 30$ (60%) and 60 for high

Table 76 Classification of Compounds Based on Eye Irritation Properties (Continued)

Tentative Rating	Requirement for Maintenance
E	1. As for M_3 except use $MTS_f \leq 80$
	2. As for M_3 except use $ITS_f \leq 60$ (60%) and 100 for high
M_x	1. $MTS_f > 80$ (60%); for $MTS_f \leq 80$, lower one level
	2. $ITS_f > 60$ (60%); otherwise lower one level

Note 1: Symbols: MTS = mean total score; ITS = individual rabbit total score. Subscripts denote scoring interval: 24, 48, or 96 hr; f = final score (7 days).

Note 2: Two requirements must be met before a tentative rating may become final. First, the mean total score for the 7-day scoring interval may not exceed 20 points if the rating is to be maintained. Second, individual total scores for at least 60% of the rabbits should be 10 points or less and in no case may any individual rabbit's total score exceed 30. If either or both of these requirements are not met, then the "tentative rating" must be raised one level, and the higher level becomes the "final rating."

Table 77 NAS Classification Method Based on Severity and Persistence

This descriptive scale, adapted from work conducted by Green et al. (1978), attaches significance to the persistence and reversibility of responses. It is based on the most severe response observed in a group of animals rather than the average response.

1. **Inconsequential or Complete Lack of Irritation**

   Exposure of the eye to a material under the specified conditions causes no significant ocular changes. No staining with fluorescein can be observed. Any changes that occur clear within 24 hr and are no greater than those caused by isotonic saline under the same conditions.

2. **Moderate Irritation**

   Exposure of the eye to the material under the specified conditions causes minor, superficial, and transient changes of the cornea, iris, or conjunctiva as determined by external or slit lamp examination with fluorescein staining. The appearance at the 24-hr or subsequent grading of any of the following changes is sufficient to characterize a response as moderate irritation: opacity of the cornea (other than a slight dulling of the normal luster), hyperemia of the iris, or swelling of the conjunctiva. Any changes that are seen clear up within 7 days.

3. **Substantial Irritation**

   Exposure of the eye to the material under the specified conditions causes significant injury to the eye, such as loss of the corneal epithelium, corneal opacity, iritis (other than a slight injection), conjunctivitis, pannus, or bullae. The effects clear up within 21 days.

4. **Severe Irritation or Corrosion**

   Exposure of the eye to the material under the specified conditions results in the same types of injury as in the previous category and in significant necrosis or other injuries that adversely affect the visual process. Injuries persist for 21 days or more.

Source: From National Academy of Sciences (1977).

Table 78 Modified NAS Classification Method Developed by Brendan J. Dunn, Department of Toxicology and Risk Assessment, Honeywell International Inc. (unpublished)

This classification scheme helps distinguish mildly irritating substances from moderately irritating ones, as well as identifying strongly and severely irritating substances. It is based on the most severe ocular response observed in a group of animals, rather than the average response, and on the persistence of the response.

1. **Nonirritation**
   Exposure of the eye to the material under the specified conditions caused no ocular changes. No tissue staining with fluorescein was observed. Slight conjunctival injection (Grade 1, some vessels definitely injected) that does not clear within 24 hr is not considered a significant change. This level of change is inconsequential as far as representing physical damage to the eye and can be seen to occur naturally for unexplained reasons in otherwise normal rabbits.
2. **Mild Irritation**
   Exposure of the eye to the material under the specified conditions caused minor and/or transient changes as determined by external or slit lamp examination or fluorescein staining. No opacity, ulceration, or fluorescein staining of the cornea (except for staining that is characteristic of normal epithelial desquamation) was observed at any grading interval. The appearance of any of the following changes was sufficient to characterize a response as mild irritation:
   - Grade 1 hyperemia of the iris that is observed at 1 hr, but resolves by 24 hr
   - Grade 2 conjunctival hyperemia that is observed at 1, 24, and/or 48 hr, but resolves by 72 hr
   - Grade 2 conjunctival chemosis that is observed at 1 hr, but diminishes to grade 1 or 0 by 24 hr; or Grade 1 conjunctival chemosis that is observed at 1, and/or 24, and/or 48 hr, but resolves by 72 hr
3. **Moderate Irritation**
   Exposure of the eye to the material under the specified conditions caused major ocular changes as determined by external or slit lamp examination or fluorescein staining. The appearance of any of the following changes was sufficient to characterize a response as moderate irritation:
   - Opacity of the cornea (other than slight dulling of the normal luster) at any observation period, but resolves by day 7
   - Ulceration of the cornea (absence of a confluent patch of corneal epithelium) at any observation period, but resolves by day 7
   - Fluorescein staining of the cornea (greater than that which is characteristic of normal epithelial desquamation) at 1, 2, 3, and/or 4 days, but no staining is found by day 7
   - Grade 1 or 2 hyperemia of the iris (circumcorneal injection) that persists for 24 hr or longer, but resolves by day 7

Table 78 Modified NAS Classification Method Developed by Brendan J. Dunn, Department of Toxicology and Risk Assessment, Honeywell International Inc. (unpublished) (Continued)

- Grade 2 conjunctival hyperemia that persists for at least 72 hr, but resolves by day 7; or Grade 3 conjunctival hyperemia observed at any observation period, but resolves by day 7
- Grade 1 or greater conjunctival chemosis that persists for 72 hr or longer, but resolves by day 7

4. **Strong Irritation (clearing within 21 days)**
   Exposure of the eye to the material under the specified conditions resulted in the type of injury described in the former category, but the effects (possibly including pannus or bullae) healed or cleared with 21 days.
5. **Severe Irritation (persisting for 21 days) or Corrosion**
   Exposure of the eye to the material under the specified conditions resulted in the type of injury described in the two former categories, but caused significant tissue destruction (necrosis) or injuries that probably adversely affected the visual process. The effects of the injuries persisted for 21 days.

Table 79 Categorization of Substances Using the Slit Lamp Biomicroscope and Fluorescein

Site	"Accept"	"Accept with Caution"	"Probably Injurious to Human Eyes"
Conjunctiva	Hyperemia without chemosis	Chemosis, less than 1 mm at the limbus	Chemosis, greater than 1 mm at the limbus
Cornea	Staining, corneal stippling[a] without confluence at 24 hr	Confluence[b] of staining at 24–48 hr	Staining with infiltration or edema
Anterior chamber	0	0	Flare[c] (visibility of slit beam; rubeosis of iris)

[a] Corneal stippling: multiple discrete punctate irregularities in the corneal epithelial layer that retain fluorescein.

[b] Confluence: uniform zones for fluorescein retention larger than 1 mm in diameter.

[c] Flare: Tyndall effect in a beam traversing the aqueous humor.

Source: From Beckley, J.H. et al. (1969) and U.S. Environmental Protection Agency (1988).

Table 80 Categorization and Labeling of Pesticides (label statements regarding eye irritation due to pesticides)

	Toxicity Category	Signal Word	Skull and Crossbones and "Poison" Required	Precautionary Statement	Practical Treatment
I.	Corrosive (irreversible destruction of ocular tissue), corneal involvement or irritation persisting for more than 21 days	Danger	No	Corrosive.[a] Causes irreversible eye damage. Harmful if swallowed. Do not get in eyes or on clothing. Wear goggles, face shield, or safety glasses.[b] Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.	*If in eyes*: flush with plenty of water. Get medical attention. *If swallowed*: promptly drink a large quantity of milk, egg whites, or gelatin solution; or, if these are not available, drink large quantities of water. Avoid alcohol. *NOTE TO PHYSICIAN*: Probable mucosal damage may contraindicate the use of gastric lavage.
II.	Corneal involvement or irritation clearing in 21 days or less	Warning	No	Causes substantial but temporary eye injury. Do not get into eyes or on clothing. Wear goggles, face shield, or safety glasses.[b] Harmful if swallowed. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.	Same as above; omit *NOTE TO PHYSICIAN* statement.

Table 80 Categorization and Labeling of Pesticides (label statements regarding eye irritation due to pesticides) (Continued)

	Toxicity Category	Signal Word	Skull and Crossbones and "Poison" Required	Precautionary Statement	Practical Treatment
III.	Corneal involvement or irritation clearing in 7 days or less	Caution	No	Causes (moderate) eye injury (irritation). Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling.	*If in eyes*: Flush with plenty of water. Get medical attention if irritation persists.
IV.	Minimal effects clearing in less than 24 hr	Caution	No	None required	None required

[a] The term *corrosive* may be omitted if the product is not actually corrosive.

[b] Choose appropriate form of eye protection. Recommendation for goggles or face shield is more appropriate for industrial, commercial, or nondomestic uses. Safety glasses may be recommended for domestic or residential use.

Source: From Camp, D.D. (1984).

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Section 6
Genetic Toxicology/ Carcinogenesis

Table 81 Mutagenicity Assay Bacteria Strains[a] Overview

TA98 TA1537 TA97 TA97a	Reverted by frame-shift mutagens
TA100 TA1535 TA102[b] (detects oxidative mutagens and cross-linking agents) WP2 *uvrA*[b] WP2 *uvrA* (pKM101)[b] (detects cross-linking agents)	Reverted by base substitution mutagens

[a] A standard battery of strains for a full mutagenicity assay usually consists of five strains consisting of TA98, TA100, TA1535, TA1537 (or TA97 or TA97a), and TA102 (or WP2 uvrA or WP2 uvrA (pKM101). Strains with TA designations are *S. typhimurium* and WP2 designations are *E. coli*.

[b] Strain TA102 and the *E. coli* strains possess A–T base pairs at the site of mutation. Other strains possess G–C base pairs at their mutation sites.

Table 82 The Genetic Code

Codon	Amino Acid	Codon	Amino Acid
UUU or UUC	Phenylalanine	UAA orUAG	Nonsense (ochre) Nonsense (amber)
UUA or UUG	Leucine	CAU or CAC	Histidine
CUU, CUC, CUA, or CUG	Leucine	CAA or CAG	Glutamine
AUU, AUC, or AUA	Isoleucine	AAU or AAC	Asparagine
AUG	Methionine	AAA or AAG	Lysine
GUU, GUC, GUA, or GUG	Valine	GAU or GAC	Aspartic acid
UCU or UCC	Serine	GAA or GAG	Glutamic acid
UCA or UCG	Serine	UGU or UGC	Cysteine
CCU, CCC, CCA, or CCG	Proline	UGA	Nonsense (umber)
ACU, ACC, ACA, or ACG	Threonine	CGU, CGC, CGA, or CGG	Arginine
GCU, GCC, GCA, or GCG	Alanine	AGU or AGC	Serine
UAU or UAC	Tyrosine	AGA or AGG	Arginine
		GGU, GGC, GGA, or GGG	Glycine

Table 83 Characteristics of Initiation, Promotion, and Progression

Initiation	Promotion	Progression
• Irreversible	• Reversible	• Irreversible
• Additive	• Nonadditive	• Karyotypic abnormalities appear accompanied by increased growth rate and invasiveness
• Dose response can be demonstrated; does not exhibit a readily measurable threshold	• Dose response having a measurable threshold can be demonstrated	• Benign and/or malignant tumor observed
• No measurable maximum response	• Measurable maximum effect	• Environmental factors influence early stage of progression
• Initiators are usually genotoxic	• Promoters are usually not mutagenic	• Progressors may not be initiators
• One exposure may be sufficient	• Prolonged and repeated exposure to promoters required	• Progressors act to advance promoted cells to a potentially malignant stage
• Must occur prior to promotion	• Promoter effective only after initiation has occurred	• Spontaneous progression can occur
• Requires fixation through cell division	• Promoted cell population dependent on continued presence of promoter	
• Initiated cells are not identifiable except as foci lesions following a period of promotion	• Causes expansion of the progeny of initiated cells, producing foci lesions	
• "Pure" initiation does not result in neoplasia without promotion	• "Pure" promoters not capable of initiation	
• Spontaneous (fortuitous) initiation can occur	• Sensitive to hormonal and dietary factors	

Source: Adapted from Pitot, H.C. (1991) and Maronpot, R.R. (1991).

Table 84 Classification of Carcinogenic Chemicals Based on Mode of Action

	Classification[a]	Mode of Action	Examples
I.	Genotoxic	Agents that interact with DNA.	
	1. Direct acting (primary carcinogen; activation-independent)	Organic chemicals; direct alteration of DNA, chromosome structure or number, metabolic conversion not required; generation of reactive electrophiles and covalent binding to DNA.	Bischloromethylether, β-propiolactone, ethylene imine
	2. Procarcinogen (secondary carcinogen; activation-dependent)	Organic chemicals; requires biotransformation to a direct-acting carcinogen (proximate carcinogen).	Nitrosamines, ethylene dibromide, vinyl chloride
	3. Inorganic carcinogen	Direct effects on DNA may occur through interference with DNA replication.	Nickel, cadmium
II.	Epigenetic	Agents for which there is no direct evidence of interaction with DNA.	
	4. Cytotoxin	Cytolethal; induction of regenerative cell proliferation; mutations may occur secondarily through several mechanisms, including release of nucleases, generation of reactive oxygen radicals, DNA replication before adduct repair; preferential growth of preneoplastic cells may be caused by selective killing of normal cells or expression of growth control genes (oncogenes).	Nitrilo triacetic acid, chloroform

Table 84 Classification of Carcinogenic Chemicals Based on Mode of Action (Continued)

	Classification[a]	Mode of Action	Examples
5.	Mitogen	Stimulation of mitogenic cell proliferation directly or via a cellular receptor; mutations may occur secondarily as a result of increased cell proliferation; preferential growth of preneoplastic cells may be caused through alteration of rates of cell birth or death.	Phenobarbital, α-hexachloro-cyclohexane
6.	Peroxisome proliferator	Generation of reactive oxygen radicals through perturbation of lipid metabolism; growth control genes may be activated directly or via a cellular receptor.	Fenofibrate, diethylhexyl phthalate, clofibrate
7.	Immunosuppressor	Enhancement of the development of virally induced, transplanted and metastatic neoplasms, possibly through impairment or loss of natural and acquired tumor resistance.	Azathioprine, cyclosporin A, 6-mercaptopurine
8.	Hormones and hormonal-altering agents	Chronic stimulation of cell growth through activation of regulatory genes; other potential modes of action include promotional effects resulting from alteration of hormonal homeostasis, inhibition of cell death (apoptosis), generation of reactive radicals.	Estrogens, diethylstilbestrol, synthetic androgens
9.	Solid-state carcinogen	Generally only mesenchymal cells/tissues affected; physical size and shape of agent is critical; mechanism of action uncertain.	Polymers (plastic), metal foils (gold), asbestos

Table 84 Classification of Carcinogenic Chemicals Based on Mode of Action (Continued)

	Classification[a]	Mode of Action	Examples
10.	Cocarcinogen	*Simultaneous* administration enhances the carcinogenic process caused by a genotoxic carcinogen; possible mechanisms include enhanced biotransformation of a procarcinogen, inhibition of detoxification of a primary carcinogen, enhanced absorption or decreased elimination of a genotoxic carcinogen.	Phorbol esters, catechol, ethanol
11.	Promoter	Administration subsequent to a genotoxic agent promotes tumor formation through enhancement of the clonal expansion of preneoplastic cells; multiple and diverse mechanisms proposed.	Phorbol esters, saccharin, croton oil
12.	Progressor	Development of initiated/promoted cells influenced; associated with alterations in biochemical and morphological characteristics, increased growth rate, invasiveness, and metastases; direct or indirect induction of structural (karyotypic) changes to chromosomes.	Arsenic salts, benzene, hydoxyurea

[a] Classifications shown are not rigid. For example, a chemical may be both genotoxic and mitogenic or cytotoxic; phorbol ester can be both a promoter and a cocarcinogen.

Source: Adapted from Weisburger, J.H. and Williams, G.M. (1980). *Additional sources*: Pitot, H.C. and Dragon, Y.P. (1993); Pitot, H.C. (1993); Maronpot, R.R. (1991); and Butterworth, B.E. and Goldsworthy, T.L. (1991).

Table 85 Reported Percentage Incidence (Range) of Spontaneous Tumor Formation in Various Mouse Strains

Organ/Tissue	CD-1		B6C3F1	
	Male	Female	Male	Female
Adrenal	0–27.9(%)	0–38	<1.0–1.4	<1.0
Body cavities	—	—	<1.0	<1.0
Brain	—	0–2.0	<0.1–0.1	0–0.1
Circulatory system	—	—	<1.0–2.9	<1.0–2.4
Heart	—	—	0.1–<1.0	0–0.1
Intestines	—	—	<1.0	<1.0
Kidney	0–2.8	0–1.4	<1.0	<0.1–<1.0
Leukemia/ lymphoma	0–8.6	1.4–25.0	1.6–19.0	1.7–33.2
Liver	0–17.3	0–7.1	15.6–40.1	2.5–10.5
Lung/trachea	0–26.0	0–38.6	9.2–22.5	3.5–7.1
Mammary gland	—	0–7.3	—	<1.0–1.3
Ovary	NA	0–4.8	NA	<1.0
Pancreas	—	—	0.1–2.1	<0.1–<1.0
Pancreatic islets	0–2.1	0–1.4	<1.0	<1.0
Pituitary	0–0.8	0–10.0	<1.0	3.2–13.1
Skin/subcutaneous	0–2.8	0–2.0	<0.1–1.9	0.1–1.6
Stomach	0–4.9	0–3.8	0.3–1.1	<1.0
Testes[a]	0–2.0	NA	<1.0	NA
Thyroid	0–2.0	—	1.0–1.1	<1.0–1.7
Urinary bladder	0–2.0	0–1.4	0–0.1	<0.1–1.0
Uterus/vagina	NA	0–13.3	NA	1.2–1.9

[a] Includes prostate and seminal vesicles.

Source: Adapted from Gad, S.C. and Weil, C.S. (1986). *Additional sources*: Chu, K. (1977), Fears, T.R. et al. (1977), Page, N.P. (1977), Gart, J.J. et al. (1979), Tarone, R.E. et al. (1981), Rao, G.N. et al. (1990), and Lang, P.L. (1987).

Table 86 Reported Percentage Incidence (Range) of Spontaneous Tumor Formation in Various Rat Strains

Organ/Tissue	F-344		Sprague-Dawley		Wistar	
	Male	Female	Male	Female	Male	Female
Adrenal	2.4–38.1(%)	4.0–12.0	1.4–7.6	2.7–4.3	0–48.6	0–57.1
Body cavities	<1.0–9.0	0.3–1.9	1.1–1.4	1.8	—	—
Brain	0.8–8.1	<1.0	1.4–2.7	0.9–1.6	0–8.0	0–6.0
Circulatory system	0.4–3.8	<1.0	0.5	—	—	—
Heart	<1.0	<1.0	—	—	0	0
Intestines	<1.0	<1.0	—	0.5	0–2.0	0–2.1
Kidney	<1.0	<1.0	1.6	0.9	0–2.0	0–2.0
Leukemia/ lymphoma	6.5–48.0	2.1–24.6	1.9–2.2	1.4–1.6	0–12.0	0–16.0
Liver	0.5–3.4	0.5–3.9	1.1	0.5–2.2	0–2.5	0–12.0
Lung/trachea	<1.0–3.0	<1.0–2.0	1.6	2.2	0–5.7	0–2.1
Mammary gland	0–1.5	8.5–41.0	0.5–2.3	36.4–45.1	0–4.0	1.3–24.0
Ovary	NA	<1.0	NA	1.1	NA	0–4.3
Pancreas	0.2–6.0	0	—	—	—	—
Pancreatic islets	0.8–4.9	0.8–1.3	0.9–2.7	0.5	0–5.9	0–4.0
Pituitary	4.7–34.7	0.3–58.6	11.2–33.2	37.3–57.6	2.3–58.3	6.7–68.0
Preputial gland	1.4–2.4	1.2–1.8	—	—	—	—
Skin/ subcutaneous	5.7–7.8	2.5–3.2	2.8–6.5	3.2–3.8	0–12.0	0–4.0
Stomach	<1.0	<1.0	—	—	0	0–2.2
Testes[a]	2.3–90.0	NA	4.2–4.3	NA	0–22.0	NA
Thyroid	3.6–12.0	4.7–10.0	1.9–3.8	1.8	0–19.3	2.5–22.4
Urinary bladder	<1.0	<1.0	0.5	—	0–2.0	0–2.0
Uterus/vagina	NA	5.5–24.6	NA	3.3–4.5	NA	1.1–25.3

[a] Includes prostate and seminal vesicles.

Source: Adapted from Gad, S.C. and Weil, C.S. (1986). *Additional Spouces:* Chu, K. (1977), Fears, T.R. et al. (1977), Page, N.P. (1977), Gart, J.J. et al. (1979), Tarone, R.E. et al. (1981), Rao, G.N. et al. (1990), Goodman, D.G. et al. (1979), Bombard, E. et al. (1986), Walsh, K.M. and Poteracki, J. (1994), Haseman, J.K. (1983).

Table 87 Frequency of Carcinogenic Response to Chemicals by Organ/System—Rats and Mice

	Number Positive at Site (%)[a]	
	Chemicals Evaluated as Carcinogenic in Rats (n = 354)[b]	**Chemicals Evaluated as Carcinogenic in Mice (n = 299)[b]**
Liver	143 (40%)	171 (57%)
Lung	31 (9%)	83 (28%)
Mammary gland	73 (21%)	14 (5%)
Stomach	60 (17%)	42 (14%)
Vascular system	26 (7%)	47 (16%)
Kidney/ureter	45 (13%)	12 (4%)
Hematopoietic system	35 (10%)	39 (13%)
Urinary bladder/urethra	37 (10%)	12 (4%)
Nasal cavity/turbinates	33 (9%)	4 (1%)
Ear/Zymbal's gland	30 (9%)	2
Esophagus	29 (8%)	7 (2%)
Small intestine	21 (6%)	3 (1%)
Thyroid gland	20 (6%)	10 (3%)
Skin	20 (6%)	1
Peritoneal cavity	17 (5%)	7 (2%)
Oral cavity	16 (5%)	1
Large intestine	15 (4%)	—
Central nervous system	15 (4%)	2
Uterus	11 (3%)	5 (2%)
Subcutaneous tissue	10 (3%)	1
Pancreas	9 (3%)	—
Adrenal gland	7 (2%)	4 (1%)
Pituitary gland	7 (2%)	4 (1%)
Clitoral gland	7 (2%)	2
Preputial gland	2	7 (2%)
Testes	6 (2%)	1
Harderian gland	—	6 (2%)
Spleen	6 (2%)	—
Ovary	—	4 (1%)
Gall bladder	—	3 (1%)
Bone	3	—
Mesovarium	2	—
Myocardium	—	2

Table 87 Frequency of Carcinogenic Response to Chemicals by Organ/System—Rats and Mice (Continued)

	Number Positive at Site (%)[a]	
	Chemicals Evaluated as Carcinogenic in Rats (n = 354)[b]	**Chemicals Evaluated as Carcinogenic in Mice (n = 299)[b]**
Prostate	2	—
Vagina	1	—

Note: Based on 354 and 299 chemicals considered carcinogenic to rats and mice, respectively, in long-term chemical carcinogenesis studies from the carcinogenic potency database (CPDB).

[a] Percentages not given when fewer than 1% of the carcinogens were active at a given site.

[b] Chemicals have been excluded for which the only positive results in the CPDB are for "all tumor-bearing animals," i.e., there is no reported target site.

Source: From Gold, L.S. et al. (1991).

Table 88 Capacity of Tissues to Undergo Hyperplasia

High capacity
- Surface epithelium
- Hepatocytes
- Renal tubules
- Fibroblasts
- Endothelium
- Mesothelium
- Hematopoietic stem cells
- Lymphoid cells

Moderate capacity
- Glandular epithelium
- Bone
- Cartilage
- Smooth muscle of vessels
- Smooth muscle of uterus

Low capacity
- Neurons
- Skeletal muscle
- Smooth muscle of GI tract

Source: From Maronpot, R.R. (1991). With permission.

Table 89 Selected Taxonomy of Neoplasia

Tissue	Benign Neoplasia[a]	Malignant Neoplasia[b]
Epithelium		
Squamous	Squamous cell papilloma	Squamous cell carcinoma
Transitional	Transitional cell papilloma	Transitional cell carcinoma
Glandular		
Liver cell	Hepatocellular adenoma	Hepatocellular carcinoma
Islet cell	Islet cell adenoma	Islet cell adenocarcinoma
Connective tissue		
Adult fibrous	Fibroma	Fibrosarcoma
Embryonic fibrous	Myxoma	Myxosarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
Muscle		
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Cardiac muscle	Rhabdomyoma	Rhabdomyosarcoma
Endothelium		
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Blood vessels	Hemangioma	Hemangiosarcoma
Lymphoreticular		
Thymus	(not recognized)	Thymoma
Lymph nodes	(not recognized)	Lymphosarcoma (malignant lymphoma)
Hematopoietic		
Bone marrow	(not recognized)	Leukemia Granulocytic Monocytic Erythroleukemia
Neural tissue		
Nerve sheath	Neurilemmona	Neurogenic sarcoma
Glioma	Glioma	Malignant glioma
Astrocytes	Astrocytoma	Malignant astrocytoma
Embryonic cells	(not recognized)	Neuroblastoma

[a] *oma*, benign neoplasm.

[b] *Sarcoma*, malignant neoplasm of mesenchymal origin; *carcinoma*, malignant neoplasm of epithelial origin.

Source: From Maronpot, R.R. (1991). With permission.

Table 90 Selected Examples of Presumptive Preneoplastic Lesions

Tissue	Presumptive Preneoplastic Lesion[a]
Mammary gland	Hyperplastic alveolar nodules (HANs) Atypical epithelial proliferation Lobular hyperplasia Intraductal hyperplasia Hyperplastic terminal duct
Liver	Foci of cellular alteration Hepatocellular hyperplasia Oval cell proliferation Cholangiofibrosis
Kidney	Karyocytomegaly Atypical tubular dilation Atypical tubular hyperplasia
Skin	Increase in dark basal keratinocytes Focal hyperplasia/hyperkeratosis
Pancreas (exocrine)	Foci of acinar cell alteration Hyperplastic nodules Atypical acinar cell nodules

[a] Many of these presumptive preneoplastic lesions are seen in carcinogenicity studies utilizing specific animal model systems. Generalizations about these presumptive preneoplastic lesions are inappropriate outside the context of the specific animal model system being used.

Source: From Maronpot, R.R. (1991). With permission.

Table 91 Animal Neoplastic Lesions of Questionable Significance to Humans

- Male rat renal tumors with α2-globulin nephropathy
- Rodent urinary bladder neoplasia
- β_2-receptor stimulant-induced rat mesovarian leiomyomas
- Rodent stomach carcinoid tumors associated with prolonged acid secretion suppression
- Rodent thyroid follicular cell tumors
- Canine mammary neoplasia related to progestagen administration
- Rodent mammary neoplasia related to estrogen administration
- Rat uterine endometrial carcinomas related to dopamine agonists
- Leydig cell tumors in rat testes
- Mouse ovarian tubulostromal adenomas

Source: Alison et al. (1994). With permission.

Table 92 Comparative Features of Benign and Malignant Neoplasms

	Benign	Malignant
General effect on the host	Little; usually do not cause death	Will almost always kill the host if untreated.
Rate of growth	Slow; may stop or regress	More rapid (but slower than "repair" tissue); autonomous; never stop or regress
Histologic features	Encapsulated; remain localized at primary site	Infiltrate or invade; metastasize
Mode of growth	Usually grow by expansion, displacing surrounding normal tissue	Invade, destroy, and replace surrounding normal tissue
Metastasis	Do not metastasize	Most can metastasize
Architecture	Encapsulated; have complex stroma and adequate blood supply	Not encapsulated; usually have poorly developed stroma; may become necrotic at center
Danger to host	Most without lethal significance	Always ultimately lethal unless removed or destroyed in situ
Injury to host	Usually negligible but may become very large and compress or obstruct vital tissue	Can kill host directly by destruction of vital tissue
Radiation sensitivity	Radiation sensitivity near that of normal parent cell; rarely treated with radiation	Radiation sensitivity increased in rough proportion to malignancy; often treated with radiation.
Behavior in tissue	Cells cohesive and inhibited by mutual contact	Cells do not cohere, frequently not inhibited by mutual contact
Resemblance to tissue origin	Cells and architecture resemble tissue of origin	Cells atypical and pleomorphic; disorganized; bizarre architecture
Mitotic figures	Mitotic figures rare and normal	Mitotic figures may be numerous and abnormal in polarity and configuration
Shape of nucleus	Normal and regular, show usual stain affinity	Irregular; nucleus frequently hyperchromatic
Size of nucleus	Normal; nucleus-to-Cytoplasm ratio near normal	Frequently large; nucleus-to-cytoplasm ratio increased
Nucleolus	Not conspicuous	Hyperchromatic and larger than normal

Source: From Maronpot, R.R. (1991). With permission.

Table 93 Criteria for Determining the Human Relevance of Animal Bioassay Results

Supportive	Not Supportive
Same exposure route as for humans	Different exposure route from that for humans
Tumors with several types of exposure	Tumors with only one type of exposure (not relevant to humans)
Tumors in several species	Tumors in only one species
Tumor site correspondence	No site correspondence across species
Tumors at multiple sites	Tumors at only one site
Tumors at sites of low spontaneous occurrence	Tumors at sites with high background incidence
Tumors in tissues analogous to human tissues	Tumors in animal tissues not relevant to humans
No evidence of cellular toxicity at the target site	Tumors only in organs displaying cellular toxicity
Tumors appear early in life	Tumors detectable only late in life
Tumors progress rapidly (benign to malignant)	Benign tumors only
Tumors usually fatal	Tumors not fatal
Similar metabolism (biotransformation) in animals and humans	Metabolic pathways differ in humans and animals
Genotoxic	Nongenotoxic
DNA-reactive	No reaction with DNA
Mechanism of tumorigenesis relevant to humans	Mechanism of tumorigenesis does not occur in humans
Structural similarity to known human carcinogens	Little structural similarity to known human carcinogens
No evidence for disruption of homeostasis	Homeostasis disrupted

Source: Modified from Ashby et al., 1990. With permission.

Table 94 Known Human Carcinogens

Aflatoxins
Alcoholic beverage consumption
4- Aminobiphenyl
Analgesic mixtures containing phenacetin
Arsenic compounds, inorganic
Asbestos
Azathioprine
Benzene
Benzidine
Beryllium and beryllium compounds
1,3-Butadiene
1,4-Butanediol dimethanesulfonate (Myleran®)
Cadmium and cadmium compounds
Chlorambucil
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (MeCCNU)
bis(Chloromethyl)ether and technical-grade chloromethyl methyl ether
Chromium hexavalent compounds
Coal tar pitches
Coal tars
Coke oven emissions
Cyclophosphamide
Cyclosporin A
Diethylstilbestrol
Dyes metabolized to benzidine
Environmental tobacco smoke
Erionite
Estrogens, steroidal
Ethylene oxide
Hepatitis B virus
Hepatitis C virus
Human Papillomas viruses: Some genital–mucosal types
Melphalan
Methoxsalen with ultraviolet A therapy (PUVA)
Mineral oils (untreated and mildly treated)
Mustard gas
2-Naphthylamine
Neutrons (ionizing radiation)
Nickel compounds
Radon

Table 94 Known Human Carcinogens (Continued)

Silica, crystalline (respirable size)
Smokeless tobacco
Solar radiation
Soots
Strong inorganic acid mists containing sulfuric acid
Sunlamps or sunbeds, exposure to
Tamoxifen
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) "dioxin"
Thiotepa
Thorium dioxide
Tobacco smoking
Vinyl chloride
Ultraviolet radiation, broad spectrum UV radiation
Wood dust
X-Rays and γ radiation

Source: National Toxicology Program (2005).

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Section 7
Neurotoxicology

Table 95 Examples of Potential Endpoints of Neurotoxicity

Behavioral Endpoints
Absence or altered occurrence, magnitude, or latency of sensorimotor reflex
Altered magnitude of neurological measurements, such as grip strength or hindlimb splay
Increases or decreases in motor activity
Changes in rate or temporal patterning of schedule-controlled behavior
Changes in motor coordination, weakness, paralysis, abnormal movement or posture, tremor, ongoing performance
Changes in touch, sight, sound, taste, or smell sensations
Changes in learning or memory
Occurrence of seizures
Altered temporal development of behaviors or reflex responses
Autonomic signs
Neurophysiological Endpoints
Change in velocity, amplitude, or refractory period of nerve conduction
Change in latency or amplitude of sensory-evoked potential
Change in EEG pattern or power spectrum
Neurochemical Endpoints
Alteration in synthesis, release, uptake, degradation of neurotransmitters
Alteration in second messenger-associated signal transduction
Alteration in membrane-bound enzymes regulating neuronal activity
Decreases in brain acetylcholinesterase
Inhibition of neurotoxic esterase
Altered developmental patterns of neurochemical systems
Altered proteins (c-*fos*, substance P)
Structural Endpoints
Accumulation, proliferation, or rearrangement of structural elements
Breakdown of cells
GFAP increases (adults)
Gross changes in morphology, including brain weight
Discoloration of nerve tissue
Hemorrhage in nerve tissue

Source: From U.S. Environmental Protection Agency (1993).

Table 96 Examples of Parameters Recorded in Neurotoxicity Safety Studies

Clinical signs of neurotoxicity (onset and duration)
Body weight changes
Changes in behavior
Observations of skin, eyes, mucous membranes, etc.
Signs of autonomic nervous system effect (e.g., tearing, salivation, diarrhea)
Changes in respiratory rate and depth
Cardiovascular changes such as flushing
Central nervous system changes such as tremors, convulsion, or coma
Time of death
Necropsy results
Histopathological findings of the brain, spinal cord, and peripheral nerves

Source: From Abou-Donia, M.B. (1992).

Table 97 Summary of Measures in the Functional Observational Battery and the Type of Data Produced by Each

Home Cage and Open Field	Manipulative	Physiological
Posture (D)	Ease of removal (R)	Body temperature (I)
Convulsions, tremors (D)	Handling reactivity (R)	Body weight (I)
Palpebral closure (R)	Palpebral closure (R)	
Lacrimation (R)	Approach response (R)	
Piloerection (Q)	Click response (R)	
Salivation (R)	Touch response (R)	
Vocalizations (Q)	Tail pinch response (R)	
Rearing (C)	Righting reflex (R)	
Urination (C)	Landing foot splay (I)	
Defecation (C)	Forelimb grip-strength (I)	
Gait (D,R)	Hindlimb grip-strength (I)	
Arousal (R)	Pupil response (Q)	
Mobility (R)		
Stereotype (D)		
Bizarre behavior (D)		

Note: D, descriptive data; R, rank order data; Q, quantal data; I, interval data; C, count data.

Source: From U.S. Environmental Protection Agency (1993).

Table 98 Toxic Signs of Acetylcholinesterase Inhibition

Muscarinic Effects[a]	Nicotinic Effects[b]	CNS Effects[c]
Bronchoconstriction	Muscular twitching	Giddiness
Increased bronchosecretion	Fasciculation	Anxiety
Nausea and vomiting	Cramping	Insomnia
(absent in rats)	Muscular weakness	Nightmares
Diarrhea		Headache
Bradycardia		Apathy
Hypotension		Depression
Miosis		Drowsiness
Urinary incontinence		Confusion
		Ataxia
		Coma
		Depressed reflex
		Seizure
		Respiratory depression

[a] Blocked by atropine.

[b] Not blocked by atropine.

[c] Atropine might block early signs.

Source: From Chan, P.K. and Hayes, A.W. (1989). With permission.

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Section 8
Immunotoxicology

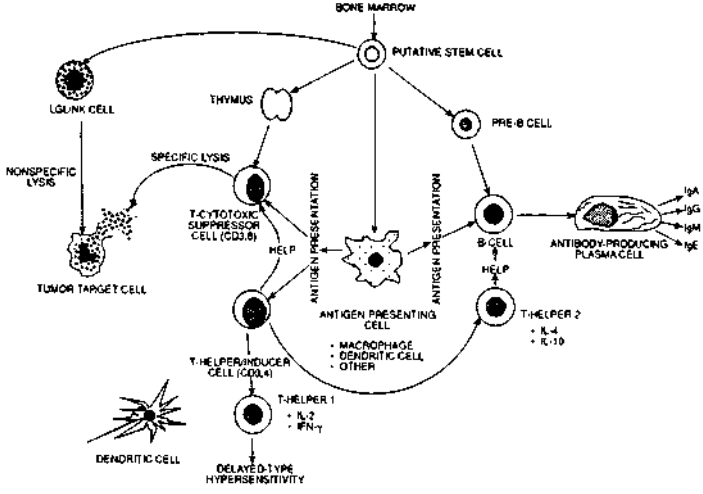

Figure 2 Cellular elements of the immune system.

Table 99 Examples of the Four Types of Hypersensitivity Responses

Agents: Clinical Manifestations	Hypersensitive Reaction	Cells Involved	Antibody	Mechanism of Cell Injury
Food additives: GI allergy Penicillin: urticaria and dermatitis	Type I (anaphylactic)	Mast cell	IgE (and others)	Degranulation and release of inflammatory mediators such as histamine, proteolytic enzymes, chemotactic factors, prostaglandins, and leukotrienes
Cephalosporins: hemolytic anemia Aminopyrine: leukopenia Quinidine, gold: thrombocytopenia	Type II (cytotoxic)	Null (K) cells[a]	IgG, IgM	Antibody-dependent cellular cytotoxicity, or complement-mediated lysis
Hydralazine: systemic lupus erythomatosis Methicillin: chronic glomerulonephritis	Type III (immune complex)	PMNs[b]	IgG, IgM	Immune complex deposition in various tissues activates complement, which attracts PMNs causing local damage by release of inflammatory mediators
Nickel, penicillin, dinitrochloro-benzene, phenothiasines: contact dermatitis	Type IV (delayed hypersensitivity)	T-cells (sensitized); macrophages	None	Release of lymphokines activates and attracts macrophages, which release mediators that induce inflammatory reactions

Note: Defined by Coombs, R.R.A. and Gell, P.G.H. (1968), Classification of allergic reactions responsible for clinical hypersensitivity and disease, in *Clinical Aspects of Immunology*, Gell, P. and Coombs, R., Eds., Blackwell Scientific Publications, Oxford, pp. 121–137.

[a] Also T-cells, monocyte/macrophages, platelets, neutrophils, and eosinophils.

[b] Polymorphonuclear leukocytes.

Source: From Norbury, K. and Thomas, P. (1990). With permission.

Table 100 Examples of Antemortem and Postmortem Findings that May Include Potential Immunotoxicity if Treatment Related

Parameter	Possible Observation (Cause)	Possible State of Immune Competence
	Antemortem	
Mortality	Increased (infection)	Depressed
Body weight	Decreased (infection)	Depressed
Clinical signs	Rales, nasal discharge (respiratory infection)	Depressed
	Swollen cervical area (sislodacryoadenitis virus)	Depressed
Physical examinations	Enlarged tonsils (infection)	Depressed
Hematology	Leukopenia/lymphopenia	Depressed
	Leukocytosis (infection/cancer)	Enhanced/depressed
	Thrombocytopenia	Hypersensitivity
	Neutropenia	Hypersensitivity
Protein electrophoresis	Hypogammaglobulinemia	Depressed
	Hypergammaglobulinemia (ongoing immune response or infection)	Enhanced/activated
	Postmortem	
Organ weights		
Thymus	Decreased	Depressed
Histopathology		
Adrenal glands	Cortical hypertrophy (stress)	Depressed (secondary)
Bone marrow	Hypoplasia	Depressed
Kidney	Amyloidosis	Autoimmunity
	Glomerulonephritis (immune complex)	Hypersensitivity
Lung	Pneumonitis (infection)	Depressed
Lymph node (see also spleen)	Atrophy	Depressed
Spleen	Hypertrophy/hyperplasia	Enhanced/activated
	Depletion of follicles	Depressed B-cells
	Hypocellularity of periarteriolar sheath	Depressed T-cells
	Active germinal centers	Enhanced/activated
Thymus	Atrophy	Depressed
Thyroid	Inflammation	Autoimmunity

Source: From Norbury, K. and Thomas, P. (1990). With permission.

Table 101 U.S. EPA Subdivision M Guidelines for Immunotoxicity Testing of Biochemical Pest Control Agents (BPCA)

I. Tier I

A. Spleen, thymus, and bone marrow cellularity.

B. Humoral Immunity—do one of the following:
   1. Primary and secondary immunoglobulin (IgG and IgM) responses to antigen; or,
   2. Antibody plaque-forming cell assay.

C. Specific cell-mediated immunity—do one of the following:
   1. One-way mixed lymphocyte reaction (MLR) assay; or,
   2. Delayed-type hypersensitivity (DTH) assay; or,
   3. Cytotoxic T-lymphocyte (CTL) assay.

D. Nonspecific cell-mediated immunity:
   1. Natural killer cell activity; and,
   2. Macrophage function.

II. Tier II

A. Tier II studies required if:
   1. Dysfunction is observed in Tier I tests.
   2. Tier I test results cannot be definitively interpreted.
   3. Data from other sources indicate immunotoxicity.

B. General testing features:
   1. Evaluate time course for recovery from immunotoxic effects.
   2. Determine whether observed effects may impair host resistance to infectious agents or to tumor cell challenge.
   3. Perform additional specific, but appropriate, testing essential for evaluation of potential risks.

Source: Adapted from Sjoblad, R. (1988).

Table 102 National Toxicology Program Panel for Detecting Immune Alterations in Rodents

Parameter	Procedures
	Screen (Tier I)
Immunopathology	• Hematology: complete blood count and differential
	• Weights: body, spleen, thymus, kidney, liver
	• Cellularity: spleen
	• Histology: spleen, thymus, lymph node
Humoral immunity	• Enumerate IgM antibody plaque-forming cells to T-dependent antigen (sRBC, KLH)
	• Lippopolysaccharide (LPS) mitogen response
Cell-mediated immunity	• Lymphocyte blastogenesis to mitogens (Con A)
	• Mixed leukocyte response against allogeneic leukocytes (MLR)
Nonspecific immunity	• Natural killer (NK) cell activity
	Comprehensive (Tier II)
Immunopathology	• Quantitation of splenic B- and T-cell numbers
Humoral-mediated immunity	• Enumeration of IgG antibody response to sRBCs
Cell-mediated immunity	• Cytotoxic T-lymphocyte (CTL) cytolysis
	• Delayed-type hypersensitivity (DTH) response
Nonspecific immunity	• Macrophage function-quantitation of resident peritoneal cells, and phagocytic ability (basal and activated by MAF)
Host resistance challenge models (endpoints)[a]	• Syngeneic tumor cells
	• PYB6 sarcoma (tumor incidence)
	• B16F10 melanoma (lung burden)
	• Bacterial models: *Listeria monocytogenes*; *Streptococcus species*
	• Viral models: Influenza
	• Parasite models: *Plasmodium yoelii* (Parasitaemia)

Note: The testing panel was developed using B6C3F1 female mice.

[a] For any particular chemical tested, only two or three host resistance models are selected for examination.

Source: Adapted from Luster, M.I. et al. (1992).

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Section 9
Reproductive/ Developmental Toxicology

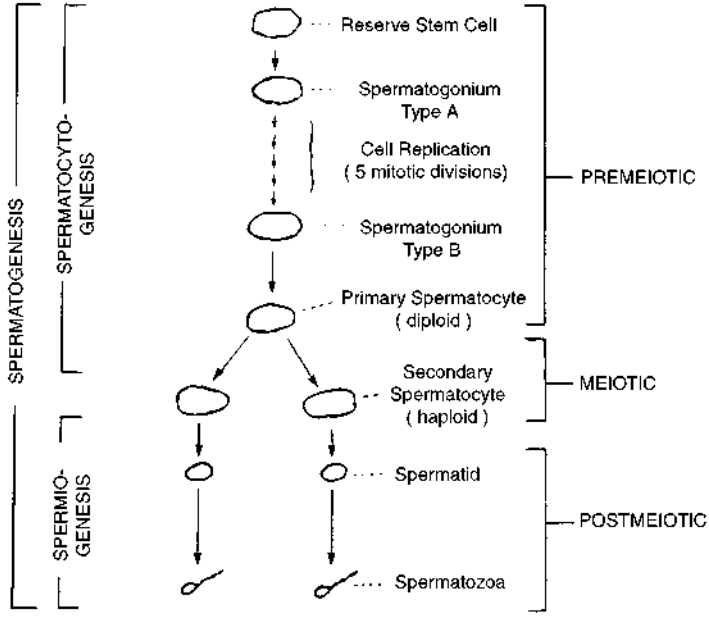

Figure 3 A general scheme of mammalian spermatogenesis. Each cycle is completed in 35 to 64 days, depending on the species, with a new cycle being initiated at the Type A spermatogonium level every 12 to 13 days.

Source: **From Ecobichon, D.J. (1992).**

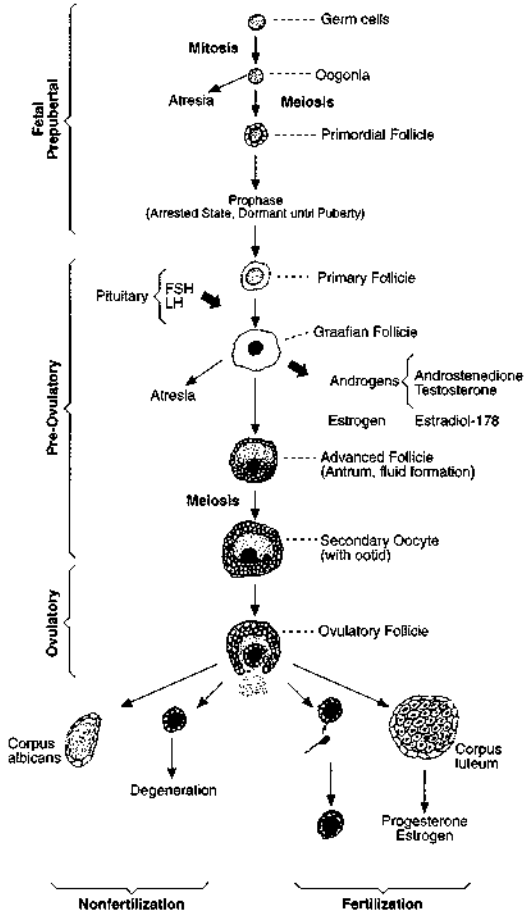

Figure 4 A general scheme of mammalian oogenesis.
Source: **From Ecobichon, D.J. (1992).**

Table 103 Reproductive Parameters for Various Species

Species	Age at Puberty	Sexual Cycle		Ovulation		Copulation		Implantation (days)	Gestation Period (days)
		Type[a]	Duration (days)	Time[b]	Type[c]	Time[b]	Length		
Mouse	5–6 wk	PE	4	2–3 hr	S	Onset of estrus		4–5	19 (19–21)
Rat	6–11 wk	PE	4–6	8–11 hr	S	1–4 hr		5–6	21–22
Rabbit	6–7 mo	PE	Indefinite	10 hr[e]	I	Anytime[f]	seconds	7–8	31 (30–35)
Hamster	5–8 wk	PE	4	Early estrus	S	Estrus[g]		5+	16 (15–18)
Guinea Pig	8–10 wk	PE	16–19	10 hr[e]	S	Estrus	seconds	6	67–68
Ferret	8–12 mo	ME	Seasonal	30–36 hr	I	Estrus	1–3 hr	12–13	42
Cat	6–15 mo	PE	Seasonal[d]	24–56 hr	I	3rd day[h]	1–2 hr	13–14	63 (52–69)
Dog	6–8 mo	ME	9	1–3 days	S	Estrus	1–2 hr	13–14	61 (53–71)
Monkey	3 yr	PE	28	9–20 days	S	Anytime[i]		9	168 (146–180)
Human	12–16 yr	PE	27–28	14 day (13–15)	S	Anytime	15–30 min	7.5	267

[a] PE = polyestrous; ME = monoestrus.

[b] Time from start of estrous cycle.

[c] I = induced ovulation: S = spontaneous ovulation.

[d] March to August.

[e] After mating

[f] Most receptive when in estrus.

[g] 8–10 pm.

[h] Of estrus, most receptive.

[i] Most receptive 2 days before ovulation.

Source: Modified from Spector, W.S. 1956.

Table 104 Breeding Characteristics of Female Laboratory Mammals Compared to Humans

Parameters	Monkey[a]	Dog	Cat	Rabbit	Mouse	Guinea Pig	Hamster	Rat	Human
Age at puberty	36 mo	6–8 mo	6–15 mo	5.5–8.5 mo	35 d	55–70 d	35–56 d	37–67 d	12–15 yr
Breeding season	October–January	Spring–fall	February–July	All year	All year	All year	All year	All year	All year
Breeding life (years)	10–15	5–10	4	1–3	1	3	1	1	35
Breeding age (months)	54	9	10	6–7	2	3	2	2–3	180
Litter size (number)	1	3–6	1–6	1–13	1–12	1–5	1–12	6–9	1
Birth weight (grams)	500–700	1100–2200	125	100	1.5	75–100	2.0	5–6	
Opening of eyes (days)	At birth	8–12	8–12	10	11	At birth	15	11	At birth
Weaning age (weeks)	16–24	6	6–9	6–7	3	2	3–4	3–4	
Weight at weaning (grams)	4400	5800	3000	1000	11–12	250	35	35–45	

Note: Data obtained from various sources, including the following: Ecobichon, D.J. (1992); Spector, W.S. (1956); Altman, P.L. and Dittmer, D.S. (1972).

[a] Monkey = *Macaca mulatta*.

Table 105 Species Variability in Parameters Involving Spermatogenesis

Parameter	Mouse	Rat	Hamster	Rabbit	Dog	Monkey	Human
Spermatogenesis duration (days)	26–35	48–53	35	28–40			74
Duration of cycle of seminiferous epithelium (days)	8.6	12.9		10.7	13.6	9.5	16
Life span of:							
B-type spermatogonia (days)	1.5	2.0		1.3	4.0	2.9	6.3
L + Z spermatocytes (days)	4.7	7.8		7.3	5.2	6.0	9.2
P + D spermatocytes (days)	8.3	12.2		10.7	13.5	9.5	15.6
Golgi spermatids (days)	1.7	2.9		2.1	6.9	1.8	7.9
Cap spermatids (days)	3.5	5.0		5.2	3.0	3.7	1.6
Testis weight (g)[a]	0.2	3.7	1.8	6.4	12.0	4.9	34.0
Daily sperm production							
per gram testis ($\times 10^6$)	54	14–22	22	25	20	23	4.4
per individual ($\times 10^6$)	5–6	80–90	70	160	300	1100	125
Sperm reserve in cauda at sexual rest ($\times 10^6$)	49	440	575	1600		5700	420
Sperm storage in epididymal tissue ($\times 10^6$)							
Caput	20		200				
Corpus	7	300	175				420
Cauda	40–50	400	200				
Transit time through epididymis at sexual rest (days)							
Caput and corpus	3.1	3.0		3.0	?	4.9	1.8
Cauda	5.6	5.1		9.7	?	5.6	3.7
Ejaculate volume (mL)	0.04	0.2	0.1	1.0	?	?	3.0
Ejaculated sperm (10^6/mL)	5.0	?	?	150	?	?	80.0
Sperm transit time from vagina to tube	15–60 min	30–60 min		3–4 hr	20 min		15–30 min

[a] Combined weight of both testes.

Source: Data obtained from various sources, including: Altman, P.L. and Dittmer, D.S. (1972); Eddy, E.M. and O'Brien, D.A. (1989); Blazak, W.F. (1989); Zenick, H. and Clegg, E.D. (1989) and Spector, W.S., Ed. (1956).

Table 106 Species Variability in Parameters Involving Oogenesis

Parameter	Mouse	Rat	Guinea Pig	Hamster	Rabbit	Cat	Dog	Monkey	Human
Sexual maturity (days)	28	46–53	84	42–54	120-240	210–245	270–425	1642	
Duration of estrus (days)	9–20 hr	9–20 hr	6–11 hr		30	4	9	4–6	
Ovulation time (days)	2–3 hr	9–20 hr	10 hr		10 hr	24–56 hr	1–3	9–20	15
Ovulation type[a]	S	S	S	S	I	I	S	S	S
Number of ova released	8	10	?	7	10	4–6	8–10	1	1
Follicle size (mm)	0.5	0.9	0.8		1.8		10		
Ovum diameter (mm)	0.07–0.087	0.07–0.076	0.075–0.107		0.110–0.146	0.12–0.13	0.135–0.145	0.109–0.173	0.089–0.091
Zona pellucida (mm membrane thickness)			0.012		0.011–0.023	0.012–0.115	0.135	0.012–0.034	0.019–0.035
Transport time (to reach site of implantation) (days)	4.5	3.0	3.5	3.0	2.5–4	4–8	6–8	3.0	3.0
Implantation (days)	4.5–5.0	5.5–6.0	6.0	4.5–5.0	7–8	13–14	13–14	9–11	8–13
Rate of transport of sperm to oviduct (min)	15	15–30	15		5–10				5–60
Rate of transport of embryo to uterus (hr)	72	95–100	80–85		60				80
Fertile life of spermatozoa in female tract (hr)	6	14	21–22		30–32				24–48
Rate of transport of ova in female tract (hr)	8–12	12–14	20	5–12	6–8				24
Segmentation (to form blastocele) (days)	2.5–4.0	4.5	5–6	3.25	3–4				5–8
Primitive streak (days)	7.0	8.5	10.0	6.0	6.5	13.0	13.0	18.0	
Duration of organogenesis (days)	7.5–16	9–17	11–25	7–14	7–20	14–26	14–30	20–45	
Gestational length (days)	20–21	21–22	65–68	16–17	31–32	58–71	57–66	164–168	

[a] Ovulation type: I, induced; S, spontaneous.

Source: Data obtained from various sources, including the following: Ecobichon, D.J. (1992); Spector, W.S., Ed. (1956); Altman, P.L. and Dittmer, D.S. (1972); Eddy, E.M. and O'Brien, D.A. (1989); Manson, J.M. and Kang, Y.S. (1989).

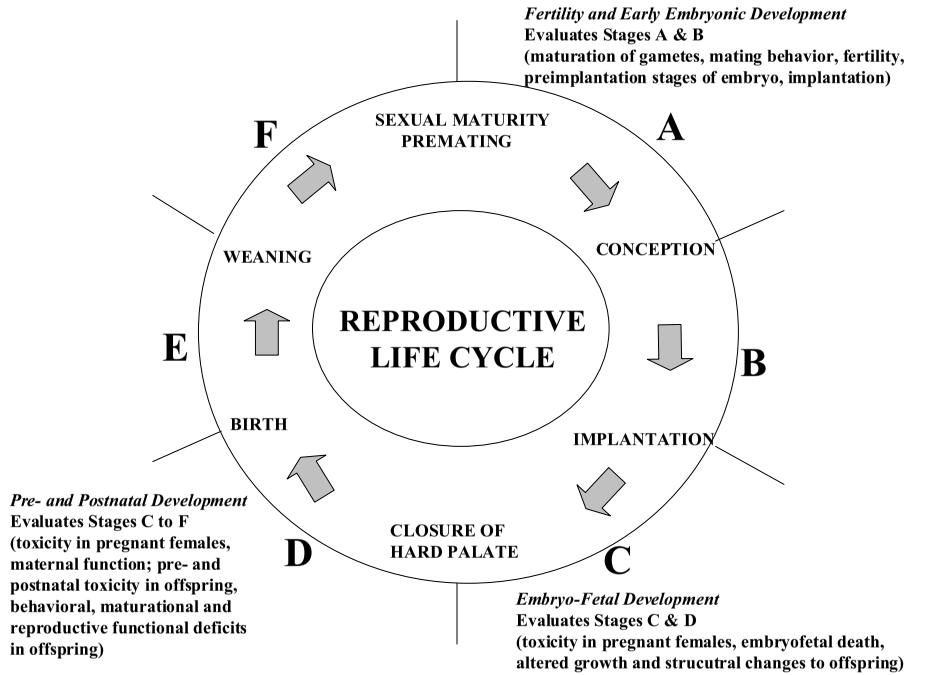

Figure 5 Graphic representation of an animal's reproductive life-cycle and corresponding relationship to the ICH reproductive life stages indicated by the letters A through F. Also shown are the specific stages evaluated by the standard segmented reproductive study designs-Fertility and Early Embryonic Development/Seg. I, Embryo-Fetal Development/Seg. II, and Pre- and Postnatal Development/Seg. III.

Table 107 Fertility and Reproductive Indices Used in Single and Multigeneration Studies

Index	Derivation
Mating	$= \frac{\text{No. confirmed copulations}}{\text{No. of estrous cycles required}} \times 100$
Male fertility	$= \frac{\text{No. males impregnating females}}{\text{No. males exposed to fertile, nonpregnant females}} \times 100$
Female fertility	$= \frac{\text{No. of females confirmed pregnant}}{\text{No. of females housed with fertile male}} \times 100$
Female fecundity	$= \frac{\text{No. of females confirmed pregnant}}{\text{No. of confirmed copulations}} \times 100$
Implantation	$= \frac{\text{No. of implantations}}{\text{No. of pregnant females}} \times 100$
Preimplantation loss	$= \frac{\text{Corpora lutea} - \text{No. of implants}}{\text{No. of Corpora lutea}} \times 100$
Parturition incidence	$= \frac{\text{No. of females giving birth}}{\text{No. of females confirmed pregnant}} \times 100$
Live litter size	$= \frac{\text{No. of litters with live pups}}{\text{No. of females confirmed pregnant}} \times 100$
Live birth	$= \frac{\text{No. viable pups born/litter}}{\text{No. pups born/litter}} \times 100$
Viability	$= \frac{\text{No. of viable pups born}}{\text{No. of dead pups born}} \times 100$
Survival	$= \frac{\text{No. of pups viable on day 1}}{\text{No. of viable pups born}} \times 100$
Pup death (day 1–4)	$= \frac{\text{No. of pups dying, postnatal days 1–4}}{\text{No. of viable pups born}} \times 100$
Pup death (days 5–21)	$= \frac{\text{No. of pups dying, postnatal days 5–21}}{\text{No. of viable pups born}} \times 100$
Sex ratio (at birth)	$= \frac{\text{No. of male offspring}}{\text{No. of female offspring}} \times 100$
Sex ratio (day 4) (day 21)	$= \frac{\text{No. of male offspring}}{\text{No. of female offspring}} \times 100$

Source: From Ecobichon, D.J. (1992).

Table 108 Basic Developmental Toxicity Testing Protocol

Phase	Time	Developmental Toxicity Testing[a]
Acclimation period	Variable number of weeks	No exposure of the animals to the test agent
Cohabitation period	Day of mating determined (Day 0)	No exposure of the animals to the test agent
Preembryonic period	Day of mating through day 5,[b] 6,[c] 7[d] of pregnancy	
Period of major embryonic organogenesis	Day 5, 6, or 7 through day 15,[bc] or 18[d] of pregnancy	Groups of pregnant animals exposed to the test agent
Fetal period	Day 15 or 18 through day 18,[b] 21,[c] or 30[d] of pregnancy	No exposure of the pregnant animals to the test agent
Term	Day 18,[b] 22,[c] or 31[d] of pregnancy	Females sacrificed (to preclude cannibalization of malformed fetuses), cesarean section performed, and young examined externally and internally

[a] Usually a sham-treated control group and three agent-treated groups are used with 20 to 25 mice or rats and 15 to 18 rabbits per group. The dose levels are chosen with the goal of no maternal or developmental effects in the low-dose group and at least maternal toxicity in the high-dose group (failure to gain or loss of weight during dosing, reduced feed and/or water consumption, increased clinical signs, or no more than 10% maternal death).

[b] Mice.

[c] Rats.

[d] Rabbits.

Source: Adapted from Johnson, E.M. (1990).

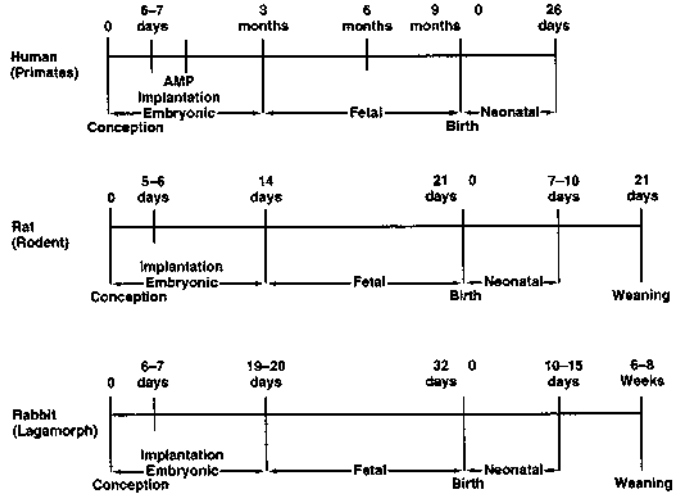

Figure 6 Developmental stages and timelines in the human, rat, and rabbit. AMP: Anticipated menstrual period. Average human menstrual cycle is 28 days, with ovulation occurring about 14 days. Rabbit ovulates following coitus. Adapted from Miller, R.K. et al. (1987).

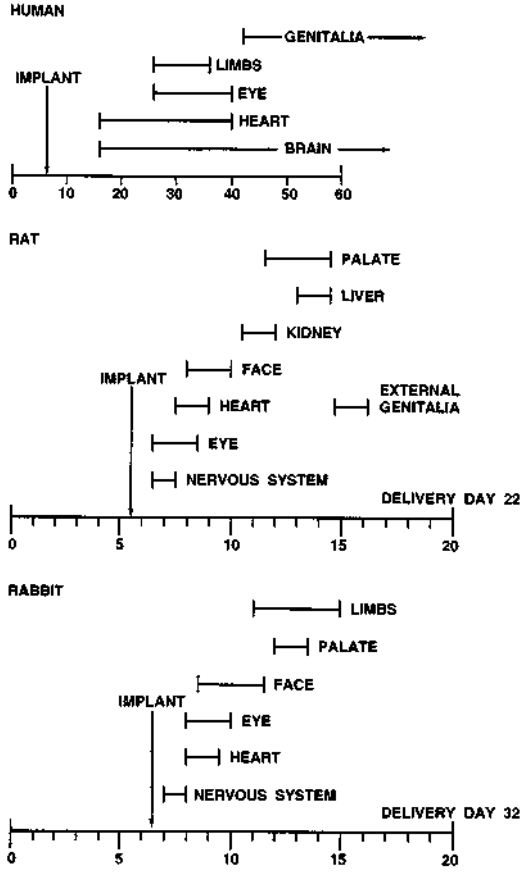

Figure 7 Critical periods of embryogenesis in the human, rat, and rabbit. Adapted from Ecobichon, D.J. (1992).

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Section 10
Clinical Pathology

Table 109 Approximate Blood Volumes in Animals Typically Used in Nonclinical Toxicology Research

Species	Typical Body Weight (kg)	Blood Volume (mL)			
		Total Volume (mL)	Weekly Sampling	Monthly Sampling	At Necropsy
Mouse	0.03	2	0.075	0.2	1
Rat	0.3	20	1	2	10
Dog	12.0	1000	50	100	400
Monkey[a]	3.0	200	10	20	100
Rabbit	3.0	200	10	20	100

[a] Rhesus or cynomolgus.

Source: Adapted from Loeb, W.F. and Quimby, F.W. (1989).

Table 110 Recommended Maximum Allowable Blood Collection Volumes for Animals[a]

One-Time Collection	Total for Multiple Collections over 1 Day	Total for Multiple Collections over 1 wk	Total for Multiple Collections over 1 mo	Total for Collections Done on a Weekly Basis
1 mL/100 g body weight	1 mL/100 g body weight	1 mL/100 g body weight	2 mL/ 100 g body weight	0.5 mL/100 g body weight per week

[a] Higher collection volumes acceptable where animals are bled under anesthesia at termination or when an equivalent volume of blood is immediately replaced.

Table 111 Common Sites for Blood Collection and Blood Volumes in Various Species

Species	Site	Approximate Blood Volume (mL/kg)	Comments
Mouse	Tail clip, tail vein, orbital sinus, and cardiac puncture	72	Anesthesia should be given for tail clip, orbital sinus, and cardiac puncture collection.
Rat	Tail clip, tail vein, jugular vein, orbital sinus, sublingual vein, and cardiac puncture	64	Anesthesia should be given for tail clip, sublingual, orbital sinus, and cardiac puncture collection. Tail clip not suitable for older animals.
Rabbit	Marginal ear vein, central ear artery, jugular vein, and cardiac puncture	56	Anesthesia should be given for cardiac puncture collection. Compression of central ear artery for a few minutes may be necessary to stop bleeding.
Dog	Cephalic vein, saphenous vein, and jugular vein	85	
Minipig	Anterior vena cava/jugular vein, marginal ear vein	65	
Primate	Cephalic vein, saphenous vein, femoral vein, and jugular vein	60	
Guinea pig	Marginal ear vein, jugular vein, and cardiac puncture	80	Anesthesia should be given for cardiac puncture collection.
Hamster	Orbital sinus, jugular vein, femoral vein, and cardiac puncture	78	Anesthesia should be given for orbital sinus and cardiac puncture collection.
Ferret	Cephalic vein, saphenous vein, jugular vein, and cardiac puncture	75	Anesthesia should be given for cardiac puncture collection.

Source: BVA/Frame/RSPCA/UFAW Joint Working Group (1993), Diehl et al. (2001).

Table 112 Erythrocyte Life Span in Various Animals[a]

Species	Mean Life Span[b] (days)
Human	117–127 (120)[c]
Dog	90–135
Cat	66–79
Pig	62–86
Rabbit	50–80
Guinea pig	70–90
Hamster	60–70
Rat	50–68 (60)[c]
Mouse	41–55

[a] Determined by use of isotopes.

[b] Range of means from various studies.

[c] Most often cited.

Table 113 Mean Control Ranges of Typical Serum Clinical Chemistry Measurements in B6C3F$_1$ Mice

Parameter	Age					
	12–14 wk	18–20 wk	32–34 wk	58–60 wk	84–86 wk	110–112 wk
Alanine aminotransferase (ALT) (IU/L)	20–50	25–100	22–90	20–50	23–60	20–60
Albumin (g/dL)	2.3–4.4	2.5–4.2	2.7–3.8	3.0–4.0	3.0–3.9	3.0–4.1
Albumin/globulin ratio	1.0–2.0	0.8–2.0	1.2–1.9	1.3–1.9	1.3–2.0	1.3–2.0
Alkaline phosphatase (IU/L)	30–80 (M) 40–140 (F)	20–55 (M) 45–85 (F)	— —	— —	— —	— —
Aspartate aminotransferase (AST) (IU/L)	40–100	64–180	—	—	—	—
Bilirubin, total (mg/dL)	—	0.1–0.5	0.1–0.5	0.1–0.5	0.1–0.5	0.1–0.5
Calcium (mg/dL)	—	8.2–11.8	—	—	—	—
Chloride (mEq/L)	—	110–128	—	—	—	—
Cholesterol, total (mg/dL)	90–160	80–130	85–150	80–150	90–160	90–175
Creatine kinase (CK) (IU/L)	50–300	—	—	—	—	—
Creatinine (mg/dL)	0.3–0.8	0.2–0.8	—	—	—	—
Globulin (g/dL)	1.5–2.5	1.0–2.7	1.6–2.4	1.8–3.1	1.6–3.0	1.8–3.0
Glucose (mg/dL)	125–200	81–165	115-170	115-170	115-170	115–170
Phosphorus, inorganic (mg/dL)	—	—	—	—	—	—
Potassium (mEq/L)	—	3.6–7.3	—	—	—	—
Protein, total (g/dL)	4.5–5.5	4.0–6.0	4.2–6.2	4.8–6.5	4.8–6.6	5.4–6.5
Sodium (mEq/L)	—	147–163	—	—	—	—
Sorbitol dehydrogenase (SDH) (IU/L)	15–50	18–57	—	—	—	—
Triglycerides (mg/dL)	75–175	75–130	100-173	90–190	110-160	90–175
Urea nitrogen (BUN) (mg/dL)	15–35	12–34	12–27	12–24	10–24	15–28

Note: — = data unavailable.

Source: Adapted from Levine, B.S. (1979–1993) and NIEHS (1985).

Table 114 Mean Control Ranges of Typical Serum Clinical Chemistry Measurements in CD-1 and BALB/c Mice of Various Ages

Parameter	CD-1 (<1 yr)	CD-1 (>1 yr)	BALB/c (1–3 mo)	BALB/c (6–12 mo)
Alanine aminotransferase (ALT) (IU/L)	30–250 (M) 30–100 (F)	20–200 (M) 20–80 (F)	— —	— —
Albumin (g/dL)	—	—	1.6–2.6	1.3–2.6
Albumin/globulin ratio	—	—	—	—
Alkaline phosphatase (IU/L)	30–70	20–75	75–275	47–102
Aspartate aminotransferase (AST) (IU/L)	75–300	75–300	40–140	70–110
Bilirubin, total (mg/dL)	0.2–0.8	0.2–0.8	0.5–1.2	0.4–1.0
Calcium (mg/dL)	8.5–11.5	6.7–11.5	7.8–10.8	6.5–9.6
Chloride (mEq/L)	110–125	110–135	—	—
Cholesterol, total (mg/dL)	90–170 (M) 60–125 (F)	60–170 (M) 50–100 (F)	165–295	100–300
Creatine kinase (CK) (IU/L)	—	—	—	—
Creatinine (mg/dL)	0.3–1.0	0.2–2.0	—	—
Globulin (g/dL)	—	—	—	—
Glucose (mg/dL)	75–175	60–150	75–150	40–160
Phosphorus, inorganic (mg/dL)	7.5–11.0	6.0–10.0	4.5–8.9	4.7–7.2
Potassium (mEq/L)	6.5–9.0	6.6–9.0	—	—
Protein, total (g/dL)	4.5–6.0	3.5–5.6	4.4–6.0	4.4–6.4
Sodium (mEq/L)	145–160	155–170	—	—
Triglycerides (mg/dL)	60–140 (M) 50–100 (F)	40–150 (M) 25–75 (F)	— —	— —
Urea nitrogen (BUN) (mg/dL)	20–40	20–70	10–30	10–30

Note: — = data unavailable.

Source: Adapted from Frithe, C.H. et al. (1980) and Wolford, S.T. et al. (1986).

Table 115 Mean Control Ranges of Typical Serum Clinical Chemistry Measurements in CD® Rats

Parameter	Age					
	10–12 wk	18–20 wk	32–34 wk	58–60 wk	84–86 wk	108–110 wk
Alanine aminotransferase (ALT) (IU/L)	10–40	10–50	10–50	20–60	20–60	20–60
Albumin (g/dL)	3.4–4.1 (M)	3.3–4.2 (M)	3.5–4.0 (M)	3.0–3.8 (M)	3.0–4.0 (M)	2.7–3.5 (M)
	3.5–4.5 (F)	3.5–4.7 (F)	4.0–5.0 (F)	3.5–4.5 (F)	3.7–4.5 (F)	3.3–3.7 (F)
Albumin/globulin ratio	1.0–1.5	1.0–1.5	1.0–1.5	0.75–1.75	0.75–1.75	0.75–1.5
Alkaline phosphatase (IU/L)	140–300 (M)	50–150 (M)	50–150 (M)	50–150 (M)	50–150 (M)	50–100 (M)
	80–100 (F)	25–150 (F)	25–100 (F)	25–100 (F)	25–100 (F)	25–100 (F)
Aspartate aminotransferase (AST) (IU/L)	45–90	45–100	45–120	60–120	75–150	75–150
Bile acids, total (μmol/L)	20–60	20–60	—	—	—	—
Bilirubin, total (mg/dL)	0.2–0.4	0.1–0.5	0.1–0.5	0.1–0.5	0.1–0.5	0.1–0.4
Calcium (mg/dL)	9.8–12.0	9.8–12.0	9.8–12.0	9.8–12.0	9.8–12.0	9.8–12.0
Chloride (mEq/L)	97–105	97–105	95–105	97–105	97–105	97–105
Cholesterol, total (mg/dL)	50–85	50–100	70–140	60–150	130–180 (M)	130–180 (M)
					100–150 (F)	90–150 (F)
Creatine kinase (CK) (IU/L)	50–400	50–300	50–500	—	—	—
Creatine (mg/dL)	0.3–0.8	0.3–0.9	0.3–1.0	0.4–0.8	0.4–0.8	0.4–1.3
γ-Glutamyltransferase (γGT) (IU/L)	0–2	0–2	0–3	0–5	0–7	0–5
Globulin (g/dL)	2.5–4.0	2.5–4.0	2.0–4.5	2.0–4.5	2.0–4.5	2.0–4.5
Glucose (mg/dL)	90–175	100–175	100–200	100–200	100–175	100–175
Lactate dehydrogenase (LDH) (IU/L)	50–400	50–400	50–500	—	—	—
Phosphorus, inorganic (mg/dL)	7.0–10.0	4.0–8.5	4.0–8.0	3.5–7.0	3.5–8.0	4.0–7.0
Potassium (mEq/L)	5.5–8.0	4.0–7.0	4.0–7.0	4.0–7.0	3.5–6.0	3.5–6.0
Protein, total (g/dL)	6.2–7.6 (M)	6.2–7.8 (M)	6.2–8.0 (M)	6.0–8.0 (M)	6.3–7.6 (M)	5.7–6.5 (M)
	6.3–8.2 (F)	6.5–8.5 (F)	7.0–9.0 (F)	6.5–8.5 (F)	6.7–8.0 (F)	6.3–7.1 (F)
Sodium (mEq/L)	140–153	140–153	140–153	140–153	140–153	140–145
Sorbitol dehydrogenase (SDH) (IU/L)	10–30	10–30	10–30	—	—	—
Triglycerides (mg/dL)	50–125	50–200	50–200	50–300	75–400	50–300
Urea nitrogen (BUN) (mg/dL)	12–18	12–20	12–20	12–18	12–18	12–30

Note: — = data unavailable.

Source: Adapted from Levine, B.S., (1979–1993) and Charles River Laboratories (1993b).

Table 116 Mean Control Ranges of Typical Serum Clinical Chemistry Measurements in F-344 Rats

Parameter	Age					
	12–14 wk	18–20 wk	32–34 wk	58–60 wk	84–86 wk	110–112 wk
Alanine aminotransferase (ALT) (IU/L)	25–45	30–62	20–40	56–100 (M) 33–65 (F)	41–80 (M) 32–50 (F)	25–60
Albumin (g/dL)	3.8–4.7	3.0–5.0	4.0–5.0	3.8–5.0	3.8–5.0	3.5–5.0
Albumin/globulin ratio	1.5–2.3	1.1–2.5	1.5–2.0	1.4–1.9	1.4–2.0	1.2–1.8
Alkaline phosphatase (IU/L)	200–300 (M) 150–250 (F)	58–154 (M) 45–120 (F)	45–80	31–68	—	—
Aspartate aminotransferase (AST) (IU/L)	50–90	50–100	—	—	—	—
Bile acids, total (µmol/L)	10–50	—	—	—	—	—
Bilirubin, total (mg/dL)	—	0.1–0.5	0.1–0.4	0.1–0.5	0.1–0.5	0.1–0.4
Calcium (mg/dL)	—	9.5–12.0	9.5–11.2	9.5–11.5	9.5–11.5	9.8–11.7
Chloride (mEq/L)	—	97–115	98–110	100–112	97–100	104–113
Cholesterol, total (mg/dL)	70–100 (M) 90–135 (F)	50–80 (M) 80–120 (F)	50–80 (M) 85–130 (F)	68–125 (M) 110–150 (F)	100–120	125–175
Creatine kinase (CK) (IU/L)	60–300	100–400	300–700	300–500	100–500	100–400
Creatine (mg/dL)	0.5–1.0	0.4–0.8	—	—	—	—
Globulin (g/dL)	1.5–2.5	1.2–2.8	2.0–3.0	2.3–3.5	2.0–3.0	2.2–3.2
Glucose (mg/dL)	100–180	90–170	80–130	90–140	90–140	90–140
Lactate dehydrogenase (LDH) (IU/L)	—	500–800	—	—	—	—
Phosphorus, inorganic (mg/dL)	—	3.9–7.3	400–800	150–400	—	—
Potassium (mEq/L)	—	3.6–5.9	4.0–5.7	4.1–5.5	4.0–5.2	4.0–5.1
Protein, total (g/dL)	6.0–7.2	5.7–7.6	6.2–7.5	6.5–7.6	6.0–7.8	6.1–8.0
Sodium (mEq/L)	—	140–155	142–158	142–156	138–149	138–146
Sorbitol dehydrogenase (SDH) (IU/L)	15–60	5–25	5–35	—	—	—
Triglycerides (mg/dL)	100–400 (M) 25–130 (F) 80–220	75–150 (M) 35–70 (F)	125–190 (M) 30–70 (F)	90–175 (M) 40–85 (F)	110–240 (M) 60–145 (F)	
Urea nitrogen (BUN) (mg/dL)	15–25	10–26	12–24	10–20	10–20	12–25

Note: — = data unavailable.

Source: Adapted from Levine, B.S. (1979–1993), NIEHS (1985), and Burns, K.F. et al. (1971).

Table 117 Mean Control Ranges of Typical Serum Clinical Chemistry Measurements in Beagle Dogs

Parameter	Age				
	6–8 mo	9–11 mo	12–14 mo	15–18 mo	19–30 mo
Alanine aminotransferase (ALT) (IU/L)	20–40	20–40	20–40	20–40	20–40
Albumin (g/dL)	2.5–3.5	2.5–3.5	2.5–3.5	2.5–4.0	2.7–4.5
Albumin/globulin ratio	0.8–1.5	0.8–1.5	0.8–1.5	0.8–2.0	0.8–2.0
Alkaline phosphatase (IU/L)	120–160 (M) 100–130 (F)	70–120 (M) 60–100 (F)	50–100	35–100	35–100
Aspartate aminotransferase (AST) (IU/L)	30–45	30–50	25–50	25–50	25–50
Bilirubin, total (mg/dL)	0.1–0.7	0.1–0.7	0.1–0.7	0.1–0.3	0.1–0.3
Calcium (mg/dL)	9.0–11.5	9.0–11.5	9.0–11.5	10.0–11.3	10.0–11.5
Chloride (mEq/L)	100–115	100–115	100–115	105–119	105–115
Cholesterol, total (mg/dL)	150–250	125–250	125–250	125–250	125–225
Creatine kinase (CK) (IU/L)	100–400	100–400	100–400	—	—
Creatinine (mg/dL)	0.5–0.8	0.7–0.9	0.7–0.9	—	—
γ-Glutamyltransferase (γGT) (IU/L)	0–5	0–5	0–5	—	—
Globulin (g/dL)	2.5–3.5	2.5–3.5	2.5–3.5	2.5–3.5	2.5–3.5
Glucose (mg/dL)	100–130	100–130	100–130	70–110	70–110
Haptoglobin (mg/dL)	50–200	50–150	25–100	—	—
Lactate dehydrogenase (LDH) (IU/L)	30–100	30–100	30–100	—	—
Phosphorus, inorganic (mg/dL)	6.0–9.0	4.0–6.0	3.0–5.0	3.0–5.0	3.0–4.7
Potassium (mEq/L)	4.2–5.0	4.2–5.0	4.2–5.0	4.1–5.1	4.2–5.2
Protein, total (g/dL)	5.5–6.5	5.5–6.5	5.5–6.5	5.5–6.5	5.7–6.6
Sodium (mEq/L)	143–147	143–147	143–147	143–153	143–153
Triglycerides (mg/dL)	30–60	30–75	30–75	—	—
Urea nitrogen (BUN) (mg/dL)	10–20	10–20	10–20	10–20	10–20

Note: — = data unavailable.

Source: Adapted from Levine, B.S. (1979–1993), Clarke, D. et al. (1992), Pickrell, J.A. et al. (1974), and Kaspar, L.V. and Norris, W.P. (1977).

Table 118 Mean Control Ranges of Typical Serum Clinical Chemistry Measurements in Nonhuman Primates of Various Ages

Parameter	Cynomolgus (3–7 yr)	Rhesus (1–2 yr)	Rhesus (3–7 yr)	Marmoset (<1.5 yr)	Marmoset (>1.5 yr)	Baboon (1–5 yr)	Baboon (6–15 yr)
Alanine amino-transferase (ALT) (IU/L)	20–60	20–50	15–40	45–75	40–70	15–50	20–50
Albumin (g/dL)	3.5–4.8	3.0–4.5	3.2–4.5	3.5–5.8	3.5–5.8	3.1–4.5	2.0–4.5
Albumin/ globulin ratio	1.0–1.5	1.0–1.5	1.0–1.5	1.0–1.5	1.0–1.5	1.0–1.5	1.0–1.5
Alkaline phosphatase (IU/L)	300–800 (M) 200–500 (F)	200–600	70–300	100–250	35–80	200–1000	100–200
Amylase (IU/L)	200–500	—[a]	—	1000–2000	500–1500	200–400	200–500
Aspartate amino-transferase (AST) (IU/L)	25–60	25–60	15–70	100–200	100–200	18–35	20–35
Bilirubin, total (mg/dL)	0.3–0.8	0.1–0.8	0.1–0.6	0.1–0.9	0.1–0.9	0.3–0.7	0.3–0.5
Calcium (mg/dL)	9.0–11.0	8.2–10.5	8.5–10.3	8.1–12.4	8.5–11.7	8.0–9.5	7.5–10.0
Chloride (mEq/L)	100–115	103–115	97–110	80–110	93–119	105–115	100–110
Cholesterol, total (mg/dL)	90–160	90–160	90–170	90–210	105–230	75–200	70–125
Creatine kinase (CK) (IU/L)	140–200	200–1000	200–600	—	—	—	—
Creatinine (mg/dL)	0.7–1.2	0.5–0.9	0.7–1.2	0.2–1.0	0.2–1.0	0.8–1.2	1.0–1.8
γ-Glutamyl-transferase (γGT) (IU/L)	40–90	—	10–60	—	—	—	—
Globulin (g/dL)	3.0–4.5	3.0–4.0	3.0–4.0	2.5–4.0	3.5–4.0	2.5–4.0	2.5–4.5
Glucose (mg/dL)	50–100	50–100	41–80	180–275	130–240	50–125	50–140
Lactate dehydrogenase (LDH) (IU/L)	300–600	130–600	125–600	125–500	100–350	100–400	100–350
Phosphorus, inorganic (mg/dL)	4.0–7.0	3.2–5.0	3.0–5.3	5.5–9.8	4.0–7.5	4.7–7.5	1.3–4.5
Potassium (mEq/L)	3.0–4.5	3.0–4.2	3.1–4.1	3.5–5.0	3.0–4.8	3.2–4.3	3.7–4.8
Protein, total (g/dL)	7.0–9.0	6.7–8.0	7.0–8.3	5.5–7.5	6.0–8.0	6.0–8.0	6.0–7.5
Sodium (mEq/L)	140–153	144–150	142–148	150–170	150–170	142–158	142–158
Triglycerides (mg/dL)	30–70	50–200	50–200	75–200	75–200	25–60	30–125
Urea nitrogen (BUN) (mg/dL)	15–25	14–26	14–25	17–35	15–32	10–25	10–25

Note: — = data unavailable.

Source: Adapted from Levine, B.S. (1979–1993), Clarke, D. et al. (1992), Kapeghian, L.C. and Verlangieri, A.J. (1984), Davy, C. W. et al. (1984), Yarbrough, L.W. et al. (1984), and Hack, C.A. and Gleiser, C.A. (1982).

Table 119 Mean Control Ranges of Typical Serum Clinical Chemistry Measurements in New Zealand White Rabbits

Parameter	Age		
	15–20 wk	25–40 wk	1–2 yr
Alanine aminotransferase (ALT) (IU/L)	25–70	25–70	25–70
Albumin (g/dL)	3.8–5.0	3.5–4.7	3.0–4.5
Albumin/globulin ratio	2.0–3.0	2.0–3.0	2.0–3.0
Alkaline phosphatase (IU/L)	50–120	40–120	15–90
Aspartate aminotransferase (AST) (IU/L)	20–50	10–35	10–30
Bilirubin, total (mg/dL)	0.1–0.5	0.1–0.5	0.2–0.6
Calcium (mg/dL)	12.0–14.0	11.0–14.0	12.0–15.0
Chloride (mEq/L)	97–110	96–108	100–110
Cholesterol, total (mg/dL)	20–60	20–60	20–60
Creatine kinase (CK) (IU/L)	200–800	200–1000	200–1000
Creatinine (mg/dL)	1.0–1.6	0.8–1.6	0.8–1.7
γ-Glutamyltransferase (γGT) (IU/L)	—	0–10	0–6
Globulin (g/dL)	1.4–1.9	1.5–2.2	1.5–2.5
Glucose (mg/dL)	100–160	100–175	80–140
Lactate dehydrogenase (LDH) (IU/L)	50–200	50–200	35–125
Phosphorus, inorganic (mg/dL)	4.6–7.2	4.0–7.0	3.0–5.0
Potassium (mEq/L)	4.0–5.2	4.0–5.0	3.3–4.5
Protein, total (g/dL)	5.4–6.6	5.5–7.0	5.5–7.5
Sodium (mEq/L)	132–144	132–145	132–150
Urea nitrogen (BUN) (mg/dL)	10–20	12–22	12–25

Note: — = data unavailable.

Source: Adapted from Levine, B.S. (1979–1993), Hewett, C.D. et al. (1989), and Yu, L. et al. (1979).

Table 120 Control Ranges of Typical Clinical Chemistry Measurements in Minipigs (Gottingen)[a]

Parameters			
Alanine aminotransferase (ALT) (IU/L)	19–331	γ-Glutamyltransferase (γGT) (IU/L)	38–108
Albumin (g/dL)	3.4–5.1	Globulin (g/dL)	0.6–3.4
Albumin/globulin ratio	1.0–6.4	Glucose (mg/dL)	53–224
Alkaline phosphatase (IU/L)	50–642	Phosphorus, inorganic (mg/dL)	4.3–11.6
Aspartate aminotransferase (AST) (IU/L)	10–799	Potassium (mEq/L)	3.1 – 9.8
Bilirubin, total (mg/dL)	0.0–0.3	Protein, total (g/dL)	5.2–7.4
Calcium (mg/dL)	9.7–12.8	Sodium (mEq/L)	132–159
Chloride (mEq/L)	91–115	Sorbitol dehydrogenase (IU/L)	0–6
Cholesterol, total (mg/dL)	34–144	Triglycerides (mg/dL)	7–58
Creatinine (mg/dL)	0.4–3.9	Total bile acids (μmol/L)	0–96
		Urea nitrogen (BUN) (mg/dL)	3.0–19.0

[a] 4–6 months of age.

Source: Marshall Farms, Unpublished personal data.

Table 121 Mean Control Ranges of Typical Hematology Measurements in B6C3F$_1$ Mice

Parameters	Age					
	12–14 wk	**18–20 wk**	**32–34 wk**	**58–60 wk**	**84–86 wk**	**110–112 wk**
Erythrocyte count (10^6/mm^3)	9.0–10.2	7.5–10.5	8.0–10.4	8.0–10.0	8.6–10.4	7.7–10.4
Hematocrit (%)	44.1–49.5	36.0–48.6	40.8–46.6	38.5–45.5	40.0–46.9	36.0–43.5
Hemoglobin (g/dL)	15.0–17.1	13.1–16.5	15.2–18.2	14.5–17.9	15.0–18.2	13.0–16.8
Leukocyte count, total (10^3/mm^3)	3.0–7.8 (M) 2.5–5.0 (F)	5.5–10.9 (M) 3.2–5.2 (F)	6.1–13.3 (M) 4.2–9.3 (F)	6.1–13.2 (M) 4.6–10.5 (F)	7.0–13.4 (M) 3.9–7.9 (F)	5.0–16.5 (M) 4.2–8.8 (F)
Mean corpuscular hemoglobin (pg)	16.6–18.8	16.9–20.2	16.4–18.9	15.8–18.0	15.9–18.3	15.7–18.7
Mean corpuscular hemoglobin conc. (g/dL)	34.6–38.4	34.6–40.4	37.1–41.2	36.5–39.0	36.2–39.4	35.7–38.8
Mean corpuscular volume (fL)	44.0–52.0	45.4–53.6	44.0–48.0	42.0–47.0	42.0–48.0	46.0–50.0
Methemoglobin (% Hgb)	—	0–3.0	0–2.5	0–1.5	0–0.9	0–1.0
Platelet count (10^3/mm^3)	700–1100	500–1000	800–1200	700–1200	400–1100	400–800
Reticulocyte count (% RBC)	0.5–2.0	1.0–3.9	0.4–2.8	0.4–1.6	0.2–2.3	0.5–2.5

Note: — = data not available.

Source: Adapted from Levine, B.S. (1979–1993) and NIEHS (1985).

Table 122 Mean Control Ranges of Typical Hematology Measurements in CD-1 and BALB/c Mice of Various Ages

Parameters	BALB/c (1–3 mo)	BALB/c (6–12 mo)	CD-1 (<1 yr)	CD-1 (>1 yr)
Erythrocyte count (10^6/mm^3)	8.5–10.5	8.8–10.6	8.0–10.0	6.0–9.0
Hematocrit (%)	42.5–47.9	38.3–46.9	36.9–46.9	28.2–41.1
Hemoglobin (g/dL)	14.5–16.8	14.2–17.0	13.6–16.8	10.4–14.9
Leukocyte count, total (10^3/mm^3)	2.0–5.7	2.0–5.0	4.0–12.0 (M) 3.5–9.7 (F)	3.4–17.0 (M) 2.4–13.4 (F)
Mean corpuscular hemoglobin (pg)	15.8–18.4	15.1–17.5	16.1–18.6	15.1–18.4
Mean corpuscular hemoglobin conc. (g/dL)	34.2–38.1	35.1–40.6	34.8–38.2	34.6–37.6
Mean corpuscular volume (fL)	46.3–50.3	40.9–45.9	44.5–49.7	41.3–51.1
Platelet count (10^3/mm^3)	—	—	700–1400	700–1500
Reticulocyte count (% RBC)	—	—	1.6–3.7	1.7–5.0

Note: — = data not available.

Source: Adapted from Frithe, C.H. et al. (1980) and Wolford, S.T. et al. (1986).

Table 123 Mean Control Ranges of Typical Hematology Measurements in CD® Rats

Parameters	Age					
	10–12 wk	18–20 wk	32–34 wk	58–60 wk	84–86 wk	108–110 wk
Activated partial thromboplastin time (s)	14.0–20.0 (M) 12.0–18.0 (F)	14.0–20.0 (M) 13.0–18.0 (F)	14.0–17.0 (M) 13.0–16.0 (F)	16.0–19.0 (M) 15.0–18.0 (F)	—	—
Erythrocyte count (10^6/mm^3)	6.8–8.5 (M) 7.0–8.2 (F)	7.0–9.8 (M) 6.5–9.2 (F)	7.0–9.6 (M) 6.5–8.8 (F)	7.0–9.2 (M) 6.5–8.5 (F)	7.0–9.2 (M) 6.0–8.5 (F)	6.2–8.2 (M) 5.8–8.0 (F)
Fibrinogen (mg/dL)	—	200–300 (M) 130–190 (F)	—	—	—	—
Hematocrit (%)	40.0–48.0	36.0–52.0	36.0–50.0	38.0–48.0	38.0–50.0	35.0–45.0
Hemoglobin (g/dL)	14.0–17.0	14.0–17.0	14.0–17.0	14.0–17.0	14.0–17.0	12.0–15.0
Leukocyte count, total (10^3/mm^3)	6.0–18.0 (M) 4.0–14.0 (F)	6.0–19.0 (M) 5.0–14.0 (F)	6.0–18.0 (M) 4.0–11.0 (F)	5.0–15.0 (M) 3.0–9.0 (F)	10.0–15.0 (M) 6.0–10.0 (F)	5.0–18.0 (M) 3.0–12.0 (F)
Mean corpuscular hemoglobin (pg)	19.0–22.0	16.0–20.0	17.0–21.0	16.0–21.0	16.0–20.0	16.0–20.0
Mean corpuscular hemoglobin conc. (g/dL)	33.0–38.0	31.0–38.0	31.0–38.0	32.0–38.0	31.0–36.0	31.0–36.0
Mean corpuscular volume (fL)	53.0–63.0	50.0–60.0	45.0–60.0	46.0–58.0	48.0–56.0	50.0–63.0
Methemoglobin (% Hgb)	0.4–1.2	0.4–1.2	0.4–1.2	—	—	—
Platelet count (10^3/mm^3)	900–1300	800–1200	700–1200	700–1200	700–1200	700–1200
Prothrombin time (s)	9.0–14.0	9.0–14.0	10.0–14.0	10.0–14.0	—	—
Reticulocyte count (% RBC)	0.2–1.0	0.2–0.8	0.2–0.8	—	—	—

Note: — = data not available.

Source: Adapted from Levine, B.S. (1979–1993) and Charles River Laboratories (1993a).

Table 124 Mean Control Ranges of Typical Hematology Measurements in F-344 Rats

Parameters	Age					
	10–12 wk	18–20 wk	32–34 wk	58–60 wk	84–86 wk	108–110 wk
Erythrocyte count (10^6/mm^3)	7.2–8.6	7.0–10.0	8.5–9.6	7.2–9.5	7.5–9.8	6.5–9.6
Hematocrit (%)	39.5–45.5	42.0–50.0	41.4–46.7	40.0–46.6	40.3–45.5	40.0–48.5
Hemoglobin (g/dL)	15.0–17.0	15.0–17.3	15.0–17.8	15.7–17.5	15.5–17.6	13.0–18.5
Leukocyte count, total (10^3/mm^3)	7.1–13.5 (M)	6.5–10.7 (M)	6.5–8.7 (M)	5.8–9.0 (M)	5.7–8.5 (M)	5.0–15.0 (M)
	5.4–11.7 (F)	4.5–7.0 (F)	4.4–6.5 (F)	4.5–6.2 (F)	3.2–6.0 (F)	3.5–8.0 (F)
Mean corpuscular hemoglobin (pg)	18.5–21.0	17.5–20.8	18.5–21.0	18.1–20.7	18.0–20.5	18.5–22.0
Mean corpuscular hemoglobin conc. (g/dL)	36.6–39.6	35.3–39.2	37.8–40.0	36.9–40.5	37.0–40.6	36.3–40.9
Mean corpuscular volume (fL)	48.0–58.0	48.3–56.1	48.0–56.0	47.0–56.0	47.0–56.0	50.0–58.0
Methemoglobin (% Hgb)	—	0–3.0	0–4.0	0–2.5	0–2.7	0–2.0
Platelet count (10^3/mm^3)	400–750	350–700	400–870	450–700	450–700	200–450
Reticulocyte count (% RBC)	1.0–2.0	0.7–2.0	0.8–2.0	0.8–2.0	0.3–1.5	0.5–2.5

Note:— = data not available.

Source: Adapted from Levine, B.S. (1979–1993) and NIEHS (1985).

Table 125 Mean Control Ranges of Typical Hematology Measurements in Beagle Dogs

Parameters	Age				
	6–8 mo	9–11 mo	12–14 mo	15–18 mo	19–30 mo
Activated partial thromboplastin time (s)	9.0–13.0	9.0–13.0	9.0–13.0	9.0–13.0	9.0–13.0
Erythrocyte count (10^6/mm^3)	6.0–7.3	6.2–8.0	6.2–8.2	5.8–7.3	5.8–7.3
Fibrinogen (mg/dL)	150–300	100–200	—	—	—
Hematocrit (%)	41.5–49.0	44.3–54.9	46.0–54.6	42.5–55.0	42.0–52.0
Hemoglobin (g/dL)	14.5–17.3	15.8–18.0	16.0–18.8	13.0–19.0	13.0–19.0
Leukocyte count, total (10^3/mm^3)	5.5–14.0	6.8–13.6	5.7–15.5	5.0–15.0	6.0–18.0
Mean corpuscular hemoglobin (pg)	21.5–25.1	21.6–24.9	22.0–25.2	22.5–26.0	23.0–26.0
Mean corpuscular hemoglobin conc. (g/dL)	33.0–37.0	33.0–36.4	34.0–36.0	30.0–34.0	30.0–34.0
Mean corpuscular volume (fL)	65.0–71.0	64.0–73.0	64.0–72.0	65.0–78.0	65.0–78.0
Methemoglobin (% Hgb)	0–2.0	0–1.5	0–1.5	—	—
Platelet count (10^3/mm^3)	150–400	150–400	150–400	150–400	150–400
Prothrombin time (s)	6.2–8.4	6.8–8.4	6.2–8.8	6.5–9.0	6.5–9.0
Reticulocyte count (% RBC)	0–0.7	0–0.7	0–0.7	0–0.7	0–0.7

Note: — = data not available.

Source: Adapted from Levine, B.S. (1979–1993), Bulgin, M.S. et al. (1970), and Jordan, J.E. (1977).

Table 126 Mean Control Ranges of Typical Hematology Measurements in Nonhuman Primates of Various Ages

Parameter	Cynomolgus (3–7 yr)	Rhesus (1–2 yr)	Rhesus (3–7 yr)	Marmoset (<1.5 yr)	Marmoset (>1.5 yr)	Baboon (1–5 yr)	Baboon (6–15 yr)
Activated partial thromboplastin time (s)	15.5–22.7	15.0–22.0	15.0–22.0	—	—	—	30–60
Erythrocyte count (10^6/mm^3)	4.5–7.2	4.4–5.8	4.2–6.2	4.2–6.2	4.6–6.8	4.2–5.7	4.0–5.3
Hematocrit (%)	31.5–37.9	31.5–39.2	29.3–39.0	30.0–42.1	37.7–47.5	31.0–43.0	34.0–42.0
Hemoglobin (g/dL)	10.4–12.4	10.8–13.5	9.8–13.1	12.6–15.0	13.5–16.8	10.8–13.5	10.3–13.1
Leukocyte count, total (10^3/mm^3)	5.3–13.4	4.5–13.3	4.3–12.2	5.5–13.0	4.6–11.3	4.9–13.0	4.8–13.9
Mean corpuscular hemoglobin (pg)	18.9–22.3	19.8–24.8	19.6–23.2	24.0–30.5	23.0–29.0	22.0–27.0	22.0–28.0
Mean corpuscular hemoglobin conc. (g/dL)	32.0–35.6	31.3–35.5	31.7–37.5	32.1–42.6	32.2–42.5	28.0–34.0	30.0–35.0
Mean corpuscular volume (fL)	57.1–63.9	66.0–74.0	56.0–70.0	66.0–76.0	68.0–77.0	63.0–80.00	75.0–91.0
Platelet count (10^3/mm^3)	150–400	200–600	200–500	200–500	200–500	200–500	200–500
Prothrombin time (s)	11.5–14.0	9.9–12.2	11.2–14.4	—	—	—	9.0–13.0
Reticulocyte count (% RBC)	0–0.5	0–1.4	0–1.5	0–5.0	0–4.7	0–2.3	0–1.9

Note: — = data not available.

Source: Adapted from Levine, B.S. (1979–1993), Kapeghian, L.C. and Verlangieri, A.J. (1984); Yarbrough, L.W. et al. (1984), and Hack, C.A. and Gleiser, C.A. (1982).

Table 127 Mean Control Ranges of Typical Hematology Measurements in New Zealand White Rabbits

Parameters	Age		
	15–20 wk	25–40 wk	1–2 yr
Activated partial thromboplastin time (s)	11.7–14.5	11.3–14.9	10.5–15.8
Erythrocyte count (10^6/mm^3)	5.5–7.0	4.8–6.7	4.9–7.0
Fibrinogen (mg/dL)	125–300	125–300	125–400
Hematocrit (%)	37.0–44.5	37.0–44.5	37.5–44.7
Hemoglobin (g/dL)	12.0–14.7	10.9–14.4	10.5–14.8
Leukocyte count, total (10^3/mm^3)	5.4–11.9	3.6–7.9	4.8–13.5
Mean corpuscular hemoglobin (pg)	20.2–23.0	21.8–24.5	20.4–23.4
Mean corpuscular hemoglobin conc. (g/dL)	32.3–34.9	32.2–34.8	30.0–34.1
Mean corpuscular volume (fl)	61.4–68.6	64.8–69.5	64.8–72.0
Platelet count (10^3/mm^3)	175–500	175–500	200–500
Reticulocyte count (% RBC)	0–2.0	0–2.0	0–3.0
Prothrombin time (s)	8.2–9.8	8.0–10.0	8.6–10.3

Source: Adapted from Levine, B.S. (1979–1993), Hewett, C.D. et al. (1989) and Jain (1986).

Table 128 Control Ranges of Typical Hematology Measurements in Minipigs (Gottingen)[a]

Parameters			
Erythrocyte count (10^6/mm^3)	6.5–10.4	Mean corpuscular hemoglobin (pg)	12.9–21.7
Hematocrit (%)	31.0–50.3	Mean corpuscular hemoglobin conc.(g/dL)	25.8–37.0
Hemoglobin (g/dL)	9.4–16.5	Mean corpuscular volume (fL)	39.8–63.9
Leukocyte count, total (10^3/mm^3)	4.5–19.7	Platelet count (10^3/mm^3)	144–1088
Neutrophils (%)	9.0– 45.5	Reticulocyte count (%RBC)	0.2–5.1
Lymphocytes (%)	55.9–81.7	Prothrombin time (s)	10.7–13.8
Monocytes (%)	0.7–8.5	Activated partial thromboplastin time (s)	12.1–17.1
Eosinophils (%)	0.2–5.9		
Basophils (%)	0.1–3.7		

[a] Age ~4–6 mo.

Source: Marshall Farms, Unpublished personal data.

Table 129 24-hr Mean Urinalysis Data with Standard Deviation (SD) and Standard Error of the Mean (SEM) in Adult Male Rats: Fischer-344, Sprague-Dawley, and Wistar

Parameters	Strain								
	F-344			Sprague-Dawley			Wistar		
	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
Volume (mL)	5.92	2.15	0.88	14.83	7.63	3.12	12.68	4.06	1.66
Volume (mL/100 g body weight)	1.78	0.556	0.227	2.824	1.339	0.547	2.453	0.761	0.311
Sodium (µEq/mL)	62.7	20.3	8.3	54.3	32.7	13.4	41.67	16.27	6.64
Potassium (µEq/mL)	197.67	32.87	13.42	168.0	75.2	30.7	146.0	37.5	15.3
Chloride (µEq/mL)	105.0	54.5	22.3	64.7	47.5	19.4	60.0	24.9	10.2
Protein (g/dL)	0.4833	0.0983	0.0401	0.5167	0.1941	0.0792	0.3667	0.0816	0.0333
Glucose (mg/dL)	7.33	17.96	7.33	0.00	0.00	0.00	0.00	0.00	0.00
ALP (IU)	154.2	54.4	22.2	87.1	53.7	21.9	141.4	43.4	17.8
LDH (IU)	3.83	9.39	3.83	34.17	83.69	34.17	0.00	0.00	0.00
Osmolality (mOsm/kg)	1312.3	210.5	86.0	1206	497	203	1197	325	133
pH	6.18	0.41	0.17	6.83	0.75	0.31	6.167	0.406	0.17
Creatinine (mg/dL)	144.2	22.8	9.3	142.0	61.9	25.3	165.7	60.7	24.8
Sodium/Cr (µEq/mg Cr)	43.2	124	5.07	35.78	7.88	3.22	25.37	7.55	3.08
Potassium/Cr (µEq/mg Cr)	137.2	11.6	4.72	117.29	15.55	6.35	91.10	16.1	6.59
Chloride/Cr (µEq/mg Cr)	70.3	35.3	14.40	39.5	25.0	10.20	36.9	14.7	5.99
Protein/Cr (g/mg Cr)	0.0039	0.00058	0.00024	0.0038	0.0012	0.00047	0.0023	0.0004	0.00016
Glucose/Cr (mg/mg Cr)	0.05	0.123	0.05	0	0	0	0	0	0

Note: Resting renal function—Each animal was placed in an individual metabolism cage for a 24-hr urine sample collection.

Table 130 24-hr Mean Urinalysis Data with Standard Deviation (SD) and Standard Error of the Mean (SEM) in Adult Female Rats: Fischer-344, Sprague-Dawley, and Wistar

Parameters	Strain								
	F-344			Sprague-Dawley			Wistar		
	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
Volume (mL)	8.82	4.32	1.76	8.43	3.43	1.40	18.22	8.07	3.29
Volume (mL/100 g body weight)	4.93	2.41	0.98	2.839	1.119	0.457	6.48	2.46	1.00
Sodium (µEq/mL)	152.0	41.4	16.9	155.2	16.2	6.6	81.7	63.5	25.9
Potassium (µEq/mL)	304.0	91.2	36.8	324.2	50.8	20.7	179.7	97.9	40.0
Chloride (µEq/mL)	205.5	61.6	25.2	249.7	78.7	32.1	104.7	79.5	32.5
Protein (g/dL)	0.3333	0.0516	0.0211	0.4667	0.1211	0.0494	0.1833	0.0983	0.0401
Glucose (mg/dL)	9.3	14.5	5.9	8.33	13.05	5.33	0.00	0.00	0.00
ALP (IU)	25.22	11.14	4.55	16.1	11.1	4.5	32.0	24.9	10.2
LDH (IU)	0.00	0.00	0.00	13.83	19.02	7.76	2.50	6.12	2.50
Osmolality (mOsm/kg)	1764	520	212	2286	650	266	1083	428	175
pH	7.00	0.632	0.26	7.83	1.17	0.48	7.50	1.23	.50
Creatinine (mg/dL)	91.8	27.8	11.4	161.5	54.2	22.1	71.50	23.98	9.79
Sodium/Cr (µEq/mg Cr)	169.9	27.7	11.32	105.5	34.6	14.13	120.9	85.0	34.72
Potassium/Cr (µEq/mg Cr)	334.6	27.7	11.32	213.5	47.5	19.39	264.1	129.3	52.77
Chloride/Cr (µEq/mg Cr)	225.6	24.6	10.06	162.8	43.8	17.90	149.9	106.8	43.62
Protein/Cr (g/mg Cr)	0.0040	0.0015	0.00062	0.0031	0.00086	0.00035	0.0027	0.0015	0.0006
Glucose/Cr (mg/mg Cr)	0.0817	0.1266	0.0517	0.0417	0.0646	0.0264	0	0	0

Note: Resting renal function—Each animal was placed in an individual metabolism cage for a 24-hr urine sample collection.

Table 131 Comparison of Biochemical Components in Urine of Normal Experimental Animals

Component (mg/kg body wt/day) or Property	Rat	Rabbit	Cat	Dog	Goat	Sheep
Volume (mL/kg body wt/day)	—	20.0–350	10.0–30.0	20.0–167	7.0–40.0	10.0–40.0
Specific gravity	1.040–1.076	1.003–1.036	1.020–1.045	1.015–1.050	1.015–1.062	1.015–1.045
pH	7.30–8.50	7.60–8.80	6.00–7.00	6.00–7.00	7.5–8.80	7.50–8.80
Calcium	3.00–9.00	12.1–19.0	0.20–0.45	1.00–3.00	1.00–3.40	1.00–3.00
Chloride	50.0–75.0	190–300	89.0–130	5.00–15.0	186–376	—
Creatinine	24.0–40.0	20.0–80.0	12.0–30.0	15.0–80.0	10.0–22.0	5.80–14.5
Magnesium	0.20–1.90	0.65–4.20	1.50–3.20	1.70–3.00	0.15–1.80	0.10–1.50
Phosphorous, inorganic	20.0–40.0	10.0–60.0	39.0–62.0	20.0–50.0	0.5–1.6	0.10–0.50
Potassium	50.0–60.0	40.0–55.0	55.0–120	40.0–100	250–360	300–420
Protein, total	1.20–6.20	0.74–1.86	3.10–6.82	1.55–4.96	0.74–2.48	0.74–2.17
Sodium	90.4–110	50.0–70.0	—	2.00–189	140–347	0.80–2.00
Urea nitrogen (g/kg/day)	1.00–1.60	1.20–1.50	0.80–4.00	0.30–0.50	0.14–0.47	0.11–0.17
Uric acid	8.00–12.0	4.00–6.00	0.20–13.0	3.1–6.0	2.00–5.00	2.00–4.00

Component (mg/kg body wt/day) or Property	Swine	Cattle	Horse	Monkey
Volume (mL/kg)	5.00–30.0	17.0–45.0	3.0–18.0	70.0–80.0
Specific gravity	1.010–1.050	1.025–1.045	1.020–1.050	1.015–1.065
pH	6.25–7.55	7.60–8.40	7.80–8.30	5.50–7.40
Calcium	—	0.10–3.60	—	10.0–20.0
Chloride	—	10.0–140	81.0–120	80.0–120
Creatinine	20.0–90.0	15.0–30.0	—	20.0–60.0
Magnesium	—	2.00–7.00	—	3.20–7.10
Phosphorous, inorganic	—	0.01–6.20	0.05–2.00	9.00–20.6
Potassium	—	240–320	—	160–245
Protein, total	0.33–1.49	0.25–2.99	0.62–0.99	0.87–2.48
Sodium	—	2.00–40.0	—	—
Urea nitrogen (g/kg/day)	0.28–0.58	0.05–0.06	0.20–0.80	0.20–0.70
Uric acid	1.00–2.00	1.00–4.00	1.00–2.00	1.00–2.00

Source: From Mitruka, B.M. and Rawnsley, H.M. (1977). With permission.

Table 132 Normal Human Laboratory Values

Blood, Plasma, or Serum		
	Reference Value	
Determination	Conventional Units	SI Units
Ammonia (NH_3)-diffusion	20–120 mcg/dL	12–70 mcmol/L
Ammonia Nitrogen	15–45 µg/dL	11–32 µmol/L
Amylase	35–118 IU/L	0.58–1.97 mckat/L
Anion Gap (Na^+-[Cl^- + HCO_3^-]) (P)	7–16 mEq/L	7–16 mmol/L
Antinuclear antibodies	Negative at 1:10 dilution of serum	Negative at 1:10 dilution of serum
Antithrombin III (AT III)	80–120 U/dL	800–1200 U/L
Bicarbonate: Arterial	21–28 mEq/L	21–28 mmol/L
Venous	22–29 mEq/L	22–29 mmol/L
Bilirubin: Conjugated (direct)	≤ 0.2 mg/dL	≤ 4 mcmol/L
Total	0.1–1 mg/dL	2–18 mcmol/L
Calcitonin	< 100 pg/mL	<100 ng/L
Calcium: Total	8.6–10.3 mg/dL	2.2–2.74 mmol/L
Ionized	4.4–5.1 mg/dL	1–1.3 mmol/L
Carbon dioxide content (plasma)	21–32 mmol/L	21–32 mmol/L
Carcinoembryonic antigen	< 3 ng/mL	< 3 mcg/L
Chloride	95–110 mEq/L	95–110 mmol/L
Coagulation screen:		
Bleeding time	3–9.5 min	180–570 s
Prothrombin time	10–13 s	10–13 s
Partial thromboplastin time (activated)	22–37 s	22–37 s
Protein C	0.7–1.4 µ/mL	700–1400 U/mL
Protein S	0.7–1.4 µ/mL	700–1400 U/mL
Copper, total	70–160 mcg/dL	11–25 mcmol/L
Corticotropin (ACTH adrenocorticotropic hormone) — 0800 hr	<60 pg/mL	<13.2 pmol/L
Cortisol: 0800 hr	5–30 mcg/dL	138–810 nmol/L
1800 hr	2–15 mcg/dL	50–410 nmol/L
2000 hr	≤50% of 0800 hr	≤50% of 0800 hr
Creatine kinase: Female	20–170 IU/L	0.33–2.83 mckat/L
Male	30–220 IU/L	0.5–3.67 mckat/L
Creatine kinase isoenzymes, MB fraction	0–12 IU/L	0–0.2 mckat/L
Creatine	0.5–1.7 mg/dL	44–150 mcmol/L
Fibrinogen (coagulation factor 1)	150–360 mg/dL	1.5–3.6 g/L

Table 132 Normal Human Laboratory Values (Continued)

Blood, Plasma, or Serum

Determination		Reference Value: Conventional Units		Reference Value: SI Units	
Follicle-stimulating hormone (FSH)					
Female		2–13 mIU/mL		2–13 IU/L	
Midcycle		5–22 mIU/mL		5–22 IU/L	
Male		1–8 mIU/ml		1–8 IU/L	
Glucose, fasting		65–115 mg/dL		3.6–6.3 mmol/L	
Glucose Tolerance Test (Oral)		mg/dL		mmol/L	
		Normal	**Diabetic**	**Normal**	**Diabetic**
Fasting		70–105	>140	3.9–5.8	>7.8
60 min		120–170	≥200	6.7–9.4	≥11.1
90 min		100–140	≥200	5.6–7.8	≥11.1
120 min		70–120	≥140	3.9–6.7	≥7.8
(γ)-Glutamyltransferase (GGT):	Male	9–50 units/L		9–50 units/L	
	Female	8–40 units/L		8–40 units/L	
Haptoglobin		44–303 mg/dL		0.44–3.03 g/L	
Hematologic tests:					
Fibrinogen		200–400 mg/dL		2–4 g/L	
Hematocrit (Hct),	female	36%–44.6%		0.36–0.446 fraction of 1	
	male	40.7%–50.3%		0.4–0.503 fraction of 1	
Hemoglobin A_{1C}		5.3%–7.5% of total Hgb		0.053–0.075	
Hemoglobin (Hb),	female	12.1–15.3 g/dL		121–153 g/L	
	male	13.8–17.5 g/dL		138–175 g/L	
Leukocyte count (WBC)		3800–9800/mcl		$3.8–9.8 \times 10^9$/L	
Erythrocyte count (RBC),	female	$3.5–5 \times 10^6$/mcl		$3.5–5 \times 10^{12}$/L	
	male	$4.3–5.9 \times 10^6$/mcl		$4.3–5.9 \times 10^{12}$/L	
Mean corpuscular volume (MCV)		80–97.6 mcm^3		80–97.6 fl	
Mean corpuscular hemoglobin (MCH)		27–33 pg/cell		1.66–2.09 fmol/cell	
Mean corpuscular hemoglobin concentration (MCHC)		33–36 g/dL		20.3–22 mmol/L	
Erythrocyte sedimentation rate (sedrate, ESR)		≤30 mm/hr		≤30 mm/hr	
Erythrocyte enzymes:		250–5000 units/10^6 cells		250–5000 mcunits/cell	
Glucose-6-phosphate dehydrogenase (G-6-PD)					

Table 132 Normal Human Laboratory Values (Continued)

Blood, Plasma, or Serum		
	Reference Value	
Determination	Conventional Units	SI Units
Ferritin	10–383 ng/mL	23–862 pmol/L
Folic acid: normal	> 3.1–12.4 ng/mL	7–28.1 nmol/L
Platelet count	150–450 × 10^3/mcl	150–450 × 10^9/L
Reticulocytes	0.5%–1.5% of erythrocytes	0.005–0.015
Vitamin B_{12}	223–1132 pg/mL	165–835 pmol/L
Iron: Female	30–160 mcg/dL	5.4–31.3 mcmol/L
Male	45–160 mcg/dL	8.1–31.3 mcmol/L
Iron binding capacity	220–420 mcg/dL	39.4–75.2mcmol/L
Isocitrate. Dehydrogenase	1.2–7 units/L	1.2–7 units/L
Isoenzymes		
Fraction 1	14%–26% of total	0.14–0.26 fraction of total
Fraction 2	29%–39% of total	0.29–0.39 fraction of total
Fraction 3	20%–26% of total	0.20–0.26 fraction of total
Fraction 4	8%–16% of total	0.08–0.16 fraction of total
Fraction 5	6%–16% of total	0.06–0.16 fraction of total
Lactate dehydrogenase	100–250 IU/L	1.67–4.17 mckat/L
Lactic acid (lactate)	6–19 mg/dL	0.7–2.1 mmol/L
Lead	≤50 mcg/dL	≤2.41 mcmol/L
Lipase	10–150 units/L	10–150 units/L
Lipids:		
Total Cholesterol		
Desirable	<200 mg/dL	<5.2 mmol/L
Borderline-high	200–239 mg/dL	<5.2–6.2 mmol/L
High	>239 mg/dL	>6.2 mmol/L
LDL		
Desirable	<130 mg/dL	<3.36 mmol/L
Borderline-high	130–159 mg/dL	3.36–4.11 mmol/L
High	>159 mg/dL	>4.11 mmol/L

Table 132 Normal Human Laboratory Values (Continued)

Blood, Plasma, or Serum		
	Reference Value	
Determination	**Conventional Units**	**SI Units**
HDL (low)	<35 mg/dL	<0.91 mmol/L
Triglycerides		
Desirable	<200 mg/dL	<2.26 mmol/L
Borderline-high	200–400 mg/dL	2.26–4.52 mmol/L
High	400–1000 mg/dL	4.52–11.3 mmol/L
Very high	>1000 mg/dL	>11.3 mmol/L
Magnesium	1.3–2.2 mEqL	0.65–1.1 mmol/L
Osmolality	280–300 mOsm/kg	280–300 mmol/kg
Oxygen saturation (arterial)	94%–100%	0.94–1 fraction of 1
PCO_2, arterial	35–45 mm Hg	4.7–6 kPa
PH, arterial	7.35–7.45	7.35–7.45
PO_2, arterial: Breathing room air[1]	80–105 mm Hg	10.6–14 kPa
On 100% O_2	>500 mm Hg	
Phosphatase (acid), total at 37°C	0.13–0.63 IU/L	2.2–10.5 IU/L or 2.2–10.5 mckat/L
Phosphatase alkaline[2]	20–130 IU/L	20–130 IU/L or 0.33–2.17 mckat/L
Phosphorus, inorganic[3] (phosphate)	2.5–5 mg/dL	0.8–1.6 mmol/L
Potassium	3.5–5 mEq/L	3.5–5 mmol/L
Progesterone		
Female	0.1–1.5 ng/mL	0.32–4.8 nmol/L
Follicular phase	0.1–1.5 ng/mL	0.32–4.8 nmol/L
Luteal phase	2.5–28 ng/mL	8–89 nmol/L
Male	<0.5 ng/mL	<1.6 nmol/L
Prolactin	1.4–24.2 ng/mL	1.4–24.2 mcg/L
Prostate specific antigen	0–4 ng/mL	0–4 ng/mL
Protein: Total	6–8 g/dL	60–80 g/L
Albumin	3.6–5 g/dL	36–50 g/L
Globulin	2.3–3.5 g/dL	23–35 g/L
Rheumatoid factor	<60 IU/mL	<60 kIU/L
Sodium	135–147 mEq/L	135–147 mmol/L
Testosterone: Female	6–86 ng/dL	0.21–3 nmol/L
Male	270–1070 ng/dL	9.3–37 nmol/L

Table 132 Normal Human Laboratory Values (Continued)

Blood, Plasma, or Serum		
	Reference Value	
Determination	Conventional Units	SI Units
Thyroid Hormone Function Tests:		
Thyroid-stimulating hormone (TSH)	0.35–6.2 mcU/mL	0.35–6.2 mU/L
Thyroxine-binding globulin capacity	10–26 mcg/dL	100–260 mcg/L
Total triiodothyronine (T_3)	75–220 ng/dL	1.2–3.4 nmol/L
Total thyroxine by RIA (T_4)	4–11 mcg/dL	51–142 nmol/L
T_3 resin uptake	25%–38%	0.25–0.38 fraction of 1
Transaminase, AST (aspartate aminotransferase, SGOT)	11–47 IU/L	0.18–0.78 mckat/L
Transaminase, ALT (alanine aminotrans ferase, SGPT)	7–53 IU/L	0.12–0.88 mckat/L
Transferrin	220–400 mg/dL	2.20–4.00 g/L
Urea nitrogen (BUN)	8–25 mg/dL	2.9–8.9 mmol/L
Uric acid	3–8 mg/dL	179–476 mcmol/L
Vitamin A (retinol)	15–60 mcg/dL	0.52–2.09 mcmol/L
Zinc	50–150 mcg/dL	7.7–23 mcmol/L

[1] Age dependent.

[2] Infants and adolescents up to 104 U/L.

[3] Infants in the first year up to 6 mg/dL.

Table 132 Normal Human Laboratory Values (Continued)

Urine		
	Reference Value	
Determination	**Conventional Units**	**SI Units**
Calcium[1]	50–250 mcg/day	1.25–6.25 mmol/day
Catecholamines: Epinephrine	<20 mcg/day	<109 nmol/day
Norepinephrine	<100 mcg/day	<590 nmol/day
Catecholamines, 24-hr	<110 µg	<650 nmol
Copper[1]	15–60 mcg/day	0.24–0.95 mcmol/day
Creatinine:		
Child	8–22 mg/kg	71–195 µmol/kg
Adolescent	8–30 mg/kg	71–265 µmol/kg
Female	0.6–1.5 g/day	5.3–13.3 mmol/day
Male	0.8–1.8 g/day	7.1–15.9 mmol/day
pH	4.5–8	4.5–8
Phosphate[1]	0.9–1.3 g/day	29–42 mmol/day
Potassium[1]	25–100 mEq/day	25–100 mmol/day
Protein		
Total	1–14 mg/dL	10–140 mg/L
At rest	50–80 mg/day	50–80 mg/day
Protein, quantitative	<150 mg/day	<0.15 g/day
Sodium[1]	100–250 mEq/day	100–250 mmol/day
Specific gravity, random	1.002–1.030	1.002–1.030
Uric acid, 24-hr	250–750 mg	1.48–4.43 mmol

[1] Diet dependent.

Note: In this table, normal reference values for commonly requested laboratory tests are listed in traditional units and in SI units. The tables are a guideline only. Values are method dependent, and "normal values" may vary among laboratories.

Source: From © 2000 by Facts and Comparisons, reprinted with permission from *Drug Facts and Comparisons. 2000 Loose Leaf Edition,* St. Louis, MO: Facts and Comparisons, a Wolters Kluwer Company.

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Section 11
Risk Assessment

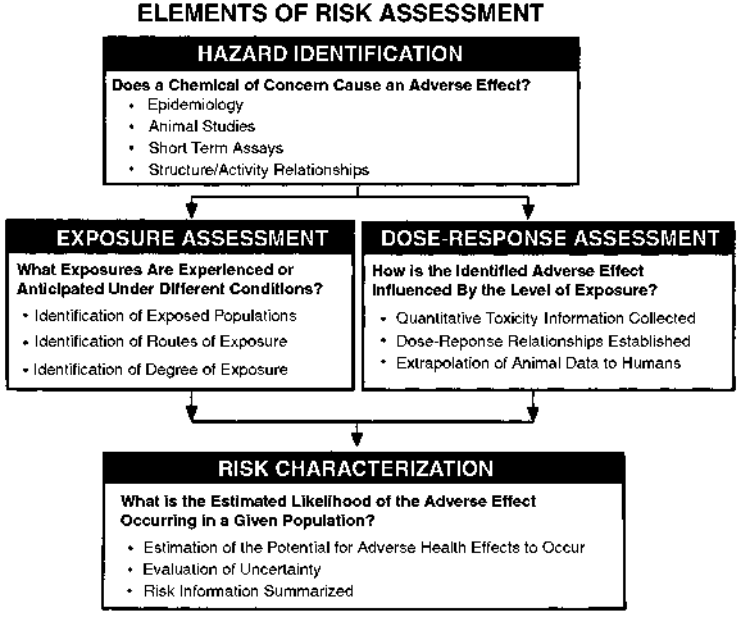

Figure 8 The four major elements of risk assessment. The information developed in the risk assessment process is utilized in the risk management where decisions are made as to the need for, the degree of, and the steps to be taken to control exposures the chemical of concern. From National Research Council (1983) ; U.S. Environmental Protection Agency (1989a); and Hopper, L.D. et al. (1992).

Table 133 Typical Factors Considered in a Risk Assessment

- Physical and chemical properties of the chemical
- Patterns of use
- Handling procedures
- Availability and reliability of control measures
- Source and route of exposure under ordinary and extraordinary conditions
- Potential for misuse
- Magnitude, duration, and frequency of exposure
- Nature of exposure (total, dermal, inhalation)
- Physical nature of the exposure (solid, liquid, vapor, etc.)
- Influence of environmental conditions of exposure
- Population exposed
    - Number
    - Sex
    - Health status
    - Personal habits (e.g., smoking)
    - Lifestyles (e.g., hobbies, activities)

Source: From Ballantyne, B. and Sullivan, J.B. (1992a).

Table 134 Major Factors that Influence a Risk Assessment

Factor	Effect
Low dose extrapolation	Can involve as many as 50 or more assumptions, each of which introduces uncertainty; often considered the greatest weakness in risk assessment.
Population variation	The use of standard exposure factors can underestimate actual risk to hypersensitive individuals. Addressing the risk assessment to the most sensitive individuals can overestimate risk to the population as a whole.
Exposure variation	The use of modeling and measurement techniques can provide exposure estimates that diverge widely from reality.
Environmental variation	Can affect actual exposures to a greater or lesser degree than assumed to exist.
Multiple exposures	Risk assessments generally deal with one contaminant for which additive, synergistic, and antagonistic effects are unaccounted; can result in underestimation or overestimation of risk.
Species differences	It is generally assumed that humans are equivalent to the most sensitive species; can overestimate or underestimate risk.
Dose based on body weight	Toxicity generally does not vary linearly with body weight but exponentially with body surface area.
Choice of dose levels	Use of unrealistically high dose levels can result in toxicity unlikely to occur at actual exposure levels. The number of animals being studied may be insufficient to detect toxicity at lower doses.
Uncertainty factors	The use of uncertainty factors in attempting to counter the potential uncertainty of a risk assessment can overestimate risk by several orders of magnitude.
Confidence intervals	The upper confidence interval does not represent the true likelihood of an event; can overestimate risk by an order of magnitude or more.
Statistics	Experimental data may be inadequate for statistical analysis. Statistical significance may not indicate biological significance, and a biologically significant effect may not be statistically significant. Statistical significance does not prove causality. Conversely, lack of statistical significance does not prove safety.

Table 135 Human Data Commonly Used in Risk Assessment

Study Type	Alternative Terms	Comments on Use
Cross-sectional	Prevalence, survey	Random sampling of a population at a given point in time to assess prevalence of a disease. Most useful for studying chronic diseases of high frequency. Cannot measure incidence. Although associations may be drawn with prevalent cases, the temporal and causal order of such associations cannot be determined.
Case-control	Retrospective, dose or case-referent	Compares previous exposure in subjects with disease to one or more groups of subjects without disease. Selection of cases and noncases can be controlled. Exposures cannot be controlled. If exposure data are available, an NOEL may be identified. Exposure history may be difficult to reconstruct outside of an occupational setting. Recall and other biases possible because of retrospective evaluation. Allows estimation of relative odds of exposure in cases and controls but not absolute risk.
Cohort	Longitudinal, prospective, incidence	Population or sample of subjects at risk of disease observed through time for outcome of interest. May fail to detect rare outcome. Many factors can be controlled for reduced bias (prospective design). Dose–response curves may be constructed if dose or exposure data are available. Allows estimation of absolute and relative risk.
Clinical trials		Type of cohort study in which investigator controls treatment (exposure). Generally not applicable to environmental issues. Intervention trials in which an exposure is removed or changed (e.g., medication, smoking, diet) are useful for evaluating causality.
Experimental studies		Controlled human exposures generally of low dose and limited exposure time. Used for hazard identification, dose–response, and risk characterization.
Case reports		Suggests nature of acute endpoints. Cannot be used to support absence of hazard.

Source: From Piantadose, S. (1992) and U.S. Environmental Protection Agency (1989b).

Table 136 Epidemiological Terms (Rates and Ratios)

Annual crude death rate	$= \dfrac{\text{Total number of deaths during a given year}}{\text{Total polulation at mid-year}} \times 1000$
Annual specific death rate	$= \dfrac{\text{Total number of deaths in a specific group during a given year}}{\text{Total population in the specific group at mid-year}} \times 100$
Proportional mortality rate	$= \dfrac{\text{Total number of deaths in a specific group}}{\text{Total number of deaths}} \times 100$
Infant mortality rate (IMR)	$= \dfrac{\text{Infant deaths}}{\text{Total live births}}$
Standard mortality rate (SMR)	$= \dfrac{\text{Observed deaths}}{\text{Expected deaths}}$
Cause-of-death ratio	$= \dfrac{\text{Deaths from a specific cause over a period of time}}{\text{Total deaths due to all causes in the same time period}} \times 100$
Incidence rate	$= \dfrac{\text{Number of new cases over a period of time}}{\text{Population at risk over the same time period}}$
Prevalence rate	$= \dfrac{\text{Number of existing cases at a point in time}}{\text{Total population}}$
Relative risk (risk ratio)	$= \dfrac{\text{Incidence among the exposed}}{\text{Incidence among the nonexposed}}$
Attributal risk (risk difference)	= Incidence among the exposed – incidence among the nonexposed
Relative odds ratio	$= \dfrac{\text{Number of exposed individuals with disease}}{\text{Number of exposed individuals without disease}} \times \dfrac{\text{Number of nonexposed individuals without disease}}{\text{Number of nonexposed individuals with disease}}$

Source: From Selevan, S.G. (1993), Hallenbeck, W.H. and Cunningham, K.M. (1986), and Gamble and Battigelli (1978).

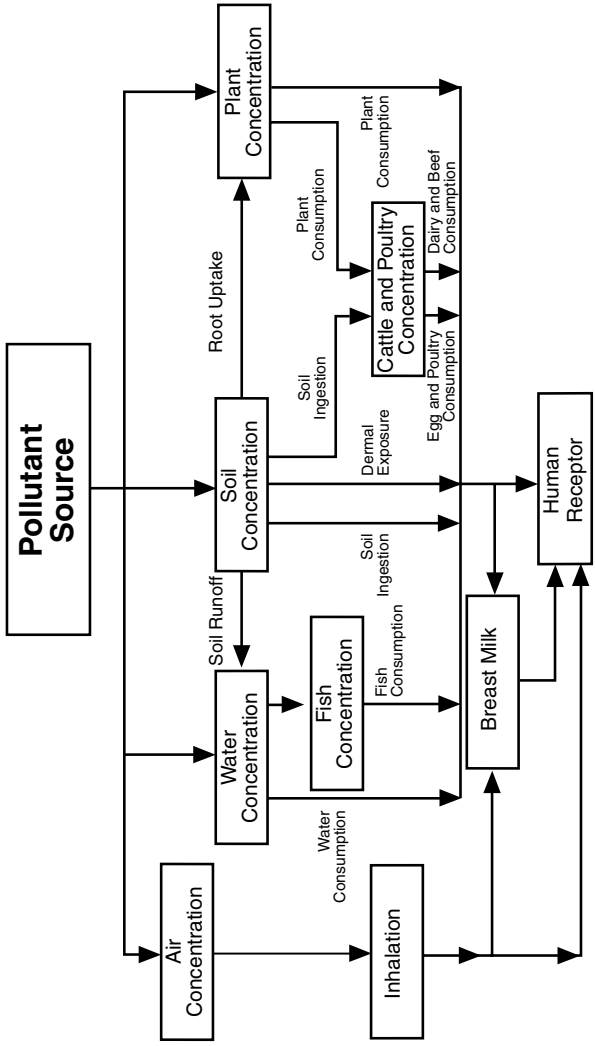

Figure 9 Exposure pathways to an environmental pollutant. Modified from Lowe, J.A., et al. (1990).

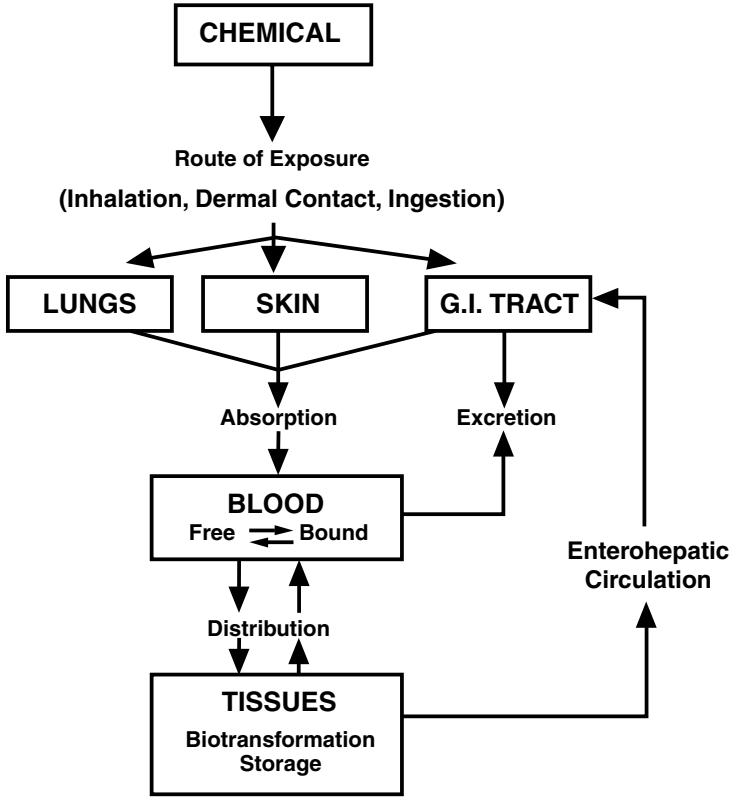

Figure 10 Diagrammatic representation of the possible pharmacokinetic fate of a chemical after exposure by inhalation, dermal contact and ingestion. The lungs and skin also have enzyme systems capable of biotransformation (not shown). The fate of a chemical after exposure can vary considerably between species. Pharmacokinetic information is essential for accurate risk assessments. Such information can be obtained from animal studies/or physiologically-based pharmacokinetic models. In the absence of such data, assumptions are often made the introduce a great degree of uncertainty into the risk assessment process. Modified from Ballantyne and Sullivan (1992a).

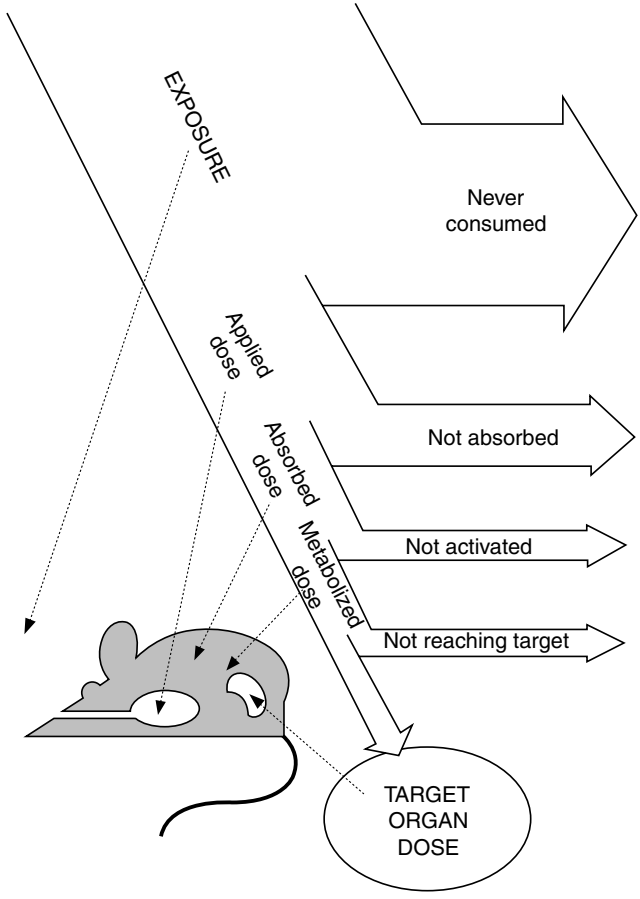

Figure 11 Representation of the relationship between ambient exposure and critical target dose and the progressive decrease in effective exposure due to various biological barriers. From ILSI (1995). *Low-Dose Extrapolation of Cancer Risks: Issues and Perspectives*. Used with permission. 1995 International Life Sciences Institute, Washington, D.C.

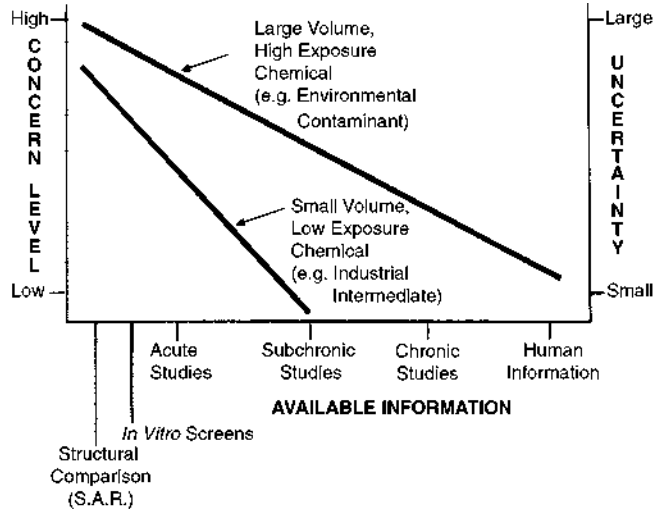

Figure 12 Relationship between the degree of uncertainty associated with the risk assessment of a chemical, the concern for human exposure, and the toxicological information available on the chemical. In practice, the larger the toxicological database available on a chemical of concern ("weight-of-evidence"), the greater the certainty (less uncertainty) that the estimated "safe" exposure level will be protective of individuals exposed to the chemical. Similarly, the concern that the risk assessment will underestimate the risk decreases with a larger toxicological database. Generally, less toxicological information will be required to reduce the concern level and uncertainty associated with a small volume, low-exposure chemical (for which the exposed population is well characterized and the exposures can be controlled) as compared with a large volume, high-exposure chemical.

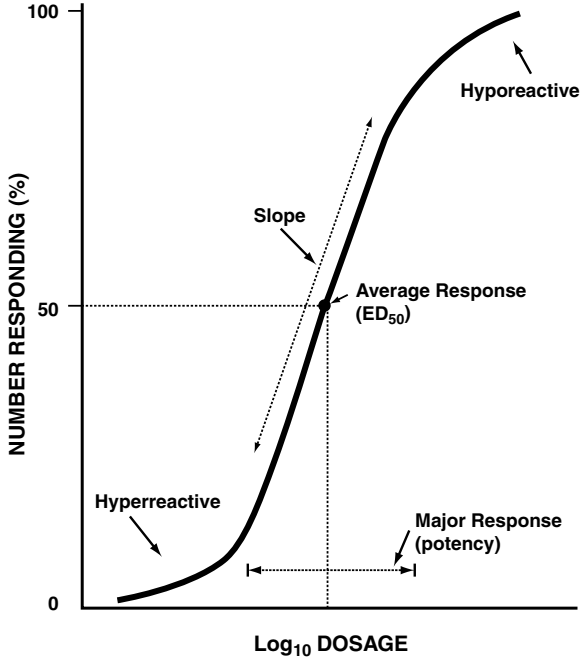

Figure 13 Typical sigmoid cumulative dose-response curve for a toxic effect which is symmetrical about the average (50% response) point. Note, dosage is presented on a log scale. The major response (potency) occurs around the average response. The midpoint of the curve is referred to as the median effective dose for the effect being considered (ED_{50}). If mortality is the endpoint, this point is referred to as the median lethal dose (LD_{50}). The 95% confidence limits are the narrowest at the midpoint which makes this the point most useful for comparison of toxicity between chemicals. The slope of the curve is determined by the increase in response as a function of incremental increases in dosage. A steep slope indicates a majority of a population will respond within a narrow dose range, while a flatter curve indicates that a much wider dose range is required to affect a majority of the exposed population. Hyperreactive and hyporeactive individuals are at the extreme left and right sides of the curve, respectively. From Ballantyne, B., (1992b).

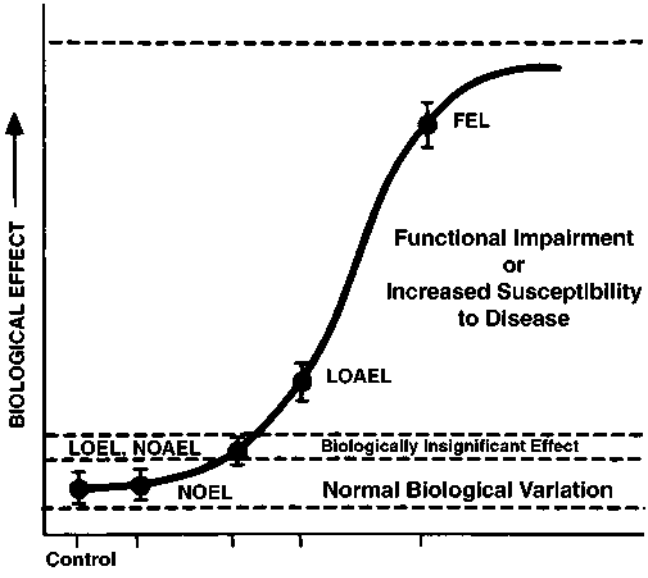

Figure 14 A dose-response curve from a typical toxicology study showing dose-related indices commonly used in risk assessment. A well-designed study should include dose levels that produce a Frank Effect (FEL), a Lowest Observable Adverse Effect (LOAEL), and either a Lowest Observable Effect (LOEL), a No Observable Adverse Effect (NOAEL), or a No Observable Effect (NOEL). A FEL is a dose or exposure level that produces unmistakable adverse health effects that cause functional impairment or increased susceptibility to disease; a LOAEL is the lowest dose or exposure level that produces and adverse health effect; a LOEL is the lowest dose or exposure level that produces an observable effect, but not to a degree which would be expected to have a significant impact on the health of the animal (the LOEL is sometimes confused with a LOAEL); a NOAEL is the highest dose or exposure level at which no adverse health effects are observed which are capable of functional impairment or increased susceptibility to disease (the NOAEL can be equivalent to the LOEL); a NOEL is the highest dose or exposure level at which no effects are observed outside of the range of normal biological variation for the species and strain under study. The effect, if any, observed at the NOEL should not be statistically significant when compared with the control group. Adapted from Ecobichon, D.J. (1992a).

Table 137 The Duration of Studies in Experimental Animals and Time Equivalents in Humans

Species	Duration of Study in Months				
	1	3	6	12	24
	Percentage of Lifespan				
Rat	4.1	12	25	49	99
Rabbit	1.5	4.5	9	18	36
Dog	0.82	2.5	4.9	9.8	20
Pig	0.82	2.5	4.9	9.8	20
Monkey	0.55	1.6	3.3	6.6	13
	Human Equivalents (in months)				
Rat	34	101	202	404	808
Rabbit	12	36	72	145	289
Dog	6.5	20	40	81	162
Pig	6.5	20	40	81	162
Monkey	4.5	13	27	61	107

Source: Adapted from Paget, G.E., (1970). From Ecobichon, D.J. (1992b). With permission.

Table 138 Comparative Mammalian Reference Values for Relative Dose Calculations

Species	Average Lifespan (yr)	Body Weight (kg)	Food Consumption (g/day)	Food Consumption Factor[a]	Water Consumption (mL/day)	Inhalation Rate (m^3/day)
Human	70	70	2000	0.028	2000	20
Mouse	1.5–2	0.03	4	0.13	6	0.052
Rat	2	0.35	18	0.05	50	0.29
Hamster	2.4	0.14	12	0.083	27	0.13
Guinea pig	4.5	0.84	34	0.040	200	0.40
Rabbit	7.8	3.8	186	0.049	410	2
Cat	17	3	90	0.030	220	1.2
Dog	12	12.7	318	0.025	610	4.3
Monkey (Rhesus)	18	8	320	0.040	530	5.4

[a] Fraction of body weight consumed per day as food.

Source: Adapted from U.S. EPA (1985).

Table 139 Comparative Mammalian Physiological Values

Parameter	Mouse	Rat	Human
	Tissue Perfusion (percentage of cardiac output)		
Brain	7.5 (2.0–13.0)	1.2	14.0 (13.0–15.0)
Heart	4.4 (2.8–6.0)	2.9	3.3 (2.6–4.0)
Kidney	24.8 (14.6–35.0)	17.8	22.0
Liver (total)	21.0	18.6 (17.0–26.0)	26.5 (26.0–27.0)
Liver (arterial only)	8.4	6.7	—
Viscera	30.3	26.3	30.0
Adipose tissue	—	4.5 (4.0–5.0)	4.7 (4.5–5.0)
	Tissue Volume (% of body weight)		
Heart	0.4	0.5	0.6
Kidney	1.5	0.9 (0.9–1.0)	1.1 (0.4–1.5)
Liver	5.0 (4.0–5.9)	4.0 (3.7–4.2)	3.0 (2.4–4.0)
GI tract	6.8	4.3 (3.0–5.5)	3.8 (3.0–4.5)
Fat	7.6 (4.0–9.8)	8.4 (7.0–9.0)	15.5 (9.0–23.1)
Blood	7.6	7.2 (4.9–9.0)	7.2
Muscle	59.0 (45.0–73.0)	59.0 (50.0–73.0)	52.4 (43.4–73.0)
Skin	14.5	16.0	4.3
Marrow	2.7	—	2.5 (2.1–2.8)
Skeletal tissue	9.0	—	—
	Cardiac Output		
Absolute (L/min)	0.0129 (0.110–0.160)	0.1066 (0.0730–0.1340)	5.59 (4.60–6.49)
Relative (L/min·kg)	0.535 (0.440–0.711)	0.327 (0.248–0.646)	0.080
	Alveolar Ventilation (L/min)		
	0.026 (0.012–0.039)	0.080 (0.075–0.085)	4.6 (4.0–5.8)
	Minute Volume		
Absolute (L/min)	0.038 (0.024–0.052)	0.169 (0.057–0.336)	7.4 (6.0–9.0)
Relative (L/min·kg)	1.533 (1.239–1.925)	0.780 (0.142–2.054)	0.089 (0.014–0.127)
	Respiratory Frequency (breaths/min)		
Relative (L/min·kg)	171 (100–213)	117 (60–153)	14 (10–16)

Note: Mean of reported values. Brackets contain range of reported values from which mean was calculated. Absence of range indicates value was from a single report. Values presented are for unanaesthetized animals.

Note: — = No data found.

Source: Data derived from U.S. EPA (1988).

Table 140 Typical Human Exposure Values Used in Risk Assessments

Body weight	
Young child (1–2 yr)	13 kg
Older child (5 yr)	20 kg
Typical adult	70 kg
Male	78 kg
Female	60 kg
Lifespan	75 yr
Inhalation rate	
Typical adult	
Male	15.2 m^3/day
Female	11.3 m^3/day
Child (<1 yr)	4.5 m^3/day
Child (1–12 yr)	8.7 m^3/day
Industrial worker (8-hr work shift)	10 m^3/day
Industrial worker (24-hr total)	20 m^3/day
Reasonable worst case	30 m^3/day
(see Table 146 for inhalation rates relative to age and degree of activity.)	
Drinking water ingestion rate	
Adult (average)	1.4 L/day (21 mL/kg-day)
Adult (90th percentile)	2.0 L/day (34 mL/kg-day)
Infant (<10 kg)	1.0 L/day
Food consumption rate	
Total average meat intake	2.1 g/kg-day
Total average vegetable intake	4.3 g/kg-day
Total average fruit intake	3.4 g/kg-day
Total average dairy intake	8.0 g/kg-day
Total grain intake	4.1 g/kg-day
Total average fish intake	20.1 g/day
Adult total food intake	2000 g/day
Breast milk intake rate	
Average	742 mL/day
Upper percentile	1033 mL/day
Exposed skin surface	
Typical adult	0.20 m^2
Reasonable worst case	0.53 m^2

Table 140 Typical Human Exposure Values Used in Risk Assessments (Continued)

Swimming or bathing (average)	
Male	1.94 m^2
Female	1.69 m^2
Soil ingestion rate	
Children	
Average	100 mg/day
Upper percentile	400 mg/day
Pica child	10 g/day
Adult (average)	50 mg/day
Activities	
a. Showering (typically one event/day)	
Average	10 min/day
95th percentile	35 min/day
(A 5 min shower is estimated to use 40 gal of water.)	
b. Bathing (typically one event/day)	
Median	20 min/event
90th percentile	45 min/event
c. Time indoors	
Children (ages 3–11)	19 hr/day
Adults	21 hr/day
Average residence volume	369 m^3
d. Time outdoors	
Children (ages 3–11)	5 hr/day
Adults	1.5 hr/day

Source: U.S. EPA, 1989d, 1997.

Table 141 Comparative Mammalian Organ Weights (g/100 g body weight)

Species	Brain	Heart	Adrenals	Kidneys[a]	Lungs	Liver	Spleen	Testes[a]
Human	1.96	0.42	0.02	0.41	0.73	2.30	0.25	0.04
Mouse	1.35	0.68	0.02	2.60	0.66	5.29	0.32	0.62
Rat	0.46	0.32	0.01	0.70	0.40	3.10	0.20	0.92
Monkey (rhesus)	2.78	0.38	0.02	0.54	1.89	2.09	0.14	0.03
Dog	0.59	0.85	0.01	0.30	0.94	2.94	0.45	0.15
Rabbit	0.40	0.35	0.02	0.70	0.53	3.19	0.04	0.13
Hamster	0.88	0.47	0.02	0.53	0.46	5.16	—	—
Guinea pig	1.33	0.53	0.07	1.17	1.18	5.14	0.21	0.65
Cat	0.77	0.45	0.02	1.07	1.04	2.59	0.29	0.07
Minipig	0.45	0.55	0.01	0.54	0.65	2.00	0.22	0.25

[a] Combined paired weight.

Table 142 Body Fluid Volumes for Men and Women

Parameter	Adult Male[a]		Adult Female[b]	
	Volume (L)	Percentage of Body Weight	Volume (L)	Percentage of Body Weight
Total body water	45.0	60	33.0	55
Extracellular water	11.25	15	9.0	15
Intracellular water	33.75	45	24.0	40
Total blood volume	5.4	7.2	4.3	7.2
Plasma volume	3.0	—	2.6	—
Erythrocyte volume	2.4	—	1.7	—

[a] Volumes calculated for an adult male with a body weight of 75 kg and a hematocrit of 45%.

[b] Volumes calculated for an adult female with a body weight of 60 kg and a hematocrit of 40%.

Source: Adapted from Plowchalk, D. et al. (1993).

Table 143 Relationship between Body Weight and Body Surface Area in a Number of Vertebrates

Species	Weight (g)	Surface Area (cm^2)
Mouse	20	46
Rat	200	325
Guinea pig	400	565
Rabbit	1,500	1,270
Cat	2,000	1,380
Monkey	4,000	2,980
Minipig	8,000	3,333
Dog	12,000	5,770
Human	70,000	18,000

Source: From Niesink, R.J.M., deVries, J., and Hollinger, M.A. (1996) and personal data.

Table 144 Constants for Estimating Surface Area (A) of Mammals

Species	Constant (K)
Rat	9.6
Mouse	9.0
Rabbit	10.0
Guinea pig	9.0
Monkey	11.8
Dog	11.0
Cat	8.7
Minipig	8.2

$A = KW^{2/3}$ where A = surface area (cm^2); K = constant; W = body weight (g).

Source: Data derived from Spector, W.S., Ed. (1956).

Table 145 Median Total Body Surface Area (m^2) for Humans by Age

Age (yr)	Males	Females
3–5	0.728	0.711
6–8	0.931	0.919
9–11	1.16	1.16
12–14	1.49	1.48
15–17	1.75	1.60
Adult	1.94	1.69

Source: Adapted from U.S. EPA (1989d).

Table 146 Summary of Human Inhalation Rates for Men, Women, and Children by Activity Level (m^3/hr)

	Resting[a]	Light[b]	Moderate[c]	Heavy[d]
Adult male	0.7	0.8	2.5	4.8
Adult female	0.3	0.5	1.6	2.9
Average adult[e]	0.5	0.6	2.1	3.9
Child, age 6	0.4	0.8	2.0	2.4
Child, age 10	0.4	1.0	3.2	4.2

Note: Values of inhalation rates for males, females, and children presented in this table represent the mean of values reported for each activity level in U.S. EPA (1985).

[a] Includes watching television, reading, and sleeping.

[b] Includes most domestic work, attending to personal needs and care, hobbies, and conducting minor indoor repairs and home improvement.

[c] Includes heavy indoor cleanup, performance of major indoor repairs and alterations, and climbing stairs.

[d] Includes vigorous physical exercise and climbing stairs carrying a load.

[e] Derived by taking the mean of the adult male and adult female values for each activity level.

Source: From U.S. EPA (1989d).

Table 147 Summary of Drug Absorption in Neonates, Infants, and Children

	Neonates	Infants	Children
Physiological Alteration			
Gastric emptying time	Irregular	Increased	Slightly increased
Gastric pH	>5	4 to 2	Normal (2–3)
Intestinal motility	Reduced	Increased	Slightly increased
Intestinal surface area	Reduced	Near adult	Adult pattern
Microbial colonization	Reduced	Near adult	Adult pattern
Biliary function	Immature	Near adult	Adult pattern
Muscular blood flow	Reduced	Increased	Adult pattern
Skin permeability	Increased	Increased	Near Adult Pattern
Possible Pharmacokinetic Consequences			
Oral absorption	Erratic—reduced	↑ rate	Near adult pattern
I. M. absorption	Variable	Increased	Adult pattern
Percutaneous absorption	Increased	Increased	Near adult pattern
Rectal absorption	Very efficient	Efficient	Near adult pattern
Presystemic clearance	<adult	>adult	>adult (↑ rate)

Note: Direction of alteration given relative to expected normal adult pattern. Data contained in the preceding table reflect developmental differences that might be expected in healthy pediatric patients. Certain conditions/disease states might modify the function and/or structure of the absorptive surface area, GI motility, and/or systemic blood flow impacting the rate or extent of absorption. Generally, neonate's age ≤ 1 mo, infant's age = 1–24 mo, child's age = 2–12 yr. As the age limits defining these developmental stages are somewhat arbitrary, some overlap in the functional capacity between these stages should be expected. Because physiological development is a dynamic process, it should be kept in mind that functional changes occur incrementally over time and do not abruptly change from one age group to another.

Source: From Ritschel, W.A. and Kerns, G.L. (1999), with permission, Table 24-1 "Summary of Drug Absorption in Neonates, Infants and Children" of the *Handbook of Basic Pharmacokinetics,* 5th Edition, p 307. © 1999 by the American Pharmaceutical Association. Originally adapted from Morselli, P.L., 1983.

Table 148 Drug Metabolism in the Neonate, Infant, and Child

	Neonates	Infants	Children
Physiological Alteration			
Liver/body weight ratio	Increased	Increased	Slightly increased
Cytochrome P450 activity	Reduced	Increased	Slightly increased
Blood esterase activity	Reduced	Normal (by 12 mo)	Adult pattern
Hepatic blow flow	Reduced	Increased	Near adult pattern
Phase 11 Enzyme Activity	Reduced	Increased	Near Adult Pattern
Possible Pharmacokinetic Consequences			
Metabolic rates	Reduced	Increased	Near adult pattern[a]
Presystemic clearance	Reduced	Increased	Near adult pattern
Total body clearance	Reduced	Increased	Near adult pattern[a]
Inducibility of Enzymes	More evident	Slightly increased	Near adult pattern[a]

Note: Direction of alteration given relative to expected normal adult patterns. Generally, neonate's age ≤ 1 mo, infant's age = 1–24 mo, child's age = 2–12 yr. As the age limits defining these developmental stages are somewhat arbitrary, some overlap in the functional capacity between these stages should be expected. Because physiological development is a dynamic process, it should be kept in mind that functional changes occur incrementally over time and do not abruptly change from one age group to another.

[a] Denotes assumption of adult pattern of activity after the conclusion of puberty. The activity of all drug-metabolizing enzymes is generally higher before compared to after puberty.

Source: From Ritschel, W.A. and Kerns, G.L. (1999), with permission, Table 24-5 "Drug Metabolism in the Neonate, Infant and Child" of the *Handbook of Basic Pharmacokinetics,* 5th Edition, p. 314. © 1999 by the American Pharmaceutical Association. Originally adapted from Morselli, P.L., 1983.

Table 149 Renal Function in the Neonate, Infant, and Child

	Neonates	Infants	Children
Physiological Alteration			
Kidney/Body Weight Ratio	Increased	Increased	Near adult values
Glomerular Filtration Rate	Reduced	Normal (by 12 mo)	Normal adult values
Active Tubular Secretion	Reduced	Near normal	Normal adult values[a]
Active Tubular Reabsorption	Reduced	Near normal	Normal adult values
Proteins present in urine	Present (30%)	Low to absent	Normally absent
Urinary Acidification Capacity	Low	Normal (by 1 mo.)	Normal adult activity
Urine Output (ml/hr/kg)	3 to 6	2 to 4	1 to 3
Urine Concentrating Capacity	Reduced	Near normal	Normal adult values
Possible Pharmacokinetic Consequences			
Active Drug Excretion	Reduced	Near normal	Normal adult pattern
Passive Drug Excretion	Reduced to Increased	Increased	Normal adult pattern
Excretion of Basic Drugs	Increased	Increased	Near normal

Note: Direction of alteration given relative to expected normal adult patterns. Generally, neonate ≤ 1 month of age, infants = 1–24 months of age, children = 2–12 years of age. As the age limits defining these developmental stages are somewhat arbitrary, some overlap in the functional capacity between these stages should be expected. Because physiological development is a dynamic process, it should be kept in mind that functional changes occur incrementally over time and do not abruptly change from one age group to another.

[a] Denotes slight increase in excretion rate for basic compounds.

From Ritschel, W.A. and Kerns, G.L. (1999) with permission, Table 24-6 "Renal Function in the Neonate, Infant and Child" of the *Handbook of Basic Pharmacokinetics*, 5th Edition, p. 315. © 1999 by the American Pharmaceutical Association. Originally adapted from Morselli, P.L., 1983.

Table 150 Plasma Protein Binding and Drug Distribution in Neonates, Infants, and Children

	Neonates	Infants	Children
Physiological Alteration			
Plasma albumin	Reduced	Near normal	Near adult pattern
Fetal albumin	Present	Absent	Absent
Total proteins	Reduced	Decreased	Near adult pattern
Total globulins	Reduced	Decreased	Near adult pattern
Serum bilirubin	Increased	Normal	Normal adult pattern
Serum-free fatty acids	Increased	Normal	Normal adult pattern
Blood pH	7.1–7.3	7.4 (normal)	7.4 (normal)
Adipose tissue	Scarce (↑CNS)	Reduced	Generally reduced
Total body water	Increased	Increased	Near adult pattern
Extracellular water	Increased	Increased	Near adult pattern
Endogenous maternal substances (ligands)	Present	Absent	Absent
Possible Pharmacokinetic Consequences			
Free fraction	Increased	Increased	Slightly increased
Apparent volume of distribution			
Hydrophilic drugs	Increased	Increased	Slightly increased
Hydrophobic drugs	Reduced	Reduced	Slightly decreased
Tissue/plasma ratio	Increased	Increased	Slightly increased

Note: Direction of alteration given relative to expected normal adult pattern. Generally, neonate's age ≤ 1 mo, infant's age = 1–24 mo, child's age = 2–12 yr. As the age limits defining these developmental stages are somewhat arbitrary, some overlap in the functional capacity between these stages should be expected. Because physiological development is a dynamic process, it should be kept in mind that functional changes occur incrementally over time and do not abruptly change from one age group to another.

Source: From Ritschel, W.A. and Kerns, G.L. (1999), with permission, Table 24-2 "Plasma Protein Binding and Drug Distribution" of the *Handbook of Basic Pharmacokinetics,* 5th Edition, p. 309. © 1999 by the American Pharmaceutical Association. Originally adapted from Morselli, P.L., 1983.

Table 151 Developmental Patterns for the Ontogeny of Important Drug-Metabolizing Enzymes in Humans

Enzyme	Known Developmental Pattern
Phase I Enzymes	
CYP2D6	Low to absent in fetal liver but present at 1 wk of age. Poor activity (i.e., 20% of adult) by 1 mo. Adult competence by 3 to 5 yr.
CYP2C19, CYP2C9	Apparently absent in fetal liver. Low activity in first 2 to 4 wk of life with adult activity reached by approximately 6 mo. Activity may exceed adult levels during childhood and declines to adult levels after conclusion of puberty.
CYP1A2	Not present in appreciable levels in human fetal liver. Adult levels reached by approximately 4 mo and exceeded in children at 1 to 2 yr. Adult activity reached after puberty.
CYP3A7	Fetal form of CYP3A, which is functionally active (and inducible) during gestation. Virtually disappears by 1 to 4 wk of postnatal when CYP3A4 activity predominates but remains present in approximately 5% of individuals.
CYP3A4	Extremely low activity at birth reaching approximately 30 to 40% of adult activity by 1 mo and full adult activity by 6 mo. May exceed adult activity between 1 to 4 yr, decreasing to adult levels after puberty.
Phase II Enzymes	
NAT2	Some fetal activity by 16 wk gestation. Poor activity between birth and 2 mo of age. Adult phenotype distribution reached by 4 to 6 mo with adult activity reached by 1 to 3 yr.
TPMT	Fetal levels approximately 30% of adult values. In newborns, activity is approximately 50% higher than adults with phenotype distribution, which approximates adults. Exception is Korean children where adult activity is seen by 7 to 9 yr.
UGT	Ontogeny is isoform specific. In general, adult activity is reached by 6 to 24 mo.
ST	Ontogeny is isoform specific and appears more rapid than that for UGT. Activity for some isoforms may exceed adult levels during infancy and early childhood.

Note: Abbreviations include: CYP, cytochrome P450; NAT2, *N*-acetyltransferase-2; TPMT, thiopurine methyltransferase; UGT, glucuronosyltransferase and ST, sulfotransferase.

Source: From Ritschel, W.A. and Kerns, G.L. (1999), with permission, Table 24-4 "Developmental Patterns for the Ontogeny of Important Drug Metabolizing Enzymes in Man" of the *Handbook of Basic Pharmacokinetics,* 5th Edition, p. 3122. © 1999 by the American Pharmaceutical Association. Originally adapted from Leeder, J.S., and Kearns, G.L., 1997.

Table 152 Frequency of Selected Adverse Pregnancy Outcomes in Humans

Event	Frequency per 100	Unit
Spontaneous abortion, 8–28 wk	10–20	Pregnancies or women
Chromosomal anomalies in spontaneous abortions, 8–28 wk	30–40	Spontaneous abortions
Chromosomal anomalies from amniocentesis	2	Amniocentesis specimens
Stillbirths	2–4	Stillbirths and livebirths
Low birth weight <2500 g	7	Livebirths
Major malformations	2–3	Livebirths
Chromosomal anomalies	0.2	Livebirths
Severe mental retardation	0.4	Children to 15 yr of age

Source: Modified from National Foundation/March of Dimes, 1981, from Manson and Wise (1991), Casarett and Doull's *Toxicology: The Basic Science of Poisons,* 4th ed., 1991. With permission of McGraw-Hill.

Table 153 Probabilities of Spontaneous Abortion in Humans

Time from Ovulation	Probability of Fetal Death in Gestation Interval (%)
1–6 days	54.6
7–13 days	24.7
14–20 days	8.2
3–5 wk	7.6
6–9 wk	6.5
10–13 wk	4.4
14–17 wk	1.3
18–21 wk	0.8
22–25 wk	0.3
26–29 wk	0.3
30–33 wk	0.3
34–37 wk	0.3
38+ wk	0.7

Source: Modified from Kline and Stein, 1985, from McGuigan, *Hazardous Materials Toxicology: Clinical Principles of Environmental Health*, 1992. With permission.

Table 154 Risk Assessment Calculations

1. Human Equivalent Dose (HED)

$$\text{HED} = (\text{Animal dose}) \times \left(\frac{\text{Animal Body Weight}}{\text{Human Body Weight}} \right)^{1/3}$$

where: Dose = mg/kg Body weight = kg

2. ppm ↔ mg/m³ Conversion

$$\text{ppm} = \frac{(\text{mg}/\text{m}^3) \times (\text{R})}{(\text{MW})}$$

where ppm = exposure concentration as ppm; mg/m³ = exposure concentration as mg/m³; R = universal gas constant (24.5 at 25°C and 760 mmHg); MW = molecular weight.

3. Airborne Concentration to Equivalent Oral Dose

$$\text{EOD} = \frac{(\text{C}) \times (\text{EL}) \times (\text{MV}) \times (\text{AF}) \times (10^{-6})}{(\text{BW})}$$

where EOD = equivalent oral dose (mg/kg); C = concentration of substance in air (mg/m³); EL = exposure length (min); MV = minute volume, species specific (mL/min); AF = absorption factor (fraction of inhaled substance absorbed), default = 1; 10^{-6} = m³ ↔ mL conversion; BW = body weight (kg).

4. Oral Dose to Equivalent Airborne Concentration

$$\text{EAC} = \frac{(\text{OD}) \times (\text{BW})}{(\text{MV}) \times (\text{AF}) \times (\text{EL}) \times (10^{-6})}$$

where EAC = equivalent airborne concentration (mg/m³); OD = oral dose (mg/kg); BW = body weight (kg); MV = minute volume, species specific (mL/min); AF = absorption factor, fraction of inhaled substance absorbed; (default = 1) EL = exposure length (min); 10^{-6} = m³ ↔ mL conversion.

5. Lifetime Exposure (hr)

Lifetime = (hours exposed) × (days exposed) × (weeks exposed) × (years exposed)
exposure per day per week per year

Note: Methods 3 and 4 are crude approximations in that the time period will be set and protracted for the inhalation and may be either bolus for gavage studies or averaged over the entire day (feeding and drinking water) for oral. They also assume that there will be no chemical reactivity associated with oral administration, no portal entry effects and that the target organ effects will be the same regardless of the route of administration.

Table 154 Risk Assessment Calculations (Continued)

6. Exposure from Ingestion of Contaminated Water

$$\text{LADD} = \frac{(\text{C}) \times (\text{CR}) \times (\text{ED}) \times (\text{AF})}{(\text{BW}) \times (\text{TL})}$$

where LADD = lifetime average daily dose (mg/kg/day); C = concentration of contaminant in water (mg/L); CR = water consumption rate (L/day); ED = exposure duration (days); AF = absorption factor (fraction of ingested contaminant absorbed) default = 1 (dimensionless); BW = body weight (kg); TL = typical lifetime (days).

7. Exposure from Dermal Contact with Contaminated Water

$$\text{LADD} = \frac{(\text{C}) \times (\text{SA}) \times (\text{EL}) \times (\text{AR}) \times (\text{ED}) \times (\text{SV}) \times (10^{-9})}{(\text{BW}) \times (\text{TL})}$$

where LADD = lifetime average daily dose (mg/kg/day); C = concentration of contaminant in water (mg/liter); SA = surface area of exposed skin (cm^2); EL = exposure length (min/day); AR = absorption rate ($\mu g/cm^2/min$); SV = specific volume of water (1 L/kg); ED = exposure duration (days); 10^{-9} = kg ↔ μg conversion; BW = body weight (kg); TL = typical lifetime (days).

8. Exposure from Ingestion of Contaminated Soil

$$\text{LADD} = \frac{(\text{C}) \times (\text{CR}) \times (\text{ED}) \times (\text{AF}) \times (\text{FC}) \times (10^{-6})}{(\text{BW}) \times (\text{TL})}$$

where LADD = lifetime average daily dose (mg/kg/day); C = concentration of contaminant in soil (mg/kg); CR = soil consumption rate (mg/day); ED = exposure duration (days); AF = absorption factor (fraction of ingested contaminant absorbed) default = 1 (dimensionless); FC = fraction of total soil from contaminated source; 10^{-6} = kg ↔ mg conversion; BW = body weight (kg); TL = typical lifetime (days).

9. Exposure from Dermal Contact with Contaminated Soil

$$\text{LADD} = \frac{(\text{C}) \times (\text{SA}) \times (\text{BF}) \times (\text{FC}) \times (\text{SDF}) \times (\text{ED}) \times (10^{-6})}{(\text{BW}) \times (\text{TL})}$$

where LADD = lifetime average daily dose (mg/kg/day); C = concentration of contaminant in soil (mg/kg); SA = surface area of exposed skin (cm^2); BF = bioavailability factor (percent absorbed/day); FC = fraction of total soil from contaminated source; SDF = soil deposition factor; amount deposited per unit area of skin ($mg/cm^2/day$); ED = exposure duration (days); BW = body weight (kg); TL = typical lifetime (days).

Table 154 Risk Assessment Calculations (Continued)

10. Exposure from Inhalation of Contaminated Particles in Air

$$\text{LADD} = \frac{(\text{C}) \times (\text{PC}) \times (\text{IR}) \times (\text{RF}) \times (\text{EL}) \times (\text{AF}) \times (\text{ED}) \times (10^{-6})}{(\text{BW}) \times (\text{TL})}$$

where LADD = lifetime average daily dose (mg/kg/day); C = concentration of contaminant on particulate (mg/kg); PC = particulate concentration in air (mg/m^3); IR = inhalation rate (m^3/hr); RF = respirable fraction of particulates; EL = exposure length (hr/day); AF = absorption factor (fraction of inhaled contaminant absorbed) default = 1; ED = exposure duration (days); 10^{-6} = kg ↔ mg conversion; BW = body weight (kg); TL = typical lifetime (days).

11. Exposure from Inhalation of Vapors

$$\text{LADD} = \frac{(\text{C}) \times (\text{IR}) \times (\text{EL}) \times (\text{AF}) \times (\text{ED})}{(\text{BW}) \times (\text{TL})}$$

where LADD = lifetime average daily dose (mg/kg/day); C = concentration of contaminant in air (mg/m^3); IR = inhalation rate (m^3/hr); EL = exposure length (hr/day); AF = absorption factor (fraction of inhaled contaminant absorbed) default = 1; ED = exposure duration (days); BW = body weight (kg); TL = typical lifetime (days).

12. Calculation of an RfD

$$\text{RfD} = \frac{(\text{NOAEL})}{(\text{UFs}) \times (\text{MF})}$$

where RfD = reference dose (mg/kg/day); UFs = uncertainty factors — generally multiples of 10 (although 3 and 1 are occasionally used, depending on the strength and quality of the data). The following uncertainty factors are usually used:

UF 10 Accounts for variation in the general population. Intended to protect sensitive subpopulations (e.g., elderly, children).

10 Used when extrapolating from animals to humans. Intended to account for interspecies variability between humans and animals.

10 Used when a NOAEL is derived from a subchronic rather than a chronic study in calculating a chronic RfD.

10 Applied when a LOAEL is used instead of an NOAEL. Intended to account for the uncertainty in extrapolating from LOAELs to NOAELs.

MF = modifying factor; multiple of 1 to 10; intended to reflect a professional qualitative assessment of the uncertainty in the critical study from which the NOAEL is derived as well as the overall quality of the database. Accounts for the uncertainty not addressed by the UFs.

Table 154 Risk Assessment Calculations (Continued)

13. Estimating LD_{50} of a Mixture

$$\frac{1}{\text{Predicted } LD_{50}} = \frac{Pa}{LD_{50} \text{ of Component a}} + \frac{Pb}{LD_{50} \text{ of Component b}} + \cdots \frac{Pn}{LD_{50} \text{ of Component n}}$$

where P = fraction of components in the mixture.

14. Time-Weighted Average (TWA) for an 8-hr Workday

$$TWA = \frac{C_1T_1 + C_2T_2 + \cdots C_nT_n}{8}$$

where C_n = concentration measured during a period of time (<8 hr); T_n = duration of the period of exposure in hours at concentration C_n ($\Sigma T = 8$).

15. Risk for Noncarcinogens (Hazard Index)

$$\text{Risk} = \frac{MDD}{ADI}$$

If: Risk > 1, a potential risk exists that may be significant.
Risk < 1, risk is insignificant.
where MDD = maximum daily dose and ADI = acceptable daily intake.

16. Lifetime Risk for Carcinogens

Risk = (LADD) × (SF)

If risks = 10^{-6}, risk is insignificant; 10^{-6}–10^{-4}, possible risk; 10^{-4}, risk may be significant.

where LADD = lifetime average daily dose (mg/kg/day); SF = slope factor or cancer potency factor $(mg/kg/day)^{-1}$ (chemical and route specific).

17. Total Risk from a Single Contaminant via Multiple Exposure Pathways

Total = Σ Risks from all exposure pathways

Example:
Total risk (from a contaminant in water) = (Risk from ingestion) + (Risk from showering) + (Risk from swimming).

Table 154 Risk Assessment Calculations (Continued)

18.	**Total Risk from Multiple Contaminants via a Single Exposure Pathway**
	Total risk = Σ Risks from all contaminants in the media
	Example:
	Total risk from contaminants, A, B, and C in water = Total risk from contaminant A + Total risk from contaminant B + Total risk from contaminant C

Note: For evaluation 17 and 18, total risk < 1 is insignificant; total risk > 1 may be significant. Both of these methods are extremely conservative and can greatly overestimate risk.

Source: From U.S. EPA (1989d); Paustenbach, D.J. and Leung, H.-W. (1993); Environ Corporation (1990); U.S. EPA (1989c); and Lynch, J.R. (1979).

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Section 12
Human Clinical Toxicology

Table 155 Some Common Clinical Presentations and Differential Diagnoses in Overdose

Presentation	Toxicological Causes	Other Medical Examples
Asymptomatic with history	Almost any drug	Not applicable
Gastrointestinal complaints	Salicylate, theophylline, iron, colchicine quinidine, almost any drug	Food poisoning, allergy, ulcer, pancreatitis, obstruction, gallstones, genitourinary
Coma	Narcotics, sedatives, antipsychotics, alcohol, tricyclics, long-lasting benzodiazepines	Infectious and metabolic encephalopathy, trauma, anoxia, cerebrovascular accident, brain death
Seizures	Theophylline, tricyclics, isoniazid, stimulants, camphor, carbon monoxide, hypoglycemic agents, alcohol withdrawal	Idiopathic, arteriovenous malformation, tumor, trauma, hypoxia, febrile, inborn errors
Psychosis and altered mental status	Anticholinergics, stimulants, withdrawal	Psychiatric, infection, metabolic/inborn errors
Acidosis	Salicylate, ethanol, methanol, ethylene glycol, cyanide drugs causing seizures	Shock, diabetes, uremia, lactic acidosis
Respiratory depression (usually with coma)	Narcotics, sedatives, benzodiazepines	Cerebrovascular accident, metabolic coma, tumor
Pulmonary edema	Salicylates, narcotics, iron, paraquat (initially)	Heart failure, disseminated intravascular coagulation
Arrhythmias	Tricylics, quinidine, anticholinergics, β-blockers, digoxin, lithium, antipsychotics, organophosphates	Atherosclerotic heart disease

Table 155 Some Common Clinical Presentations and Differential Diagnoses in Overdose (Continued)

Hypotension	Narcotics, sedatives, tricyclics, antipsychotics, β-blockers, theophylline, iron	Heart failure, shock, hypovolemia, disseminated intravascular coagulation
Hypertension	Cocaine, amphetamines, cyanide, nicotine, clonidine (initially)	Essential, pheochromocytoma, carcinoid, hyperrenin states, renal failure
Ataxia	Antiepileptics, barbiturates, alcohol, lithium, organomercury	Cerebellar degeneration

Source: From Osterloh, 1990. Reprinted with permission.

Table 156 Toxicological Syndromes by Class of Drug[a]

Narcotics

Heroin, morphine, codeine, oxycodone, hydromorphone, hydrocodenone, propoxyphene, pentazocine, meperidine, diphenoxylate, fentanyl and derivatives, buprenorphine, methadone

- CNS depression (somnolent → coma)
- Slowed respiratory rate
- T° normal or low
- If BP decreases, pulse does not increase
- Pinpoint pupils
- DTR usually decreases

Alcohols—Barbiturates

Ethanol, methanol, isopropanol, ethylene glycol, amo-, pento-, seco-, buta-, phenobarbital, butalbital, glutethimide, methaqualone, ethchlorvynol, phenytoin

- CNS depression (stuporous → coma)
- Ataxia
- T° usually decreases
- DTR decreases
- Metabolic acidosis with alcohols and ethylene glycol except isopropanol
- If BP decreases, pulse may increase

Anticholinergics

Atropine, scopolamine, antihistamines, phenothiazines, tricyclics, quinidine, amantadine, jimsonweed, mushrooms

- Delirious
- Increased pulse, increased T°
- Skin flushed, warm, pink
- Dry (no sweating)
- Decreased bowel sounds
- Urinary retention
- Blurred vision
- Arrhythmias, prolonged QT

Stimulants

Cocaine, amphetamines and derivatives (e.g., ice, MDA, MDMA, DOB), phencyclidine, lysergic acid, psilocybin

- Acute psychosis (nonreality)
- Increased pulse, increased BP, increased T°
- Increased respiratory rate
- Agitation
- Increased muscle tone/activity
- Dilated pupils
- Sweating
- Seizures

Antidepressants

- Anticholinergic syndrome
- Hypotension
- Coma
- Seizures
- Sinus tachycardia (early)
- Supraventricular tachycardia (early)
- Widened QRS, QT
- Ventricular arrhythmias

Benzodiazepines

- CNS depression
- Respiratory depression
- BP, pulse, T° not greatly affected
- DTR intact

Table 156 Toxicological Syndromes by Class of Drug[a] (Continued)

Phenothiazines	
Decreased BP, decreased T°	Anticholinergic syndrome (see above)
Rigidity, dystonias, torticollis	Seizures
Pinpoint pupils	
Salicylates	
Abdominal pain	Shock
Respiratory alkalosis (early)	Diaphoresis
Metabolic acidosis	Hypoglycemia
Theophylline	
Tachycardia	Hypotension
Hypokalemia	Seizures
Iron	
Abdominal pain	Acidosis
GI bleeding	Renal failure
Hypotension	Cardiovascular collapse
Hypovolemia	
Lithium	
Tremor	Hyperreflexia
Chorea	Rigidity
Abdominal pain	Seizures
Isoniazid	
Metabolic acidosis	Hepatitis
Seizures	
Oral Hypoglycemics	
Hypoglycemia	Diaphoresis
Coma	
Acetaminophen	
Liver necrosis	
β-blockers	
Bradycardia	Hypotension with slowed cardiac conduction
Hyperglycemia	

[a] Abbreviations: CNS = central nervous system; BP = blood pressure; DTR = deep tendon reflexes; GI = gastrointestinal; QRS, QT = electrocardiogram parameters; MDA = methylenedioxy amphetamine; MDMA = 3,4-methylenedioxy methamphetamine; DOB = 4-bromo-2, 5-dimethoxyamphetamine.

Source: From Osterloh, 1990. Reprinted with permission.

Table 157 Common Drugs Included on Most Toxicology Screens

Alcohols—Ethanol, methanol, isopropanol, acetone
Barbiturates/sedatives—Amobarbital, secobarbital, pentobarbital, butalbital, butabarbital, phenobarbital, glutethimide, ethchlorvynol, methaqualone
Antiepileptics—Phenytoin, carbamazepine, primadone, phenobarbital
Benzodiazepines—Chlordiazepoxide, diazepam, alprazolam, temazepam
Antihistamines—Diphenhydramine, chlorpheniramine, brompheniramine, tripelennamine, trihexiphenidyl, doxylamine, pyrilamine
Antidepressants—Amitriptyline, nortriptyline, doxepin, imipramine, desipramine, trazedone, amoxapine, maprotiline
Antipsychotics—Trifluoperazine, perphenazine, prochlorperazine, chlorpromazine
Stimulants—Amphetamine, methamphetamine, phenylpropanolamine, ephedrine, MDA, MDMA (other phenylethylamines), cocaine, phencyclicline
Narcotics analgesics—Heroin, morphine, codeine, oxycodone, hydrocodone, hydromorphone, meperidine, pentazocine, propoxyphene, methadone
Other analgesics—Salicylates, acetaminophen
Cardiovascular drugs—Lidocaine, propranolol, metoprolol, quinidine, procainamide, verapamil
Others—Theophylline, caffeine, nicotine, oral hypoglycemics, strychnine

Source: From Osterloh, 1990. Reprinted with permission.

Reference

Osterloh, J. (1990), Utility and reliability of emergency toxicologic testing, *Emerg. Med. Clin. N. Am.* 8, 693.

Section 13
Industrial Chemical Toxicology

Table 158 Combined Tabulation of Toxicity Classes

		Various Routes of Administration			
Toxicity Rating	**Commonly Used Term**	**LD_{50} Single Oral Dose Rats**	**Inhalation 4-hr Vapor Exposure Mortality 2/6–4/6 Rats**	**LD_{50} Skin Rabbits**	**Probable Lethal Dose for Human**
1	Extremely toxic	≤1 mg/kg	<10 ppm	≤5 mg/kg	A taste, 1 grain
2	Highly toxic	1–50 mg	10–100 ppm	5–43 mg/kg	1 teaspoon, 4 cc
3	Moderately toxic	50–500 mg	100–1000 ppm	44–340 mg/kg	1 ounce, 30 gm
4	Slightly toxic	0.5–5 g	1000–10,000 ppm	0.35–2.81 g/kg	1 cup, 250 gm
5	Practically nontoxic	5–15 g	10,000–100,000 ppm	2.82–22.59 g/kg	1 quart, 1000 gm
6	Relatively harmless	>15 g	>100,000 ppm	>22.6 g/kg	>1 quart

Source: Adapted from Hodge, H.C. and Sterner, J.H. (1949). With permission.

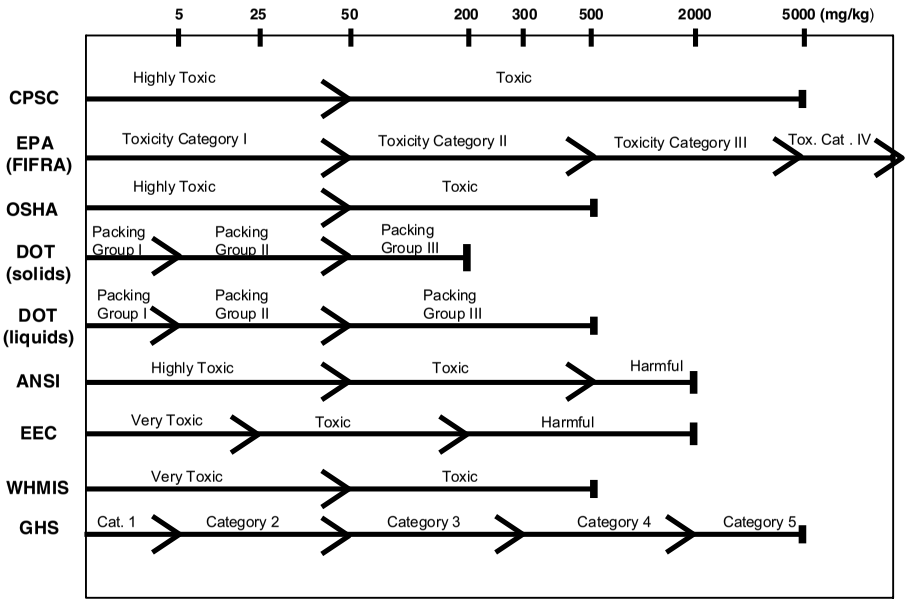

Figure 15 Toxicity classifications based on rat acute oral LD_{50}. CPSC = Consumer Product Safety Commission; EPA = U.S. Environmental Protection Agency (FIFRA = Federal Insecticide, Fungicide and Rodenticide Act); OSHA = U.S. Occupational Safety and Health Administration; DOT = U.S. Department of Transportation; ANSI = American National Standards Institute; EEC = European Economic Community; WHMIS = Workplace Hazardous Materials Information System (Canada); GHS = Global Harmonized System. Use the following example of the DOT (solids) classification to help interpret the values of this figure: Packing Group I (≤5 mg/kg); Packing Group II (>5 mg/kg to ≤50 mg/kg); Packing Group III (>50 mg/kg to ≤200 mg/kg). (Adapted from Schurger, M.G. and McConnell, F. (1989), Eastman Chemicals, Kingsport, TN).

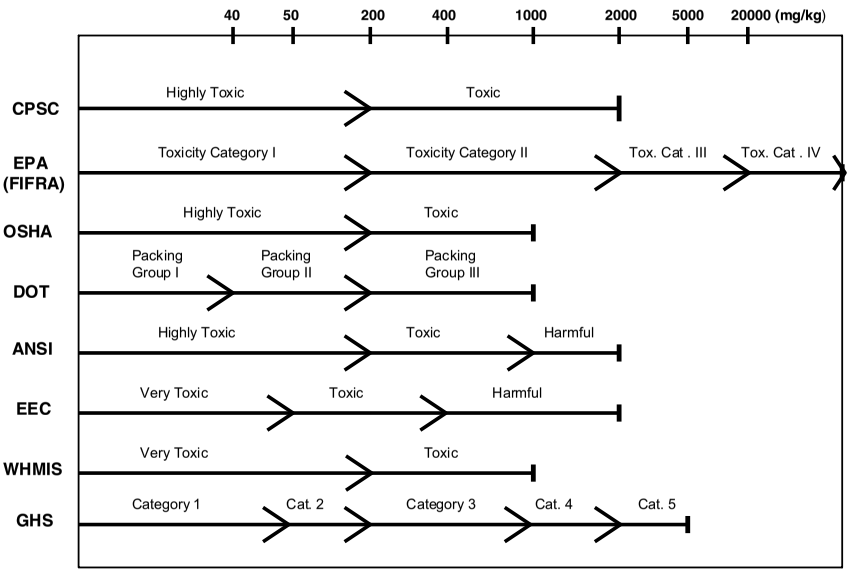

Figure 16 Toxicity classifications based on rabbit or rat acute dermal LD_{50}. CPSC = Consumer Product Safety Commission; EPA = U.S. Environmental Protection Agency (FIFRA = Federal Insecticide, Fungicide and Rodenticide Act); OSHA = U.S. Occupational Safety and Health Administration; DOT = U.S. Department of Transportation; ANSI = American National Standards Institute; EEC = European Economic Community; WHMIS = Workplace Hazardous Materials Information System (Canada); GHS = Global Harmonized System. Refer to the legend of Figure 15 to help interpret the values of this figure. (Adapted from Schurger, M.G. and McConnell, F. (1989), Eastman Chemicals, Kingsport, TN).

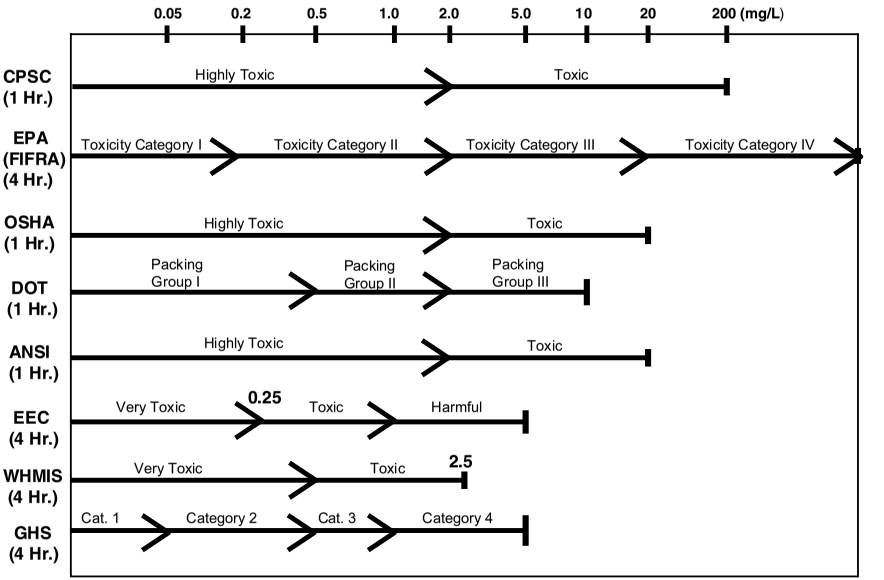

Figure 17 Toxicity classifications based on rat acute inhalation LC_{50}. CPSC = Consumer Product Safety Commission; EPA = U.S. Environmental Protection Agency (FIFRA = Federal Insecticide, Fungicide and Rodenticide Act); OSHA = U.S. Occupational Safety and Health Administration; DOT = U.S. Department of Transportation; ANSI = American National Standards Institute; EEC = European Economic Community; WHMIS = Workplace Hazardous Materials Information System (Canada); GHS = Global Harmonized System. Refer to the legend of Figure 15 to help interpret the values of this figure. (Adapted from Schurger, M.G. and McConnell, F. (1989), Eastman Chemicals, Kingsport, TN).

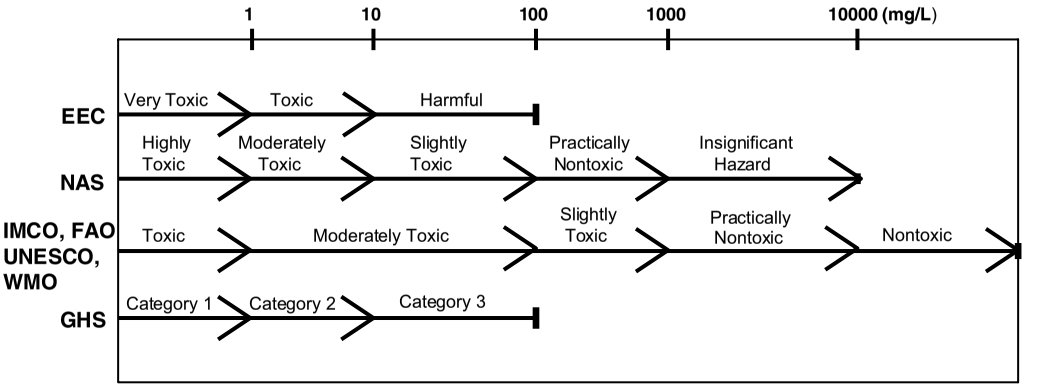

Figure 18 Toxicity classifications based on fish acute LC_{50}. EEC = European Economic Community; NAS = U.S. National Academy of Sciences; IMCO = Inter-government Maritime Consultive Organization; FAO = Food and Agriculture Organization; UNESCO = United Nations Educational, Scientific and Cultural Organization; WMO = World Meteorological Organization; GHS = Global Harmonized System. Refer to the legend of Figure 15 to help interpret the values of this figure. (Adapted from Schurger, M.G. and McConnell, F. (1989), Eastman Chemicals, Kingsport, TN).

Table 159 EPA, IARC, and EEC Classification Schemes for Carcinogens

Agency	Category	Classification	Description
United States Environmental Protection Agency (EPA) (1986)	A	Carcinogenic to humans	Sufficient evidence from epidemiology studies to support a causal association
	B1	Probably carcinogenic to humans	Limited evidence in humans from epidemiology studies
	B2	Probably carcinogenic to humans	Sufficient evidence from animal studies but inadequate or no data in humans
	C	Possibly carcinogenic to humans	Limited or equivocal evidence from animal studies but inadequate or no data in humans
	D	Not classifiable as to human carcinogenicity	Inadequate or no data from animals and inadequate or no data in humans
	E	Evidence of noncarcinogenicity for humans	No evidence of carcinogenicity in at least two animal species and no evidence in humans
United States Environmental Protection Agency (EPA) (2005)		Carcinogenic to humans	This descriptor indicates strong evidence of human carcinogenicity based on epidemiology and experimental information including exposure and mode-of-action associations.
		Likely to be carcinogenic to humans	This descriptor is appropriate when the weight of evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the preceding descriptor, *Carcinogenic to humans*

Table 159 EPA, IARC, and EEC Classification Schemes for Carcinogens (Continued)

Agency	Category	Classification	Description
		Suggestive evidence of carcinogenic potential	This descriptor is appropriate when the available information is suggestive of carcinogenicity and a concern for potential carcinogenic effects in humans is raised, but the information is judged not sufficient for a stronger conclusion.
		Inadequate information to assess carcinogenic potential	This descriptor is appropriate when available information is judged inadequate for applying one of the other descriptors.
		Not likely to be carcinogenic to humans	This descriptor is appropriate when the available information is considered robust for deciding that there is no basis for human hazard concern.
International Agency for Research on Cancer (IARC)	1	Carcinogenic to humans	Sufficient epidemiological evidence for carcinogenicity in humans or sufficient evidence of carcinogenicity from animals studies with strong evidence for a carcinogenic mechanism relevant to humans.
	2A	Probably carcinogenic to humans	Sufficient evidence from animal studies and limited evidence in humans.
	2B	Possibly carcinogenic to humans	Sufficient evidence from animal studies but inadequate evidence in humans or limited evidence in humans and less than sufficient evidence in animals.
	3	Not classifiable as to human carcinogenicity	Inadequate data to classify
	4	Not carcinogenic	Sufficient evidence of noncarcinogenicity in humans and/or animals.

Table 159 EPA, IARC, and EEC Classification Schemes for Carcinogens (Continued)

Agency	Category	Classification	Description
European Economic Community (EEC)	1	Known to be carcinogenic to humans	Sufficient evidence to establish a causal association between human exposure and cancer.
	2	Regarded as being carcinogenic to humans	Sufficient evidence to provide a strong presumption that human exposure may result in cancer. Based on long-term animal studies and/or other relevant information.
	3	Causes concern due to possible carcinogenic effects	Inadequate information to make a satisfactory assessment. Some evidence from animal studies but insufficient to place in category 2.

Source: U.S. EPA (2007), Ecobichon (1992), European Economic Community (1993).

Table 160 EPA Categories of Toxicological Concerns

Category	Concern
Acid chlorides	**Environmental toxicity[a].** Concern is greater if the log octanol–water partition coefficient (log K_{ow}) < 8 or if molecular weight (mol. wt) < 1000.
Acrylamides	**Human health and environmental toxicity.** The acrylamides of greatest concern are those with a labile substituent, e.g., methylol acrylamides, that may release acrylamide *per se* under metabolic conditions. Members of this class are considered potential carcinogens, heritable mutagens, developmental and reproductive toxicants, and are potential neurotoxins. Structures with an acrylamide equivalent wt. ≥ 5000 are presumed *not* to pose a hazard under *any* condition.
Acrylates and methacrylates	**Environmental toxicity.** Particularly if the log of the octanol–water partition coefficient (Log P) < 5. Concerns typically confined to species with mol. wt. < 1000.
	Human health. Some individual compounds are irritants and sensitizers.
Aldehydes	**Environmental toxicity.** Generally, mol. wt. < 1000.
Aliphatic amines	**Environmental toxicity.** Generally, mol. wt. < 1000.
Alkoxy silanes	**Human health and environmental toxicity.** There is a concern for lung toxicity, if such substances are inhaled.
Aluminum compounds	**Environmental toxicity.** Soluble forms of aluminum especially with solubility > 1 ppb.
Anhydrides, carboxylic acid	**Human health.** Potential for pulmonary sensitization; also developmental or reproductive toxicity. Generally, if mol. wt. < 500.
Anilines	**Environmental toxicity.** Generally, if log K_{ow} < 7.38 and mol. wt. is < 1000.
Azides	**Environmental toxicity.** Generally, mol. wt. < 1000.
Benzotriazoles	**Environmental toxicity.** Generally, mol. wt. < 1000 is expected to manifest toxicity.
Benzotriazole-hindered phenols	**Human health and environmental toxicity.** Liver, kidney, and hematological and immune system effects.
Boron compounds	**Human health and environmental toxicity.** Male and female reproductive toxicity, hematotoxicity, and neurotoxicity.
Cobalt and compounds	**Environmental toxicity.** Generally, if log K_{ow} < 8.0, mol. wt. Is < 1000 and water solubility > 1 ppb.

Table 160 EPA Categories of Toxicological Concerns (Continued)

Category	Concern
Dianilines	**Human health and environmental toxicity.** Potential carcinogens and mutagens. Also, potential retinotoxic agents, reproductive and systemic toxicants.
Diazoniums (aromatic only)	**Environmental toxicity.** Those with mol. wt. < 1000 are of concern.
Dichlorobenzidine-based Pigments	**Human health and environmental toxicity.** Concern for mutagenicity/carcinogenicity.
Diisocyanates (two or more isocynate groups)	**Human health.** Potential dermal and pulmonary sensitization and other lung effects. Some may be carcinogenic. Structures with an isocyanate equivalent weight of >5000 are presumed not to pose a hazard under any conditions.
Dithiocarbamates	**Environmental toxicity.** Generally, mol. wt. < 1000.
Dyes: Acid and amphoteric	**Environmental toxicity.** Particularly if the substance is water-soluble and mol. wt. is around 1000 or less.
Dyes: Cationic	**Environmental toxicity.** Any dye bearing one or more net positive charges. No mol. wt. threshold.
Dyes: Aminobenxothiazole AZO	**Human health and environmental toxicity.** There are mutagenicity/carcinogenicity concerns. There is also potential for liver, thyroid, and neurotoxicity. Ecotoxicity concerns generally relate to chronic toxicity.
Epoxides	**Human health and environmental toxicity.** Concerns for cancer and reproductive effects. Structures with epoxy equivalent weights ≥ 1000 are presumed not to pose a hazard under any conditions.
Esters	**Environmental toxicity.** Compounds with molecular weights > 1000 are not of concern.
Ethylene glycol ethers	**Human health.** Irritation of skin, eyes, and mucous membranes; hemolysis, bone-marrow damage, and leukopenia of both lymphocytes and granulocytes; direct and indirect kidney damage; liver damage, immunotoxicity, and central nervous system depression. Also, developmental and reproductive toxicants.
Hindered amines	**Human health.** May be toxic to the immune system, liver, blood, the male reproductive system, and the gastrointestinal tract.
Hydrazines and related compounds	**Human health and environmental toxicity.** Concerns for carcinogenicity and chronic effects to liver, kidney, and blood.

Table 160 EPA Categories of Toxicological Concerns (Continued)

Category	Concern
Imides	**Environmental toxicity.** Compounds with mol. wt. < 1000 are of greater concern.
Lanthanides or rare earth metals	**Environmental toxicity.** Mol. wt < 1000.
ß-Napthylamines (monosulfonated)	**Human health.** Potential mutagens and carcinogens. Concern is restricted to those compounds where the sulfonate or sulfatoethlysulfone group is on the ring *distal* to the ß-amino group.
Neutral organics	**Environmental toxicity.** The molecular weights of neutral organics of concern are generally < 1000 and the octanol–water partition coefficients (log P) are < 8.
Nickel compounds	**Human health and environmental toxicity.** Concern for genotoxicity/carcinogenicity, fetotoxicity, and dermatotoxicity.
Organotins	**Human health and environmental toxicity.** Eye and skin irritants, systemic effects (primarily neurotoxicity), and immunotoxicity. Some organotins are probable human carcinogens.
Peroxides	**Human health and environmental toxicity.** Compounds assessed on a case-by-case basis.
Persistent, bioaccumulative, and toxic (PBT) chemicals (e.g., DDT)	**Human health, environmental toxicity, and fate.** PBT chemical substances are chemicals that partition to water, sediment, or soil and are not removed at rates adequate to prevent their accumulation in aquatic or terrestrial species, with the potential to pose a risk via food-chain toxicity. Concern for chemicals with persistence (transformation half-life) > 2 months, bioaccumulation > 1000 (log Kow = 4.2) and mol. wt < 1000.
Phenolphthaleins	**Human health.** Concern for carcinogenicity.
Phenols	**Environmental toxicity.** Compounds of greater concern have mol. wt. < 1000.
Phosphates, inorganic	**Environmental toxicity.** High concern for eutrophication.
Phosphinate esters	**Environmental toxicity.** Generally, if log K_{ow} < 8.0, mol. wt. < 1000.
Polyanionic polymers (and monomers)	**Environmental toxicity.** Compounds must be water soluble or water self-dispersing to be in this category.
Polycationic polymers	**Environmental toxicity.** The polymers must be water soluble or water dispersible and the molecular weights are generally > 300.

Table 160 EPA Categories of Toxicological Concerns (Continued)

Category	Concern
Polynitroaromatics	**Environmental toxicity.** Concern is for compounds with mol. wt. < 1000.
Respirable, poorly soluble particulates	**Human health.** Particles < 10 μm. Effects on the lung ranging from inflammation to fibrosis and, potentially, cancer.
Rosin	**Environmental toxicity.** Category includes rosin, abietic acid, abientinic acid and their salts, and polymeric forms with mol. wt < 1000.
Stilbene, derivatives of 4,4-bis(triazin-2-ylamino)-	**Human health.** Developmental/reproductive toxicity concerns for some stilbenes on a case-by-case basis.
Thiols	**Environmental toxicity.** Mol. wt < 1000.
Triarylmethane pigments/dyes with nonsoluble groups	**Human health and environmental toxicity.** Developmental/reproductive toxicity and carcinogenicity concerns.
Substituted triazines	**Environmental toxicity.** If log K_{ow} < 8.0, mol. wt. < 1000.
Surfactants: anionic	**Environmental toxicity.** No mol. wt. boundary.
Surfactants: Cationic (quaternary ammonium)	**Environmental toxicity.** Little ecotoxicity is expected when the carbon chain length exceeds 22 carbons.
Surfactants: Nonionic	**Environmental toxicity.** Acute aquatic toxicity increases with the hydrophobic chain length. Aquatic toxicity is decreased with increasing number of ethoxylate groups.
Vinyl esters	**Human health and environmental toxicity.** Concern for carcinogenicity, neurotoxicity, and reproductive toxicity.
Vinyl sulfones	**Human health and environmental toxicity.** Concern for mutagenicity and carcinogenicity.
Soluble complexes of zinc	**Environmental toxicity.**
Zirconium compounds	**Environmental toxicity.** Concern for mol. wt < 1000.

[a] Environmental toxicity usually indicates toxicity to algae, Daphnids, and/or fish although concerns for other environmental effects could exist.

Source: U.S. Environmental Protection Agency (2002).

Table 161 Criteria Defining "High-Exposure" Chemicals

- Production greater than 100,000 kg
- More than 1000 workers exposed
- More than 100 workers exposed by inhalation to greater than 10 mg/kg/day
- More than 100 workers exposed by inhalation to 1–10 mg/day for more than 100 days/yr
- More than 250 workers exposed by routine dermal contact for more than 100 days/yr
- Presence of the chemical in any consumer product in which the physical state of the chemical in the product and the manner of use would make exposure likely
- More than 70 mg/yr of exposure via surface water
- More than 70 mg/yr of exposure via air
- More than 70 mg/yr of exposure via groundwater
- More than 10,000 kg/yr release to environmental media
- More than 1000 kg/yr total release to surface water after calculated estimates of treatment

Source: From U.S. EPA (1988).

Table 162 European Notification of a New Substance: Information and Test Data Required

Annual Total	Cumulative Total	Data Requirements (Refer to Table 163)
<10 kg		Exempt
10–100 kg		Annex VII C
100–1000 kg	500 kg	Annex VII B
>1000 kg (1 tonne)	5000 kg	Annex VII A
>10 tonnes	50 tonnes	Level 1 (may be required[a])
>100 tonnes	500 tonnes	Level 1
>1000 tonnes	5000 tonnes	Level 2

[a] Testing at 10/50 tonnage thresholds will depend on the nature of the chemical, its uses, and the results of existing tests.

Source: From Brooker, P.C. (1993). With permission.

Table 163 Data Requirements for European Notification

Annex VII C

Supply at 10–100 kg/yr

Flash point/flammability
Acute toxicity (oral or inhalation)

Annex VII B

(Supply at 100–1000 kg/yr or 500 kg cumulative)

Melting point/boiling point
Water solubility
Partition coefficient (n-octanol/water)
Flashpoint/flammability
Vapor pressure (may be required)

Acute toxicity (oral or inhalation)
Skin irritation
Eye irritation
Skin sensitization
Ames test

Biodegradation
Daphnia acute toxicity test (may be required)

Annex VII A

"The Base Set"

(Supply at >1000 kg/yr or 5000 kg cumulative)

Melting point/boiling point
Relative density
Vapor pressure
Surface tension
Water solubility
Partition coefficient (n-octanol/water)

Acute toxicity (two routes)
Skin irritation
Eye irritation
Skin sensitization
28-Day repeat dose toxicity

Acute toxicity for fish
Acute toxicity for *Daphnia*
Algal growth inhibition
Bacterial inhibition

Flash point flammability
Explosive properties
Self-ignition temperature
Oxidizing properties
Granulometry

Ames test
In vitro cytogenetics
Reproductive toxicity screen
Toxicokinetic assessment (derived from base set data)

Biodegradation
Hydrolysis as a function of pH
Soil adsorption/desorption screen

Table 163 Data Requirements for European Notification (Continued)

Level 1 Studies[a] Annex VIII

(Supply at >10[b] or 100 tonnes/yr or 50[b] tonnes cumulative)

Analytical method development	21-Day Daphnia toxicity
Physicochemical properties of thermal decomposition products	Further fish toxicity studies
	Bioaccumulation study
	Test on higher plants
Fertility study (one generation)	Earthworm toxicity
Teratology study	Inherent biodegradation
Subchronic/chronic toxicity study	Further adsorption/desorption
Additional mutagenicity studies	
Basic toxicokinetics	

Level 2 Studies[c] Annex VIII

(Supply at >1000 tonnes/yr or 5000 tonnes cumulative)

Chronic toxicity study	Additional test for accumulation, degradation, and mobility
Carcinogenicity study	
Fertility study (two-generation)	Additional test for adsorption/desorption
Developmental toxicity (peri- and postnatal)	Further fish toxicity studies
Teratology study (different species from level 1)	Bird toxicity studies
	Toxicity studies with other organisms
Biotransformation	
Pharmacokinetics	
Additional test to investigate organ or system toxicity	

[a] Studies required at level 1 are on a negotiated basis. Negotiations begin once a trigger tonnage has been exceeded. Studies chosen will be based on (1) the quantity supplied, (2) the results of the Base-Set Tests, and (3) the degree of exposure to humans and the environment.

[b] Testing at the 10/50 tonnage thresholds will depend on the nature of the chemical, its uses, and the results of earlier tests.

[c] Studies required at level 2 are on a negotiated basis. Negotiations begin once a trigger tonnage has been exceeded. Studies chosen will be based on: (1) the quantity supplied, (2) the results of earlier tests, and (3) the degree of exposure to humans and the environment.

Source: From Brooker, P.C. (1993). With permission.

Table 164 Selected OECD Guidelines for Testing of Chemicals

Mammalian

#401	Acute oral toxicity, LD50
#402	Acute dermal toxicity
#403	Acute inhalation toxicity
#404	Acute dermal irritation/corrosion
#405	Acute eye irritation
#406	Contact sensitization
#407	Repeated-dose 28-day oral toxicity (rodent)
#408	Repeated-dose 90-day oral toxicity (rodent)
#409	Repeated-dose 90-day oral toxicity (non-rodent)
#410	Repeated-dose 28-day dermal toxicity
#411	Repeated-dose 90-day dermal toxicity
#412	Repeated-dose 28-day inhalation toxicity
#413	Repeated-dose 90-day inhalation toxicity
#414	Developmental toxicity study
#415	One-generation reproduction
#416	Two-generation reproduction
#417	Metabolism and pharmacokinetics
#418	Acute exposure delayed neurotoxicity of organophosphorus substances
#419	Repeated exposure delayed neurotoxicity of organophosphorus substances
#420	Acute oral toxicity, fixed dose procedure
#421	Reproductive/developmental toxicity screen
#422	Combined repeated-dose 28-day oral toxicity/developmental toxicity screen
#423	Acute oral toxicity, acute toxic class
#424	Neurotoxicity screening battery
#425	Acute oral toxicity, up and down method
#451	Carcinogenicity
#452	Chronic toxicity
#453	Combined chronic toxicity/carcinogenicity

Genetox

#471	Reverse mutation assay/*Salmonella* (Ames test)
#472	Reverse mutation assay/*E. coli*
#473	*In vitro* mammalian chromosome aberration test
#474	Micronucleus test
#475	*In vivo* bone marrow mammalian chromosome aberration test
#476	*In vitro* mammalian cell gene mutation test (mouse lymphoma)
#477	Sex-linked recessive lethal test (Drosophila)
#478	Rodent dominant lethal test (mouse)
#479	*In vitro* sister chromatid exchange (SCE) assay

Table 164 Selected OECD Guidelines for Testing of Chemicals (Continued)

#480	Gene mutation assay/*Saccharomyces*
#481	Mitotic recombination assay/*Saccharomyces*
#482	*In vivo* unscheduled DNA synthesis (UDS)
#483	Mammalian spermatogonial chromosome aberration assay
#484	Mouse spot test
#485	Mouse heritable translocation assay
#486	Mitotic recombination assay/*Saccharomyces*
Ecotox/Aquatic	
#106	Absorption/desorption
#201	Algal growth inhibition
#202	Acute toxicology/*Daphnia*
#203	Acute toxicity/fish
#204	14-Day prolonged toxicity/fish
#205	Avian dietary toxicity
#206	Avian reproduction
#207	Acute toxicity/earthworm
#208	Terrestrial plant growth test
#209	Activated sludge respiration inhibition
#210	Fish early-life-stage toxicity
#211	21-Day *Daphnia* reproduction
#301	Ready biodegradability
#302	Inherent biodegradability
#305	Bioaccumulation/fish

Table 165 Risk (R) Phrases Used in the European Community (EU)

R1	Explosive when dry
R2	Risk of explosion by shock, friction, fire, or other sources of ignition
R3	Extreme risk of explosion by shock, friction, fire, or other sources of ignition
R4	Forms very sensitive explosive metallic compounds
R5	Heating may cause an explosion
R6	Explosive with or without contact with air
R7	May cause fire
R8	Contact with combustible material may cause fire
R9	Explosive when mixed with combustible material
R10	Flammable
R11	Highly flammable
R12	Extremely flammable
R14	Reacts violently with water
R15	Contact with water liberates extremely flammable gases
R16	Explosive when mixed with oxidizing substances
R17	Spontaneously flammable in air
R18	In use may form flammable/explosive vapor–air mixture
R19	May form explosive peroxides
R20	Harmful by inhalation
R21	Harmful in contact with skin
R22	Harmful if swallowed
R23	Toxic by inhalation
R24	Toxic in contact with skin
R25	Toxic if swallowed
R26	Very toxic by inhalation
R27	Very toxic in contact with skin
R28	Very toxic if swallowed
R29	Contact with water liberates toxic gas
R30	Can become highly flammable in use
R31	Contact with acids liberates toxic gas
R32	Contact with acids liberates very toxic gas
R33	Danger of cumulative effects
R34	Causes burns
R35	Causes severe burns
R36	Irritating to the eyes
R37	Irritating to the respiratory system
R38	Irritating to the skin
R39	Danger of very serious irreversible effects
R40	Limited evidence of a carcinogenic effect
R41	Risk of serious damage to the eyes

Table 165 Risk (R) Phrases Used in the European Community (EU) (Continued)

R42	May cause sensitization by inhalation
R43	May cause sensitization by skin contact
R44	Risk explosion if heated under confinement
R45	May cause cancer
R46	May cause heritable genetic damage
R48	Danger of serious damage to health by prolonged exposure
R49	May cause cancer by inhalation
R50	Very toxic to aquatic organisms
R51	Toxic to aquatic organisms
R52	Harmful to aquatic organisms
R53	May cause long-term adverse effects in the aquatic environment
R54	Toxic to flora
R55	Toxic to fauna
R56	Toxic to soil organisms
R57	Toxic to bees
R58	May cause long-term adverse effects to the environment
R59	Dangerous for the ozone layer
R60	May impair fertility
R61	May cause harm to the unborn child
R62	Possible risk of impaired fertility
R63	Possible risk of harm to the unborn child
R64	May cause harm to breastfed babies
R68	Possible risk of irreversible effects
Combination of Particular Risks	
R14/15	Reacts violently with water, liberating extremely flammable gases
R15/29	Contact with water liberates toxic, extremely flammable gas
R20/21	Harmful by inhalation and in contact with skin
R20/21/22	Harmful by inhalation, in contact with skin and if swallowed
R20/22	Harmful by inhalation and if swallowed
R21/22	Harmful in contact with skin and if swallowed
R23/24	Toxic by inhalation and when in contact with skin
R23/24/25	Toxic by inhalation, in contact with skin, and if swallowed
R23/25	Toxic by inhalation and if swallowed
R24/25	Toxic in contact with skin and if swallowed
R26/27	Very toxic by inhalation and in contact with skin
R26/27/28	Very toxic by inhalation, when in contact with skin, and if swallowed
R26/28	Very toxic by inhalation and if swallowed
R27/28	Very toxic in contact with skin and if swallowed

Table 165 Risk (R) Phrases Used in the European Community (EU) (Continued)

R36/37	Irritating to eyes, respiratory system
R36/37/38	Irritating to eyes, respiratory system and skin
R36/38	Irritating to eyes and skin
R37/38	Irritating to respiratory system and skin
R39/23	Toxic: danger of very serious irreversible effects through inhalation
R39/23/24	Toxic: danger of very serious irreversible effects through inhalation and in contact with skin
R39/23/24/25	Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed
R39/23/25	Toxic: danger of very serious irreversible effects through inhalation and if swallowed
R39/24	Toxic: danger of very serious irreversible effects in contact with skin
R39/24/25	Toxic: danger of very serious irreversible effects in contact with skin and if swallowed
R39/25	Toxic: danger of very serious irreversible effects if swallowed
R39/26	Very toxic: danger of very serious irreversible effects through inhalation
R39/26/27	Very toxic: danger of very serious irreversible effects through inhalation and in contact with skin
R39/26/27/28	Very toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed
R39/26/28	Very toxic: danger of very serious irreversible effects through inhalation and if swallowed
R39/27	Very toxic: danger of very serious irreversible effects in contact with skin
R39/27/28	Very toxic: danger of very serious irreversible effects in contact with skin and if swallowed
R39/28	Very toxic: danger of very serious irreversible effects if swallowed
R68/20	Harmful: possible risk of irreversible effects through inhalation
R68/20/21	Harmful: possible risk of irreversible effects through inhalation and in contact with skin
R68/20/21/22	Harmful: possible risk of irreversible effects through inhalation, in contact with skin and if swallowed
R68/20/22	Harmful: possible risk of irreversible effects through inhalation and if swallowed
R68/22	Harmful: possible risk of irreversible effects if swallowed
R68/21	Harmful: possible risk of irreversible effects in contact with skin
R68/21/22	Harmful: possible risk of irreversible effects in contact with skin and if swallowed
R42/43	May cause sensitization by inhalation and skin contact
R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation

Table 165 Risk (R) Phrases Used in the European Community (EU) (Continued)

R48/20/21	Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin
R48/20/21/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin, and if swallowed
R48/20/22	Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed
R48/21	Harmful: danger of serious damage to health by prolonged exposure in contact with skin
R48/21/22	Harmful: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed
R48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed
R48/23	Toxic: danger of serious damage to health by prolonged exposure through inhalation
R48/23/24	Toxic: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin
R48/23/24/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin, and if swallowed
R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed
R48/24	Toxic: danger of serious damage to health by prolonged exposure in contact with skin
R48/24/25	Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed
R48/25	Toxic: danger of serious damage to health by prolonged exposure if swallowed
R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
R51/53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
R52/53	Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment

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Section 14
Pharmaceutical and Related Toxicology

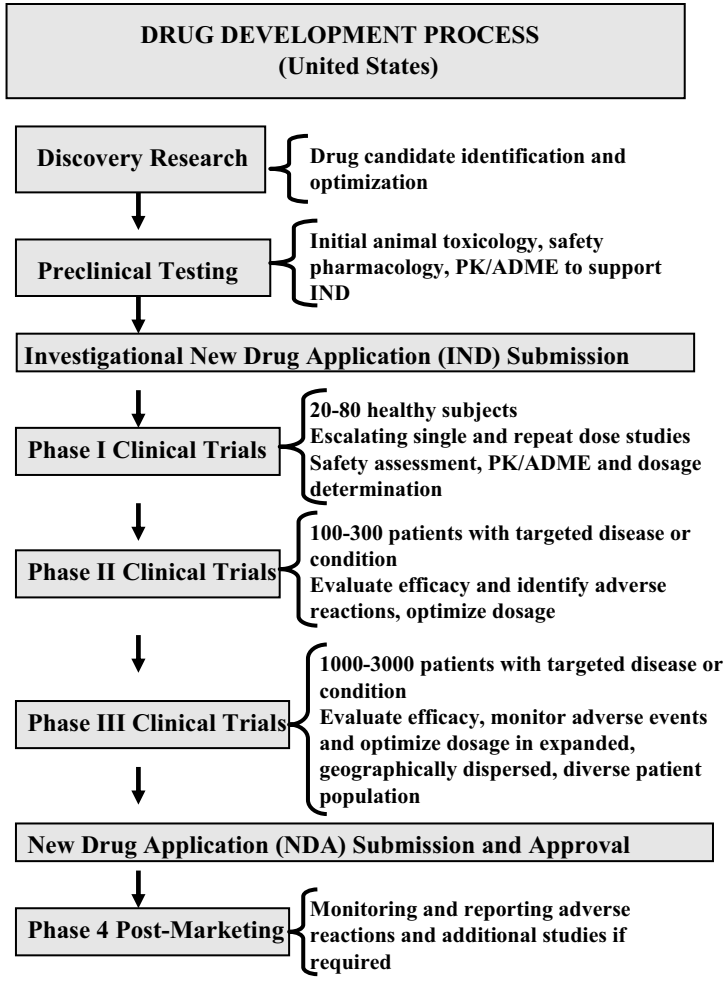

Figure 19 An overview of the drug development process in the United States.

Table 166 Typical Timing of Nonclinical Toxicology and Safety Pharmacology Studies in Drug Development

Development Phase	Study Type
Discovery	- hERG/other cardiac ion channel assays - *In vitro* bacterial mutagenicity screening assay - *In vitro* chromosome aberration screening assay - *In vitro* Cellular Toxicity
For IND and prior to phase I clinical studies	- Single-dose acute studies in rodent and nonrodent - 7-day dose range-finding studies in rodent and nonrodent - 2-week/4-week repeat-dose studies in rodent and nonrodenta - Bacterial mutagenicity - *In vitro* chromosome aberrations - *In vivo* micronucleus - hERG IC_{50} - CNS, respiratory, and cardiovascular safety pharmacology (renal and GI can be addressed in repeated dose studies) - Intravenous/perivascular irritation, rat or rabbit (if appropriate).
Prior to phase II clinical studies	- Range finding for developmental and reproductive studies - Female fertility, rat - Embryo-fetal development, rabbit and rat - 1- or 3-mo repeat-dose studies in rodent and nonrodent[a] - ADME studies - Occupational studies (skin, eye irritation, and contact sensitization)
Prior to phase III clinical studies	- 6-mo rodent and 6- or 9-mo nonrodent repeat-dose studies[a] - Male fertility, rat - Prenatal/perinatal toxicity, rat
For NDA	- Metabolite studies as appropriate. - Excipient/impurity qualification studies as appropriate - 3-mo mouse dose range-finding study to support carcinogenicity study (for chronic indication[b]) - Rat and mouse carcinogenicity (for chronic indication[b]) - Juvenile rat studies to support pediatric indication (if applicable) - Additional studies to address special issues (e.g., immunotoxicology)

[a] Refer to Table 167 for study length.

[b] Chronic indication is commonly defined as continuous treatment for 6 mo or longer, or discontinuous/intermittent treatment for a cumulative total of 6 mo or more.

Table 167 Minimal Duration for Repeated Dose Toxicology Studies to Support Drug Clinical Trials and Marketing

Clinical Trial Duration	Rodent		Nonrodent	
	Phase I, II, and III[a]	Phase III[b] and Marketing	Phase I, II, and III[a]	Phase III[b] and Marketing
Single dose	2–4 wk[c]		2 wk[c]	
Up to 2 wk	2–4 wk[c]	1 mo	2 wk[c]	1 mo
Up to 1 mo	1 mo	3 mo	1 mo	3 mo
Up to 3 mo	3 mo	6 mo	3 mo	3 mo[d]
Up to 6 mo	6 mo	6 mo	6 mo	Chronic[e]
>6 mo	6 mo	6 mo	Chronic[e]	Chronic[e]

[a] Phase III in United States and Japan. (In Japan, longer duration toxicology studies should be considered as per the EU if there are no phase II trials of equivalent duration to the planned phase III trials)

[b] Phase III in the EU.

[c] 2-wk studies are the minimal duration in the United States and the EU although a single-dose study with extended examinations can support single-dose human trials in the United States. Japan requires 4-wk rodent studies as a minimum.

[d] Chronic nonrodent study recommended for marketing for clinical use >1 mo.

[e] Nonrodent chronic study of 9 mo in duration is generally acceptable in all regions. A study of 6 mo duration may be acceptable in the EU.

Note: As a general rule, the duration of the animal studies should be equal to or exceed the human clinical trials.

Source: ICH (1997), ICH (1998).

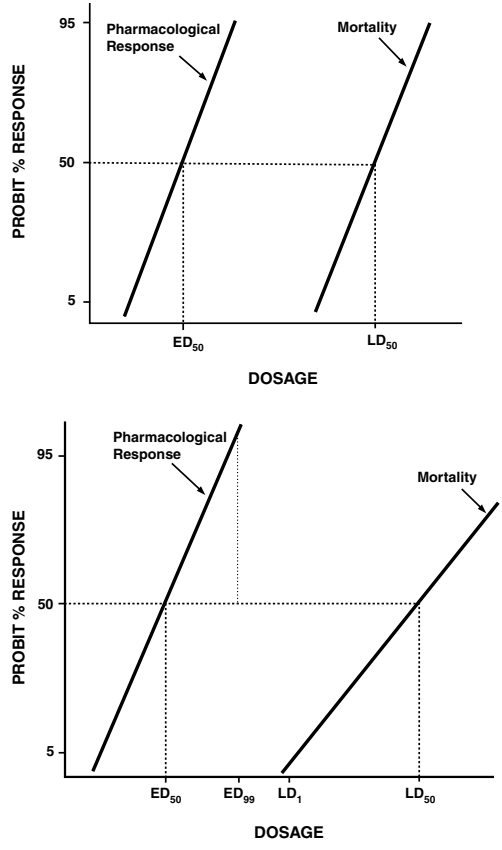

Figure 20 A simplistic method for assessing ``safety ratios'' for drugs is by comparing the ratio of the therapeutically effective dose (ED_{50}) and lethal dose (LD_{50}); this ratio of LD_{50}/ED_{50} is referred to as the therapeutic index (TI_{50}). For parallel pharmacological effect and lethality dose-response lines, the therapeutic index will be similar over a wide range of doses (upper graph). The therapeutic index may be misleading if the dose-response lines for pharmacological and lethal effects are not parallel (lower graph). As this graph shows, the margin based on LD_{50} and ED_{50} may be reasonable. However, due to the shallow slope of the mortality dose-response line, the therapeutic index will be significantly lower at the 1% and 5% level, thus the hyperreactive group may be at greater risk. In such a case, a better index of safety will be the ratio of the LD_1/ED_{99}, which is referred to as the margin of safety. From Ballatyne, B. (1992). With Permission.

Table 168 Order for Reporting Toxicology Data for an IND/NDA

Study Type	Species[a]	Route of Administration	Dose/group (present in order of increasing dose)	Study Results
Acute studies	Mouse	Intended route for human use followed by:		Mortality
Repeat-dose studies (*in order of increasing duration*) -Subchronic -Chronic	Rat			Body weight
	Hamster	Oral	Untreated control	Food/water consumption
	Other rodents	Intravenous	Vehicle control	Physical examinations (*including clinical observations, EEG, ophthalmic exam, etc.*)
Genotoxicity studies -*In vitro* -*In vivo*	Rabbit	Intramuscular	Low dose	
	Dog	Intraperitoneal	Middle doses	
Carcinogenicity studies	Monkey	Subcutaneous	High dose	
	Other nonrodent mammals	Inhalation	Positive or comparative controls	
Reproduction studies -Fertility and early embryonic development -Embryofetal development -Prenatal and postnatal development	Nonmammals	Topical		Hematology
		Other *in vivo*		Serum chemistry
		In vitro		Urinalysis
				Organ weights
Local tolerance studies				Gross pathology
Other toxicity studies (*e.g., immunogenicity and studies on metabolites and impurities*)				Histopathology

[a] Males preceding females for each species. Data for adult animals should precede that for infant, geriatric, or disease model animals (if applicable).

Table 169 Pharmacokinetics: Basic Overview

Pharmacokinetics/toxicokinetics: *What the body does to a drug/chemical.*
Pharmacodynamics/toxicodynamics: *What a drug/chemical does to a body.*

Cmax: *Maximum drug plasma concentration.*
Tmax: *Time for drug to reach the maximum plasma concentration.*
AUC: *Area under the plasma concentration curve for a defined period beginning at time zero.*
T1/2: *Plasma half-life of drug.*

The preceding four parameters can be determined directly from data generated from bioanalytical analysis of drug in plasma at various times after dose administration.

Total clearance (Cl): *The overall rate at which drug is cleared from the plasma.*

$Cl = dose/AUC$

Volume of distribution (Vd): *The ratio of the amount of drug in the body at any time and the corresponding plasma concentration.*

$Vd = Cl/(0.693/T1/2)$

Bioavailability (F): *Fraction of administered dose that reaches systemic circulation.*

$F = AUC_{ev}/AUC_{iv}$

where ev = extravascular administration
iv = intravenous administration

Table 170 Comparative Physiological Values for Frequently Used Pharmacokinetic Determinations

	Mouse (20 g)	Rat (250 g)	Rabbit (2.5 kg)	Monkey (5 kg)	Dog (10 kg)	Human (70 kg)
Total body water (mL)	14.5	167	1,790	3,465	6,036	42,000
Intracellular fluid (mL)	—	92.8	1,165	2,425	3,276	23,800
Extracellular fluid (mL)	—	74.2	625	1,040	2,760	18,200
Plasma volume (mL)	1.0	7.8	110	224	515	3,000
Urine flow (mL/d)	1.0	50.0	150	375	300	1,400
Bile flow (mL/d)	2.0	22.5	300	125	120	350
GFR (mL/min)	0.28	1.31	7.8	10.4	61.3	125
Cardiac blood flow (mL/min)	8.0	74.0	530	1,086	1,200	5,600
Liver blood flow (mL/min)	1.8	13.8	177	218	309	1,450
Renal blood flow (mL/min)	1.3	9.2	80	138	216	1,240

Source: Adapted from Davies, B. and Morris, T. (1993).

Table 171 Table for Predicting Human Half-Life of Xenobiotics from Rat Half-Life

Rat Half-Life (hr)	Lower (%)			Human Half-Life Estimate (hr)	Upper (%)		
	95	90	80		80	90	95
0.01	0.019	0.025	0.034	0.106	0.327	0.451	0.598
0.02	0.034	0.045	0.062	0.189	0.574	0.790	1.045
0.03	0.048	0.064	0.087	0.264	0.799	1.098	1.450
0.04	0.062	0.081	0.111	0.335	1.011	1.387	1.830
0.05	0.074	0.098	0.134	0.404	1.213	1.664	2.193
0.06	0.087	0.114	0.156	0.469	1.408	1.930	2.543
0.07	0.099	0.130	0.178	0.533	1.598	2.189	2.882
0.08	0.110	0.146	0.199	0.596	1.782	2.441	3.213
0.09	0.122	0.161	0.220	0.657	1.963	2.687	3.536
0.1	0.13	0.18	0.24	0.72	2.14	2.93	3.85
0.2	0.24	0.31	0.43	1.27	3.78	5.17	6.79
0.3	0.34	0.44	0.60	1.78	5.28	7.21	9.47
0.4	0.43	0.56	0.77	2.26	6.70	9.14	12.00
0.5	0.51	0.68	0.92	2.72	8.05	10.99	14.42
0.6	0.60	0.79	1.07	3.17	9.36	12.77	16.76
0.7	0.68	0.89	1.22	3.60	10.63	14.51	19.04
0.8	0.76	1.00	1.36	4.02	11.88	16.20	21.26
0.9	0.84	1.10	1.50	4.44	13.09	17.86	23.44
1	0.92	1.20	1.64	4.84	14.29	19.49	25.57
2	1.63	2.13	2.91	8.60	25.40	34.66	45.47
3	2.27	2.98	4.07	12.04	35.59	48.58	63.76
4	2.88	3.78	5.16	15.28	45.24	61.76	81.09
5	3.46	4.54	6.20	18.39	54.49	74.42	97.74
6	4.02	5.28	7.21	21.39	63.46	86.69	113.88
7	4.56	5.99	8.19	24.31	72.18	98.64	129.61
8	5.08	6.68	9.14	27.15	80.71	110.32	144.99
9	5.60	7.36	10.06	29.94	89.07	121.77	160.08
10	6.1	8.0	11.0	32.7	97.3	133.0	174.9
20	10.7	14.1	19.4	58.1	174.0	238.3	313.9
30	14.9	19.7	27.0	81.3	244.6	335.6	442.4
40	18.8	24.9	34.1	103.2	311.6	427.9	564.7
50	22.6	29.8	41.0	124.1	376.1	516.9	682.7
60	26.2	34.6	47.5	144.4	438.6	603.3	797.2
70	29.6	39.2	53.9	164.1	499.5	687.5	909.1

Table 171 Table for Predicting Human Half-Life of Xenobiotics from Rat Half-Life (Continued)

Rat Half-Life (hr)	Lower (%)			Human Half-Life Estimate (hr)	Upper (%)		
	95	90	80		80	90	95
80	33.0	43.6	60.1	183.3	559.2	770.0	1018.7
90	36.3	48.0	66.1	202.1	617.7	851.1	1126.4
100	39.5	52.3	72.0	220.6	675.2	930.8	1232.4
200	68.9	91.4	126.5	391.9	1214.2	1679.5	2230.5
300	95.2	126.7	175.7	548.6	1712.7	2374.3	3159.3
400	119.8	159.7	221.7	696.4	2186.8	3036.7	4046.6
500	143.2	191.0	265.6	837.9	2643.8	3676.1	4904.4
600	165.5	221.1	307.7	974.7	3087.5	4297.9	5739.6
700	187.1	250.1	348.5	1107.6	3520.5	4905.5	6556.7
800	208.1	278.3	388.1	1237.3	3944.6	5501.3	7358.6
900	228.5	305.8	426.8	1364.3	4361.2	6086.9	8147.4
1000	248.4	332.7	464.6	1488.9	4771.1	6663.7	8925.0
1100	267.9	359.0	501.7	1611.3	5175.1	7232.7	9692.5

Note: The following examples indicate how this table is used. For a xenobiotic with a rat half-life of 0.8 hr, the prediction or best guess of the human half-life is 4.02 hr. The table indicates that the actual half-life would fall between 1.0 and 16.2 hr with a confidence of 90%. Values falling between those indicated in the table can be linearly interpolated, for example, a rat half-life of 2.7 hr gives a human half-life of 11.01 hr.

Source: From Bachmann, K. M. et al. (1996). With permission.

Table 172 Table for Predicting Human Volume of Distribution from Rat Volume of Distribution

Rat volume (L/kg)	Lower (%)			Human Volume Estimate (L/kg)	Upper (%)		
	95	90	80		80	90	95
0.01	0.002	0.003	0.004	0.011	0.031	0.041	0.054
0.02	0.004	0.005	0.007	0.020	0.057	0.076	0.099
0.03	0.006	0.008	0.011	0.029	0.082	0.109	0.141
0.04	0.008	0.010	0.014	0.038	0.105	0.141	0.182
0.05	0.010	0.013	0.017	0.046	0.128	0.172	0.222
0.06	0.012	0.015	0.020	0.055	0.151	0.202	0.261
0.07	0.013	0.017	0.023	0.063	0.174	0.232	0.299
0.08	0.015	0.019	0.026	0.071	0.196	0.261	0.337
0.09	0.017	0.022	0.029	0.079	0.217	0.290	0.374
0.1	0.019	0.024	0.032	0.087	0.239	0.319	0.411
0.2	0.035	0.045	0.060	0.164	0.445	0.593	0.762
0.3	0.051	0.065	0.087	0.236	0.641	0.853	1.096
0.4	0.066	0.085	0.113	0.307	0.831	1.105	1.419
0.5	0.081	0.104	0.139	0.376	1.016	1.352	1.735
0.6	0.096	0.123	0.164	0.443	1.198	1.593	2.045
0.7	0.111	0.142	0.189	0.510	1.377	1.832	2.350
0.8	0.125	0.160	0.213	0.575	1.554	2.067	2.652
0.9	0.139	0.178	0.237	0.640	1.729	2.299	2.950
1	0.15	0.20	0.26	0.70	1.90	2.53	3.25
2	0.29	0.37	0.49	1.32	3.57	4.75	6.09
3	0.41	0.53	0.70	1.91	5.16	6.87	8.82
4	0.53	0.69	0.91	2.48	6.71	8.93	11.47
5	0.65	0.84	1.18	3.03	8.23	10.96	14.08
6	0.77	0.99	1.32	3.58	9.72	12.95	16.64
7	0.88	1.14	1.51	4.11	11.19	14.92	19.17
8	0.99	1.28	1.71	4.64	12.65	16.86	21.68
9	1.11	1.42	1.90	5.17	14.09	18.79	24.17
10	1.21	1.56	2.08	5.69	15.52	20.70	26.63
20	2.25	2.90	3.88	10.66	29.32	39.20	50.54
30	3.22	4.16	5.57	15.40	42.60	57.04	73.63
40	4.15	5.37	7.20	19.99	55.54	74.46	96.23
50	5.06	6.54	8.78	24.48	68.24	91.59	118.48
60	5.94	7.69	10.33	28.88	80.77	108.50	140.45
70	6.80	8.81	11.84	33.22	93.14	125.22	162.21
80	7.65	9.91	13.34	37.49	105.39	141.79	183.79
90	8.48	11.00	14.81	41.72	117.54	158.23	205.22

Note: See note of previous table for examples of how this table is used.

Source: From Bachmann, K. M. et al. (1996). With permission.

Table 173 Animal/Human Dose Conversions

Species	To Convert Dose in mg/kg to Dose in mg/m^2, Multiply by k_m Shown Below	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, do Either of the Following	
		Divide Animal Dose by	Multiply Animal Dose by
Human			
Adult (60 kg)	37	—	—
Child (20 kg)[b]	25	—	—
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micropig	27	1.4	0.73
Minipig	35	1.1	0.95

[a] Assumes a 60 kg human. For species not listed or for weights outside the standard ranges, HED (human equivalent dose) can be calculated from the following formula:

$$HED = \text{animal dose (mg/kg)} \times (\text{animal weight (kg)}/\text{human weight (kg)})^{0.33}$$

[b] This km is provided for reference only because healthy children will rarely be volunteers in phase I trials.

[c] Includes cynomolgus, rhesus, and stumptail.

Source: U.S. Food and Drug Administration (2005).

Table 174 FDA Pregnancy Categories

Category A:	Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
Category B:	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Or Animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
Category C:	Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, but the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. Or There are no animal reproduction studies, and no adequate and well-controlled studies in humans.
Category D:	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (e.g., the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
Category X:	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit (e.g., safer drugs or other forms of therapy are available). This drug is contraindicated in women who are or may become pregnant.

Source: U.S. CFR (2006a).

Table 175 DEA Controlled Substances Schedules

Schedule I	Drug or substance has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and there is a lack of accepted safety for its use under medical supervision (e.g., heroin, lysergic acid diethylamide/LSD, methaqualone).
Schedule II	Drug or substance has a high potential for abuse and has a currently accepted medical use in treatment in the United States with or without severe restrictions. Abuse of the drug or substance may lead to severe psychological or physical dependence (e.g., morphine, cocaine, methadone, methamphetamine).
Schedule III	The drug or substance has less potential for abuse than drugs or other substances in Schedules I and II and has a currently accepted medical use in treatment in the United States. Abuse of the drug or substance may lead to moderate or low physical dependence or high psychological dependence (e.g., codeine, hydrocodone with acetaminophen).
Schedule IV	The drug or substance has a low potential for abuse relative to the drugs or other substances in Schedule III and has a currently accepted medical use in treatment in the United States. Abuse of the drug or substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III (e.g., Darvon®, Valium®).
Schedule V	The drug or substance has a low potential for abuse relative to other drugs or other substances in Schedule IV and has a currently accepted medical use in treatment in the United States. Abuse of the drug or substance may lead to limited physical dependence or psychological dependence relative to drugs or other substances in Schedule IV. (e.g., cough medicines with codeine).

Source: U. S. Drug Enforcement Agency (2007).

Table 176 Typical Values[a] for Control Animals in Pulmonary Safety Pharmacology Studies

Species	Respiratory Rate (breaths/min)	Tidal Volume (mL)	Minute Volume (mL/min)	Resistance (cmH_2O/mL/s)	Compliance (mL/cmH_2O)
Sprague-Dawley rat (conscious)[b]	190 (173–206)	0.95 (0.91–1.00)	175 (157–183)	—	—
Sprague-Dawley rat (anesthetized)[c]	116 (114–118)	1.49 (1.40–1.56)	172 (160–181)	0.07 (0.06–0.08)	1.07 (1.03–1.10)

[a] Mean (range).

[b] Plethysmographic chamber (head-out).

[c] Urethane.

Table 177 Typical Values[a] for Control Animals in Cardiovascular Safety Pharmacology Studies

Species	Mean Arterial Pressure (mmHg)	Diastolic Pressure (mmHg)	Systolic Pressure (mmHg)	Heart Rate (beats/min)	QTc(s)
Beagle dog (conscious)[b]	114 (108–127)	90 (83–106)	135 (127–148)	106 (93–135)	0.25 (0.24–0.26)
Beagle dog (anesthetized)[c]	75 (58–90)	61 (48–74)	95 (73–120)	115 (99–141)	—

[a] Mean (range).

[b] Telemetered.

[c] Isoflurane.

Source: Dr. George Thomas, Calvert Laboratories Inc., Olyphant, PA.

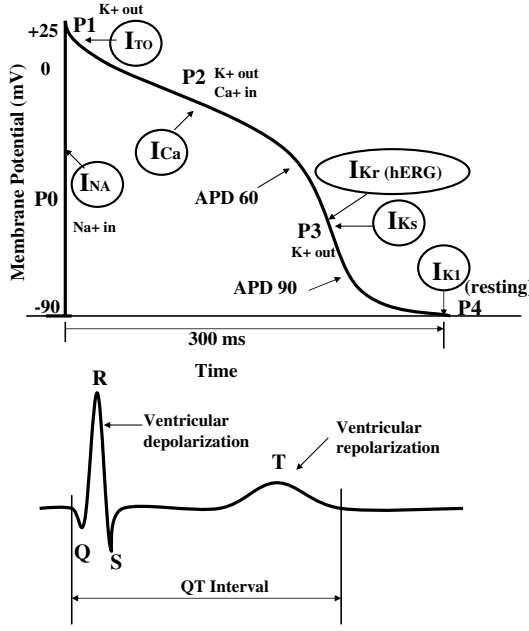

Figure 21 Correlation between the cardiac action potential and the QT interval of the surface electrocardiogram (ECG) is depicted. The temporal contributions of the various ion channel currents (I) to the action potential are shown. The action potential consists of five distinct phases (P0 to P4). Depolarization occurs in Phase 0 related to an influx of sodium ions and corresponding to the QRS complex of the ECG. Repolarization occurs in phases 1 to 3, restoring the resting membrane potential. The whole process lasts approximately 300 ms. The T wave of the ECG corresponds to ventricular repolarization. The duration of the QT interval on the ECG is defined as the duration between the beginning of the QRS complex and the end of the T wave. The Human Ether-a-go-go Related Gene Product (hERG) channel is the potassium channel that allows a potassium current to pass that corresponds to the rapidly activating delayed rectifier K^+ current. Significant inhibition of the hERG channel results in prolongation of the QT interval, which is believed to be associated with an increased propensity to develop a fatal ventricular tachyarrhythmia called *Torsades de Pointes*. APD_{60} and APD_{90} values, corresponding to the time where 60% and 90% of the resting membrane potential is restored, are typically reported in the Purkinje Fiber Assay.

Table 178 Substances Generally Recognized as Safe (GRAS)

Multiple Purpose Food Substances
Glutamic acid
Glutamic acid hydrochloride
Hydrochloric acid
Phosphoric acid
Sodium acid pyrophosphate
Aluminum sulfate
Aluminum ammonium sulfate
Aluminum potassium sulfate
Aluminum sodium sulfate
Caffeine
Calcium phosphate
Caramel
Glycerin
Methylcellulose
Monoammonium glutamate
Monopotassium glutamate
Silica aerogel
Sodium carboxymethylcellulose
Sodium caseinate
Sodium citrate
Sodium phosphate
Sodium aluminum phosphate
Sodium tripolyphosphate

Sequestrants
Sodium acid phosphate
Calcium diacetate
Calcium hexametaphosphate
Monobasic calcium phosphate
Dipotassium phosphate
Disodium phosphate
Sodium gluconate
Sodium hexametaphosphate
Sodium metaphosphate
Sodium phosphate
Sodium pyrophosphate
Tetra sodium pyrophosphate
Sodium tripolyphosphate

Table 178 Substances Generally Recognized as Safe (GRAS) (Continued)

Stabilizers
Chondrus extract

Anticaking Agents
Aluminum calcium silicate
Calcium silicate
Magnesium silicate
Sodium aluminosilicate
Sodium calcium aluminosilicate hydrated
Tricalcium silicate

Chemical Preservatives
Ascorbic acid
Erythorbic acid
Sorbic acid
Thiodiproprionic acid
Ascorbyl palmitate
Butylated hydroxyanisole
Butylated hydroxytoluene
Calcium ascorbate
Calcium sorbate
Dilauryl thiopropionate
Potassium bisulfite
Potassium metabisulfite
Potassium sorbate
Sodium ascorbate
Sodium bisulfite
Sodium metabisulfite
Sodium sorbate
Sodium sulfite
Sulfur dioxide
Tocopherols

Nutrients
Ascorbic acid
Biotin
Calcium phosphate
Calcium pyrophosphate
Choline bitartrate
Choline chloride
Sodium phosphate

Table 178 Substances Generally Recognized as Safe (GRAS) (Continued)

Tocopherols
α-Tocopherol acetate
Zinc chloride
Zinc gluconate
Zinc oxide
Zinc stearate
Zinc sulfate

Source: U.S. CFR (2006b).

Table 179 The ISO Standard 10993-1 Guidance for Selection of Biocompatibility Tests as Modified by the FDA

Device Categories			Biological Effect[b]									
Body Contact		Contact Duration[a]	Cytotoxicity	Sensitization	Irritation or Intracutaneous	Systemic Toxicity (Acute)	Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatability	Chronic Toxicity	Carcinogenicity
Surface devices	Skin	A	x	x	x							
		B	x	x	x							
		C	x	x	x							
	Mucosal membrane	A	x	x	x							
		B	x	x	x	o	o		o			
		C	x	x	x	o	x	x	o		o	
	Breached or compromised surfaces	A	x	x	x	o						
		B	x	x	x	o	o		o			
		C	x	x	x	o	x	x	o		o	

Table 179 The ISO Standard 10993-1 Guidance for Selection of Biocompatibility Tests as Modified by the FDA (Continued)

Device Categories			Biological Effect[b]										
Body Contact		Contact Duration[a]	Cytotoxicity	Sensitization	Irritation or Intracutaneous	Systemic Toxicity (Acute)	Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatability	Chronic Toxicity	Carcinogenicity
External communicating devices	Blood path, indirect	A	x	x	x	x				x		
		B	x	x	x	x	o			x		
		C	x	x	o	x	x	x	o	x	x	x
	Tissue/bone/ dentin communicating+	A	x	x	x	o						
		B	x	x	o	o	o	x	x			
		C	x	x	o	o	o	x	x		o	x
	Circulating blood	A	x	x	x	x		o^		x		
		B	x	x	x	x	o	x	o	x		
		C	x	x	x	x	x	x	o	x	x	x
Implant devices	Tissue/bone	A	x	x	x	o						
		B	x	x	o	o	o	x	x			
		C	x	x	o	o	o	x	x		x	x
	Blood	A	x	x	x	x			x	x		
		B	x	x	x	x	o	x	x	x		
		C	x	x	x	x	x	x	x	x	x	x

[a] A = limited (24 hr); B = prolonged (24 hr to 30 days); C = permanent (>30 days).

[b] x = ISO Evaluation Tests for Consideration; o = additional tests that may be applicable.

Note: + = Tissue includes tissue fluids and subcutaneous spaces; ^ = for all devices used in extra-corporeal circuits.

Source: Adapted from U.S. Food and Drug Administration (1995).

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Section 15
Miscellaneous Information

Table 180 Comparison of Physiological Parameters for Different Human Body Organs

Organ	Weight (kg)	Percentage of Body Volume	Percent Water	Blood Flow (mL/min)	Plasma Flow (mL/min)	Blood Flow (mL/kg)	Blood Flow Fraction
Adrenal glands		0.03	—	25	15		
Blood	5.4	7	83	5000			
Bone	10	16	22	250	150		
Brain	1.5	2	75	700	420	780	
Fat	10	10	10	200	120		0.05
Heart	0.3	0.5	79	200	120	250	
Kidneys	0.3	0.4	83	1100	660	1200	
Liver	1.5	2.3	68	1350	810	1500	0.25
Portal				1050	630		
Arterial				300	180		
Lungs	1.0	0.7	79	5000	3000		
Muscle	30	42	76	750	450	900	0.19
Skin	5	18	72	300	180	250	
Thyroid gland	0.03	0.03	—	50	30		
Total body		100	60	5000	3000		

Note: Data are for a hypothetical 70 kg human.
Source: Adapted from Illing (1989).

Table 181 Comparison of the Blood Flow/Perfusion and Oxygen Consumption of Liver, Lung, Intestine, and Kidney of the Rat *In Vivo* and in Organ Perfusion

Parameter (unit)	Liver	Lung	Intestine	Kidney
In vivo				
Blood flow (mL min^{-1})	13–20	55–70	5–8	4–6
Blood pressure S/D (torr)[a]	150/100	25/10	150/100	150/100
pO_2-arterial (torr)	95	40	95	95
pO_2-venous (torr)	40	100	50	70
O_2-consumption (μL min^{-1})	500–800	From air	40–160	100–200
In perfusion				
Perfusion flow (mL min^{-1})	30–50	50	6	20–35
Perfusion pressure (torr)	100–120	10–20	100–120	100–120
pO_2-arterial (torr)	600	600	400	600
pO_2-venous (torr)	200	?	180	400
Max. O_2-supply[b] (μL min^{-1})	380–630	?	120[c]	120–220

Note: These values are indicative of the most common values measured for the various organs in a rat of 250 to 300 g. The figures provided for the kidney apply to a single kidney. The values measured in organ perfusions may differ greatly, depending on the setup, method of gassing, etc.

[a] S = systolic; D = diastolic.

[b] Calculated from pO_2-arterial, pO_2-venous, and perfusion flow.

[c] With 20% FC-43 emulsion in KRB; other figures apply to KRB without erythrocytes or oxygen carrier (KRB = Krebs-Ringer buffer).

From Niesink, R.J.M. et al. (1996), Toxicology: Principles and Applications, CRC Press, Boca Raton, FL.

Table 182 Comparison of Physiological Characteristics of Experimental Animals and Humans

Species	Body Weight (kg)	Surface Area (m^2)	Energy Metabolism[a]		Cardiac Function					Arterial Blood Pressure (mm Hg)	
			cal/kg/day	cal/m^2/day	Heart Weight (g/100g)	Heart Rate (beats/min)	Stroke Volume (mL/beat)	Cardiac Output (l/min)	Cardiac Index (l/m^2/m)	Systolic	Diastolic
Rat	0.1–0.5	0.03–0.06	120–140 (B)	760–905 (B)	0.24–0.58	250–400	1.3–2.0	0.015–0.079	1.6	88–184	58–145
Rabbit	1–4	0.23	47	810	0.19–0.36	123–330	1.3–3.8	0.25–0.75	1.7	95–130	60–90
Monkey	2–4	0.31	49 (B)	675	0.34–0.39	165–240	8.8	1.06	—	137–188	112–152
Dog	5–31	0.39–0.78	34–39 (B)	770–800 (B)	0.65–0.96	72–130	14–22	0.65–1.57	2.9	95–136	43–66
Human	54–94	1.65–1.83	23–26 (B)	790–910 (B)	0.45–0.65	41–108	62.8	5.6	3.3	92–150	53–90
Pig	100–250	2.9–3.2	14–17 (B)	1100–1360 (B)	0.25–0.40	55–86	39–43	5.4	4.8	144–185	98–120
Ox	500–800	4.2–8.0	15 (B)	1635 (B)	0.31–0.53	40–58	244	146	—	121–166	80–120
Horse	650–800	5.8–8.0	25 (R)	2710–2770 (R)	0.39–0.94	23–70	852	188	4.4	86–104	43–86

[a] B = basal; R = resting.

Source: From Mitruka, B.M. and Rawnsley, H.M. (1977). With permission.

Table 183 Comparison of Certain Physiological Values of Experimental Animals and Humans

Species	Body Temperature (°C)	Whole Blood Volume (mL/kg body wt.)	Plasma Volume (mL/kg body weight)	Plasma pH	Plasma CO_2 Content (mM/L)	CO_2 Pressure (mmHg)
Mouse	36.5 ± 0.70	74.5 ± 17.0	48.8 ± 17.0	7.40 ± 0.06	22.5 ± 4.50	40.0 ± 5.40
Rat	37.3 ± 1.40	58.0 ± 14.0	31.3 ± 12.0	7.35 ± 0.09	24.0 ± 4.70	42.0 ± 5.70
Hamster	36.0 ± 0.50	72.0 ± 15.0	45.5 ± 7.50	7.39 ± 0.08	37.3 ± 2.50	59.0 ± 5.00
Guinea pig	37.9 ± 0.95	74.0 ± 7.00	38.8 ± 4.50	7.35 ± 0.09	22.0 ± 6.60	40.0 ± 9.80
Rabbit	38.8 ± 0.65	69.4 ± 12.0	43.5 ± 9.10	7.32 ± 0.03	22.8 ± 8.60	40.0 ± 11.5
Chicken	41.4 ± 0.25	95.5 ± 24.0	65.6 ± 12.5	7.52 ± 0.04	23.0 ± 2.50	26.0 ± 4.50
Cat	38.6 ± 0.70	84.6 ± 14.5	47.7 ± 12.0	7.43 ± 0.03	20.4 ± 3.50	36.0 ± 4.60
Dog	38.9 ± 0.65	92.6 ± 29.5	53.8 ± 20.1	7.42 ± 0.04	21.4 ± 3.90	38.0 ± 5.50
Monkey	38.8 ± 0.80	75.0 ± 14.0	44.7 ± 13.0	7.46 ± 0.06	29.3 ± 3.8	44.0 ± 4.8
Pig	39.3 ± 0.30	69.4 ± 11.5	41.9 ± 8.90	7.40 ± 0.08	30.2 ± 2.5	43.0 ± 5.60
Goat	39.5 ± 0.60	71.0 ± 14.0	55.5 ± 13.0	7.41 ± 0.09	25.2 ± 2.8	50.0 ± 9.40
Sheep	38.8 ± 0.80	58.0 ± 8.50	41.9 ± 12.0	7.48 ± 0.06	26.2 ± 5.00	38.0 ± 8.50
Cattle	38.6 ± 0.30	57.4 ± 5.00	38.8 ± 2.50	7.38 ± 0.05	31.0 ± 3.0	48.0 ± 4.80
Horse	37.8 ± 0.25	72.0 ± 15.0	51.5 ± 12.0	7.42 ± 0.03	28.0 ± 4.00	47.0 ± 8.50
Human	36.9 ± 0.35	77.8 ± 15.0	47.9 ± 8.70	7.39 ± 0.06	27.0 ± 2.00	42.0 ± 5.00

Source: From Mitruka, B.M. and Rawnsley, H.M. (1977). With permission.

Table 184 Overview of Major Mammalian Hormones

Source	Hormone	Target	Major Effect
Anterior pituitary	Growth hormone (GH)	Multiple sites	Stimulates bone and muscle growth and metabolic functions
	Adrenocorticotropic hormone (ACTH)	Adrenal cortex	Stimulates secretion of adrenal cortex hormones
	Thyroid stimulating hormone (TSH)	Thyroid	Stimulates secretion of thyroid hormone
	Follicle-stimulating hormone (FSH)	Ovaries Testes	Stimulates production of ova and sperm
	Luteinizing hormone (LH)	Ovaries Testes	Stimulates ovulation and production of estrogen, progesterone, and testosterone
	Prolactin (LTH)	Mammary Ovary	Stimulates milk production and maintains estrogen and progesterone secretion
	Melanocyte-stimulating hormone (MSH)	Melanocyte	Stimulates dispersal of pigment
Hypothalamus/ posterior pituitary	Oxytocin	Uterus Mammary	Stimulates contraction of uterus and secretion of milk
	Antidiuretic hormone (ADH)	Kidney	Promotes water retention
Thyroid	Triiodothyronine (T_3) and thyroxin (T_4)	Multiple	Stimulates and maintains metabolism
	Calcitonin	Bone	Lowers blood calcium
Parathyroid	Parathyroid hormone	Bone Kidney Digestive tract	Raises blood calcium
Ovary	Estrogens (estradiol)	Uterus Multiple sites	Stimulates growth of uterine lining, promotes development and maintenance of secondary sex characteristics
Ovary/placenta	Progesterone	Uterus Breast	Promotes growth of uterine lining
Placenta	Chrorionic gonadotropin	Anterior pituitary	Stimulates release of FSH and LH

Table 184 Overview of Major Mammalian Hormones (Continued)

Source	Hormone	Target	Major Effect
Testis	Androgens (testosterone)	Multiple sites	Supports spermatogenesis, promotes development and maintenance of secondary sex characteristics
Adrenal cortex	Glucocorticoids (cortisol)	Multiple sites	Raises blood glucose
	Mineralocorticoids (aldosterone)	Kidney	Maintains sodium and phosphate balance
Adrenal medulla	Epinephrine (adrenalin) Norepinephrine	Muscle Liver Blood vessels	Raises blood glucose, increases metabolism, and constricts certain blood vessels
Pineal gland	Melatonin	Multiple sites	Regulates biorhythms, influences reproduction in some species
Pancreas	Insulin	Multiple sites	Lowers blood glucose
	Glucagon	Liver Fatty tissue	Raises blood glucose
Thymus	Thymosin		Stimulates T-lymphocytes
Gastrointestinal Tract			
Duodenum	Secretin	Pancreas	Stimulates secretion of pancreatic enzymes
	Cholescystokinin	Gallbladder	Stimulates release of bile
Stomach	Gastrin	Stomach Intestinal tract	Stimulates acid secretion and contraction of intestinal tract

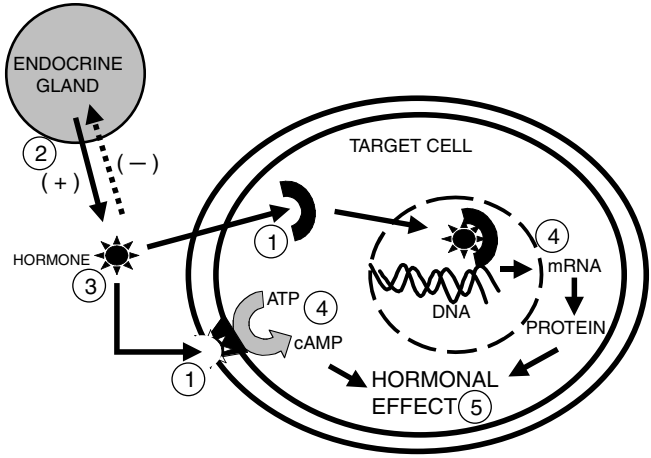

Figure 22 A generalized schematic of mammalian hormonal regulation showing major points for potential disruption/modulation. Endocrine disrupters/modulators are defined as exogenous substances that can alter or modulate endocrine function resulting in adverse effects at the level of the organism, its progeny, and/or populations of organisms. The site of action most focused on for these substances is at the target cell hormone receptor (1). A substance that has an affinity for binding to either a peptide-hormone membrane receptor or a steroid-hormone cytoplasmic receptor might act either as an agonist inducing the hormonal action or as an antagonist, preventing the natural hormone from inducing its effect. However, endocrine disrupters/modulators need not interact with a receptor to affect hormonal regulation. They may affect the synthesis and secretion of the hormone or its regulatory control at the endocrine gland (2) or the transport or elimination of the hormone (3) resulting in increased or decreased levels of hormone reaching the target cell. Endocrine disrupters/ modulators might interfere with or alter the cellular mechanisms through which the hormone exerts its effect (4). For steroid hormones this involves gene activation and synthesis of specific proteins or for peptide hormones, activation of a second-messenger sequence producing cellular effects such as enzyme activation and alteration of cell membrane permeability. Endocrine disrupters/modulators may alter the temporal expression of the hormonal effect (5), such as causing the premature expression of the hormonal effect at a critically sensitive period during sexual development.

Table 185 Tissue Localization of Xenobiotic-Metabolizing Enzymes

Relative Amount	Tissue
High	Liver
Medium	Lung, kidney, intestine
Low	Skin, testes, placenta, adrenals
Very low	Nervous system tissues

Table 186 Metabolic Phase I and Phase II Reactions

Phase I	Phase II
Oxidation	Glucuronidation
Reduction	Glucosidation
Hydrolysis	Ethereal sulfation
Isomerization	Methylation
Others	Acetylation
	Amino acid conjugation
	Glutathione conjugation
	Fatty acid conjugation
	Condensation

Table 187 Major Cytochrome P450 Enzymes

	Substrates	Substrate Examples	Comments
Subfamily CYP1A			
13% of human liver cytochrome P450 enzymes metabolizes ~4% of drugs			
CYP1A1	Polycyclic aromatic hydrocarbons	7-ethoxyresorufin, interferon	Expressed only after exposure to inducers (human), induced in placenta and lung after exposure to cigarette smoke
CYP1A2	Aromatic and heterocyclic amines, neutral or basic lypophylic planar drugs	Phenacetin, caffeine, estradiol	Present in most human livers, induced by cigarette smoke
Subfamily CYP2A			
CYP2A1		Testosterone	Expressed in liver
CYP2A6		Coumarin	Expressed in liver. Important in precarcinogen activation. Exhibits significant ethnic-related genotypic or phenotypic deficiencies
Subfamily CYP1B			
CYP1B1		7-ethoxyresorufin	TCDD inducible in keratinocytes, present in other tissues after exposure to inducers
Subfamily CYP2B			
CYP2B1		Testosterone	Expressed in liver and extrahepatic tissues
CYP2B6		Coumarin, cyclophosphamide	Expressed in human liver. Activates aflatoxin B1. Induced by phenobarbital

Table 187 Major Cytochrome P450 Enzymes (Continued)

	Substrates	Substrate Examples	Comments
Subfamily CYP2C			
20% of human liver cytochrome P450 enzymes metabolizes ~10% of drugs			
CYP2C8		Paclitaxel	Expressed in human liver and at lower levels in intestine. CYP2C in rats
CYP2C9	Neutral or acidic, often amphipathic drugs	Diclofenac, ibuprofen	Expressed in human liver and at lower levels in intestine
CYP2C19	Limited range of drugs, primarily psychotherapeutic agents	(*S*)-mephenytoin phenobarbitone	Expressed in human liver and at lower levels in intestine. Polymorphic in humans
Subfamily CYP2D			
2% of human liver cytochrome P450 enzymes metabolizes ~30% of drugs			
CYP2D1		Bufuralol, debrisoquine	Rat and human
CYP2D6	Lipophylic aryl-alkyl-amines	Bufuralol, amitriptyline, haloperidol, chlorpromazine, lidocaine, oxycodone	Responsible for a common genetic defect in oxidation of many drugs in humans. Not inducible
Subfamily CYP2E			
7% of human liver cytochrome P450 enzymes metabolizes ~2% of drugs			
CYP2E1	Drugs with mol. wt. < 200, volatile anesthetics	p-Nitrophenol, benzene, ethanol, aniline, chlorzoxazone, acetaminophen, and halothane	Expressed in human liver and inducible by a variety of mechanisms

Table 187 Major Cytochrome P450 Enzymes (Continued)

	Substrates	Substrate Examples	Comments
Subfamily CYP3A			
30% of human liver cytochrome P450 enzymes metabolizes ~50% of drugs			
CYP3A3			Expressed in liver of most adults
CYP3A4	A wide range of lipopyhilic, neutral, or basic compounds.	6β-testosterone, erythromycin, cyclosporin, terfenidine, verapamil, and hydorcortisone	Most abundant P450 in human liver. Plays a major role in the metabolism of drugs
CYP3A5		See CYP3A4	Expressed in about 20% of human liver samples
CYP3A7		See CYP3A4	Expressed in human fetal liver and kidney
Subfamily CYP4A			
CYP4A11		Lauric acid	Not extensively studied in humans

Note: Bold = key enzyme in drug metabolism.

Table 188 Xenobiotic Steady State and Half-Life

Number of Half-Life	Xenobiotic Steady State (%)	Xenobiotic Left in Body (%)
1	50.00	50.00
2	75.00	25.00
3	87.50	12.50
4	93.75	6.25
5	96.87	3.13

Note: It takes four to five half-life values to reach the steady state.

Table 189 Greek Alphabet

Greek Letter		Greek Name	English Equivalent	Greek Letter		Greek Name	English Equivalent
A	α	Alpha	a	N	ν	Nu	n
B	β	Beta	b	Ξ	ξ	Xi	x
Γ	γ	Gamma	g	O	o	Omicron	o
Δ	δ	Delta	d	Π	π	Pi	p
E	ε	Epsilon	ĕ	P	ρ	Rho	r
Z	ζ	Zeta	z	Σ	σ	Sigma	s
H	η	Eta	$\bar{e}$	T	τ	Tau	t
Θ	θ ϑ	Theta	th	Y	υ	Upsilon	u
I	ι	Iota	i	Φ	ϕ φ	Phi	ph
K	κ	Kappa	k	X	χ	Chi	ch
Λ	λ	Lambda	l	Ψ	ψ	Psi	ps
M	μ	Mu	m	Ω	ω	Omega	o

Source: From Beyer, W.H. (1991).

Table 190 Prefixes and Symbols for Decimal Multiples and Submultiples

Factor	Prefix	Symbol
10^{18}	exa	E
10^{15}	peta	P
10^{12}	tera	T
10^{9}	giga	G
10^{6}	mega	M
10^{3}	kilo	k
10^{2*}	hecto	h
10^{1*}	deka	da
10^{-1*}	deci	d
10^{-2*}	centi	c
10^{-3}	milli	m
10^{-6}	micro	μ
10^{-9}	nano	n
10^{-12}	pico	p
10^{-15}	femto	f
10^{-18}	atto	a

Note: The preferred multiples and submultiples listed above change the quantity by increments of 10^{3} or 10^{-3}. The exceptions to these recommended factors are indicated by the asterisk.

Source: From Beyer, W.H. (1991).

Table 191 Table of Equivalents

kg	=	1000 g, 1 million mg, 2.2 lb
g	=	1000 mg, 1 million µg, approx. 0.035 oz.
mg	=	1000 µg, 1 million ng
µg	=	1000 ng
l	=	approx. 1 quart, approx. 33 oz.
lb	=	16 oz., 454.5 g, 0.45 kg
oz.	=	28.4 g
acre	=	4047 m^2
hectare	=	2.5 acres
cm^2	=	0.0001 m^2
m^2	=	10,000 cm^2
When referring to the concentration of a chemical in food or other medium:		
mg/kg	=	ppm, µg/g
mg/L	=	ppm = 0.0001%
µg/kg	=	ppb, ng/g
ng/kg	=	ppt
ppm	=	mg/kg, µg/g
ppb	=	µg/kg, ng/g
ppt	=	ng/kg

Source: From Beyer, W.H. (1991); Lide, D.R. (1992).

Table 192 Approximate Metric and Apothecary Weight Equivalents

Metric	Apothecary	Metric	Apothecary
1 gram (g)	= 15 grains	0.05 g (50 mg)	= $^{3}/_{4}$ grain
0.6 g (600 mg)	= 10 grains	0.03 g (30 mg)	= $^{1}/_{2}$ grain
0.5 g (500 mg)	= $7^{1}/_{2}$ grains	0.015 g (15 mg)	= $^{1}/_{4}$ grain
0.3 g (300 mg)	= 5 grains	0.001 g (1 mg)	= 1/80 grain
0.2 g (200 mg)	= 3 grains	0.6 mg	= 1/100 grain
0.1 g (100 mg)	= $1^{1}/_{2}$ grains	0.5 mg	= 1/120 grain
0.06 g (60 mg)	= 1 grain	0.4 mg	= 1/150 grain

Approximate household, apothecary, and metric volume equivalents

Household	Apothecary	Metric
1 teaspoon (t or tsp)	= 1 fluidram (f_3)	= 4 or 5 mL[a]
1 tablespoon (T or tbs)	= $^{1}/_{2}$ fluid ounce (f_3)	= 15 mL
2 tablespoons	= 1 fluid ounce	= 30 mL
1 measuring cupful	= 8 fluid ounces	= 240 mL
1 pint (pt)	= 16 fluid ounces	= 473 mL
1 quart (qt)	= 32 fluid ounces	= 946 mL
1 gallon (gal)	= 128 fluid ounces	= 3785 mL

[a] 1 mL = 1 cubic centimeter (cc); however, mL is the preferred measurement term today.

Source: From Beyer, W.H. (1991).

Table 193 Conversion Factors: Metric to English

To Obtain	Multiply	By
Inches	Centimeters	0.3937007874
Feet	Meters	3.280839895
Yards	Meters	1.093613298
Miles	Kilometers	0.6213711922
Ounces	Grams	$3.527396195 \times 10^{-2}$
Pounds	Kilograms	2.204622622
Gallons (U.S. Liquid)	Liters	0.2641720524
Fluid ounces	Milliliters (cc)	$3.381402270 \times 10^{-2}$
Square inches	Square centimeters	0.1550003100
Square feet	Square meters	10.76391042
Square yards	Square meters	1.195990046
Cubic inches	Milliliters (cc)	$6.102374409 \times 10^{-2}$
Cubic feet	Cubic meters	35.31466672
Cubic yards	Cubic meters	1.307950619

Source: From Beyer, W.H. (1991).

Table 194 Conversion Factors: English to Metric

To Obtain	Multiply	By
Microns	Mils	25.4
Centimeters	Inches	**2.54**
Meters	Feet	**0.3048**
Meters	Yards	**0.9144**
Kilometers	Miles	**1.609344**
Grams	Ounces	28.34952313
Kilograms	Pounds	**0.45359237**
Liters	Gallons (U.S. Liquid)	**3.785411784**
Milliliters (cc)	Fluid ounces	29.57352956
Square centimeters	Square inches	**6.4516**
Square meters	Square feet	**0.09290304**
Square meters	Square yards	**0.83612736**
Milliliters (cc)	Cubic inches	**16.387064**
Cubic meters	Cubic feet	$2.831684659 \times 10^{-2}$
Cubic meters	Cubic yards	0.764554858

Note: Boldface numbers are exact; others are given to ten significant figures where so indicated by the multiplier factor.

Source: From Beyer, W.H. (1991).

Table 195 Temperature Conversion Factors

°F = 9/5 (°C) + 32
Fahrenheit temperatures = 1.8 (temperature in kelvins) – 459.67
°C = 5/9 [(°F) – 32)]
Celsius temperature = temperature in kelvins – 273.15
Fahrenheit temperature = 1.8 (Celsius temperature) + 32

Conversion of Temperatures

From	To	
°Celsius	°Fahrenheit	$t_F = (t_C \times 1.8) + 32$
	Kelvin	$T_K = t_C + 273.15$
	°Rankine	$T_R = (t_C + 273.15) \times 18$
°Fahrenheit	°Celsius	$t_C = \frac{t_F - 32}{1.8}$
	Kelvin	$T_K = \frac{t_F - 32}{1.8} + 273.15$
	°Rankine	$T_R = t_F + 459.67$
Kelvin	°Celsius	$t_C = T_K - 273.15$
	°Rankine	$T_R = T_K \times 1.8$
°Rankine	°Fahrenheit	$t_F = T_R - 459.67$
	Kelvin	$T_K = \frac{T_R}{1.8}$

Source: From Beyer, W.H. (1991); Lide, D.R. (1992).

Table 196 Temperature Conversions

°F	°C	°F	°C	°F	°C	°F	°C	°F	°C
–10	–23.3	35	+1.6	85	29.4	135	57.2	185	85.0
–5	–20.5	40	4.4	90	32.2	140	60.0	190	87.8
0	–17.8	45	7.2	95	35.0	145	62.8	195	90.5
+5	–15.0	50	10.0	100	37.8	150	65.5	200	93.3
10	–12.2	55	12.8	105	40.5	155	68.3	205	96.1
15	–9.4	60	15.5	110	43.3	160	71.1	210	98.9
20	–6.6	65	18.3	115	46.1	165	73.9	212	100
25	–3.9	70	21.1	120	48.9	170	76.6		
30	–1.1	75	23.9	125	51.6	175	79.4		
32	0	80	26.6	130	54.4	180	82.2		

Table 197 Conversion of Human Hematological Values from Traditional Units into SI Units

Constituent	Traditional Units	Multiplication Factor	SI Units
Clotting time	min	60	sec
Prothrombin time	sec	1.0	sec
Hematocrit (erythrocytes, volume fraction)	%	0.01	fraction of 1
Hemoglobin	g/100 mL	0.6205	mmol/L
Leukocyte count (leukocytes, number concentration)	per mm^3	10^6	10^9/L
Erythrocyte count (erythrocytes, number concentration)	million per mm^3	10^6	10^{12}/L
Mean corpuscular volume (MCV)	μ^3	1.0	fL
Mean corpuscular hemoglobin (MCH) (Erc-Hemoglobin, amount of substance)	pg	0.06205	fmol
Mean corpuscular hemoglobin concentration (MCHC) (Erc-Hemoglobin, substance concentration)	%	0.6205	mmol/L
Erythrocyte sedimentation rate	mm/hr	1.0	mm/hr
Platelet count (blood platelets, number concentration)	mm^3	10^6	10^9/L
Reticulocyte count (Erc-Reticulocytes, number fraction)	% red cells	0.01	fraction of 1

Note: To convert xenobiotic concentrations to or from SI units: Conversion factor (CF) = 1000/mol. wt.; conversion *to* SI units: µg/mL × CF = µmol/L; conversion *from* SI units: µmol/L ÷ CF = µg/mL.

Source: From Young, D.S. (1975).

Table 198 Conversion of Laboratory Values from Traditional Units into SI Units

Constituent	Traditional Units	Multiplication Factor	SI Units
Bilirubin (direct)	mg/100 mL	43.06	µmol/L
Conjugated	mg/100 mL	17.10	µmol/L
Total	mg/100 mL	17.10	µmol/L
Calcium	mg/100 mL	0.2495	mmol/L
Carbon dioxide	mEq/L	1.0	mmol/L
Chloride	mEq/L	1.0	mmol/L
Creatine phosphokinase (CPK)	mU/mL	0.01667	µmol S^{-1}/L
Creatinine	mg/100 mL	88.40	µmol/L
Glucose	mg/100 mL	0.05551	mmol/L
Lactic dehydrogenase	mU/mL	0.01667	µmol S^{-1}/L
Cholesterol	mg/100 mL	0.02586	mmol/L
Magnesium	mEq/L	0.50	mmol/L
P_{CO2}	mmHg	0.1333	kPa
P_{O2}	mmHg	0.133	kPa
Phosphorus, inorganic	mg/100 mL	0.3229	mmol/L
Protein, total	g/100 mL	10	g/L
Protein, electrophoreses			
Albumin	% total	0.01	fraction of 1
Globulin, α_1	% total	0.01	fraction of 1
α_2	% total	0.01	fraction of 1
β	% total	0.01	fraction of 1
γ	% total	0.01	fraction of 1
Potassium	mEq/L	1.0	mmol/L
Sodium	mEq/L	1.0	mmol/L
Urea nitrogen	mg/100 mL	0.3569	mmol/L
Uric acid	mg/100 mL	0.65948	mmol/L

Source: Modified from Young, D.S. (1975).

Table 199 Transformation of Percentages into Logits

Percentage	0	1	2	3	4	5	6	7	8	9
50	0	0.04	0.08	0.12	0.16	0.20	0.24	0.28	0.32	0.36
60	0.41	0.45	0.49	0.53	0.58	0.62	0.66	0.71	0.75	0.80
70	0.85	0.90	0.94	0.99	1.05	1.10	1.15	1.21	1.27	1.32
80	1.38	1.45	1.52	1.59	1.66	1.73	1.82	1.90	1.99	2.09
90	2.20	2.31	2.44	2.59	2.75	2.94	3.18	3.48	3.89	4.60
99	4.60	4.70	4.82	4.95	5.11	5.29	5.52	5.81	6.21	6.91

Source: From Tallarida, R.J. (1992).

Table 200 Transformation of Percentages into Probits

Percentage	0	1	2	3	4	5	6	7	8	9
0	[—]	2.67	2.95	3.12	3.25	3.36	3.45	3.52	3.59	3.66
10	3.72	3.77	3.82	3.87	3.92	3.96	4.01	4.05	4.08	4.12
20	4.16	4.19	4.23	4.26	4.29	4.33	4.36	4.39	4.42	4.45
30	4.48	4.50	4.53	4.56	4.59	4.61	4.64	4.67	4.69	4.72
40	4.75	4.77	4.80	4.82	4.85	4.87	4.90	4.92	4.95	4.97
50	5.00	5.03	5.05	5.08	5.10	5.13	5.15	5.18	5.20	5.23
60	5.25	5.28	5.31	5.33	5.36	5.39	5.41	5.44	5.47	5.50
70	5.52	5.55	5.58	5.61	5.64	5.67	5.71	5.74	5.77	5.81
80	5.84	5.88	5.92	5.95	5.99	6.04	6.08	6.13	6.18	6.23
90	6.28	6.34	6.41	6.48	6.55	6.64	6.75	6.88	7.05	7.33
99	7.33	7.37	7.41	7.46	7.51	7.58	7.65	7.75	7.88	8.07

Source: From Tallarida, R.J. (1992).

Table 201 Molarity, Molality, Normality, Osmolarity Calculations

1. $$\text{Molarity (M)} = \frac{\text{number of moles of solute}}{\text{liter of solution}}$$

   $$\text{Where: Number of moles} = \frac{\text{grams of chemical}}{\text{molecular weight}}$$

2. $$\text{Molality (m)} = \frac{\text{number of moles of solute}}{\text{kilogram of solution}}$$

3. $$\text{Normality (N)} = \frac{\text{number of equivalents of solute}}{\text{liter of solution}}$$

   $$\text{Where: Number of equivalents} = \frac{\text{grams of chemical}}{\text{equivalent weight}}$$

   $$\text{Equivalent weight} = \frac{\text{molecular weight}}{n}$$

   For acids and basis, n = The number of replaceable H^+ or OH^- ions per molecule

4. Normality = n Molarity
   Where: n = number of replaceable H^+ or OH^- ions per molecule
5. Osmolarity = n Molarity
   Where: n = number of dissociable ions per molecule

Table 202 Solution Calculations

1. $$\text{Volume percent (\% v/v)} = \frac{\text{Volume of solute}}{\text{Volume of solution}} \times 100$$

2. $$\text{Weight percent (\% w/w)} = \frac{\text{Weight of solute}}{\text{Weight of solution}} \times 100$$

3. $$\text{Weight/volume percent (\% w/v)} = \frac{\text{Weight of solute (g)}}{\text{Volume of solution (ml)}} \times 100$$

4. $$\text{Milligram percent (mg\%)} = \frac{\text{Weight of solute (mg)}}{\text{100 mL of solution}} \times 100$$

5. $$\text{Parts per million (ppm)} = \frac{\text{Weight of solute}}{\text{Weight of solution}} \times 10^6$$

6. Parts per million (for gases)

$$\text{ppm} = \frac{(\text{mg}/\text{m}^3)(\text{R})}{\text{Molecular weight}}$$

Where: R = 24.5 at 25°C.

7. (volume C) (concentration C) = (volume D) (concentration D)
Where: C = Concentrated solution
D = Dilute solution

This relationship is useful in preparing dilute solutions from concentrated solutions.

Table 203 pH Calculations

1. $pH = -\log[H^+] = \log \frac{1}{[H+]}$

2. $pH = pKa + \log \frac{[A^\pm]}{[HA]}$

Where: $HA \leftrightarrow H^+ + A^-$
(weak acid) (conjugate base)
$pK_a = -\log Ka$
(equilibrium constant)

Table 204 Information Disclosed on a Material Safety Data Sheet (MSDS)

SECTION 1.	**Chemical Product and Company Identification**
	Product Name
	Generic Names/Synonyms
	Product Use
	Manufacturer's Name and Address
	Name and Phone Number of the Person/Group Who Prepared the MSDS
	Date MSDS was Prepared
	Emergency Phone Number
SECTION 2.	**Composition/Information on Ingredients**
	Ingredient Names
	CAS Numbers
	Percentage by Weight
SECTION 3.	**Hazards Identification**
	Potential Human Health Hazards:
	To Skin (irritancy, sensitization)
	To Eyes (irritancy)
	Via Inhalation (acute effects)
	Via Ingestion (acute effects)
	Delayed Effects (chronic effects)
	Carcinogenicity, reproductive and developmental effects, mutagenicity, other
SECTION 4.	**First Aid Measures**
	Specific First-Aid Measures for Various Routes of Exposure
	Notes to Physician Including Antidotes and Medical Conditions Affected by the Product

Table 204 Information Disclosed on a Material Safety Data Sheet (MSDS) (Continued)

SECTION 5.	**FireFighting Measures**	
	Flammable Properties (flashpoint, autoignition temperature, etc.)	
	Extinguishing Media	
	Hazardous Combustion Products	
	Explosion Hazards	
	Firefighting Precautions and Instructions	
SECTION 6.	**Accidental Release Measures**	
	Procedures to be Followed in Case of Spill or Other Release	
SECTION 7.	**Handling and Storage**	
	Normal Handling Procedures	
	Storage Recommendations	
SECTION 8.	**Exposure Controls/Personal Protection**	
	Engineering Controls	
	Personal Protective Equipment	
	Exposure Guidelines (TLV, PEL, other)	
SECTION 9.	**Physical and Chemical Properties**	
	Appearance	Boiling Point
	Physical State	Melting Point
	Odor	Vapor Pressure
	Specific Gravity	Vapor Density
	Solubility	Evaporation Rate
	pH	Percent Volatiles
SECTION 10.	**Stability and Reactivity**	
	Stability Conditions	
	Incompatibilities	
	Hazardous Decomposition Products	
	Hazardous Polymerization	
SECTION 11.	**Toxicity Information**	
	Acute Effects (LD_{50}, LC_{50})	
	Subchronic and Chronic Effects	
	Irritancy	
	Sensitization	
	Neurotoxicity	
	Reprotoxicity	
	Developmental Toxicity	
	Mutagenicity	
SECTION 12.	**Ecological Information**	
	Aquatic Toxicity	
	Terrestrial Toxicity	

Table 204 Information Disclosed on a Material Safety Data Sheet (MSDS) (Continued)

	Bioaccumulation Potential
	Biodegradability
	Microbial Toxicity
SECTION 13.	**Disposal Information**
SECTION 14.	**Shipping Information**
	D.O.T. Hazard Class
	D.O.T. I.D. Number
SECTION 15.	**Regulatory Information**
	TSCA Inventory Status
	Other Federal, State, Local
	Foreign Regulatory Information
SECTION 16.	**Information not covered in the other 15 sections**

Table 205 Mammalian Toxicology Tests—Cost and Material Requirements

Study Type	Typical Costs[d]($)	Estimated Material Requirements[e]
Acute Oral Toxicity in Rats, Limit Test	4,000	25 g
Acute Oral Toxicity in Rats, LD_{50} (4 levels)	14,000	50 g
Acute Dermal Toxicity in Rabbits, Limit Test	5,000	50 g
Acute Dermal Toxicity in Rabbits, LD_{50} (4 levels)	16,000	100 g
Acute Whole-Body Inhalation Toxicity in Rats, Limit Test	20,000	100–5,000 g
Acute Whole-Body Inhalation Toxicity in Rats, LC_{50}	50,000	500–50,000 g
Primary Eye Irritation in Rabbits[a]	3,800	7.5 g
Primary Skin Irritation in Rabbits[a]	3,800	7.5 g
Dermal Sensitization in G. Pigs, Maximization[b]	12,000	40–80 g
Dermal Sensitization in G. Pigs, Buehler Type[b,c]	10,500	40–80 g
1-Month Oral Toxicity in Rats, Gavage	200,000	250 g
1-Month Whole-Body Inhalation Toxicity in Rats	325,000	1–200 kg
1-Month Intravenous Toxicity in Rats	240,000	20 g
1-Month Dermal Toxicity in Rats	220,000	250 g
1-Month Oral Toxicity in Dogs, Capsule	290,000	2.5 kg
1-Month Intravenous Toxicity in Dogs	300,000	200 g
3-Month Oral Toxicity in Rats, Gavage	325,000	750 g
3-Month Dietary Toxicity Study in Rats	300,000	800 g
3-Month Whole-Body Inhalation Toxicity in Rat	550,000	3–600 kg
3-Month Dermal Toxicity in Rats	350,000	750 g
3-Month Oral Toxicity in Dogs, Capsule	350,000	8 kg
3-Month Dietary Toxicity Study in Dogs	375,000	10 kg
6-Month Oral Toxicity in Rats, Gavage	450,000	2 kg
1-Year Oral Toxicity in Dogs, Capsule	1,300,000	30 kg
24-Month Oncogenicity in Mice, Gavage	1,750,000	1.5 kg
24-Month Oncogenicity in Rats, Gavage	1,750,000	18 kg
24-Month Whole-Body Inhalation in Rats	3,750,000	20–4,000 kg
General Fertility and Reproductive Performance (Segment 1) in Rats	200,000	750 g
Developmental Toxicity Study (Segment II) in Rats	115,000	200 g
Range-Finding Developmental Toxicity Study in Rabbits	60,000	400 g

Table 205 Mammalian Toxicology Tests—Cost and Material Requirements (Continued)

Study Type	Typical Costs[d]($)	Estimated Material Requirements[e]
Developmental Toxicity Study (Segment II) in Rabbits	175,000	800 g
Perinatal and Postnatal Study (Segment III) in Rats	270,000	750 g
2-Generation Reproduction Study in Rats	450,000	8 kg

[a] Additional cost if extended observation periods are required.

[b] Additional cost for positive control.

[c] Number of induction times may vary.

[d] Based on 2007 costs. Costs generally increase by 4–7% per year at a minimum.

[e] Material requirements, especially for longer-term studies by whole-body inhalation, can vary considerably depending on toxic potency of the chemical substance as well as its physical properties (e.g., dust versus gas for inhalation studies).

Table 206 Genetic Toxicology Tests—Cost and Material Requirements

Study Type	Typical Costs[a] ($)	Estimated Material Requirements (g)
Ames Assay	6,000	1.5–5
Mouse Lymphoma Assay	29,000	5
In Vitro Chromosome Aberrations (CHO)	24,000	5
In Vitro Chromosome Aberrations (Human Lymphocytes)	33,000	5
In Vitro Chromosome Aberrations (Rat Lymphocytes)	32,000	5
In Vivo Chromosome Aberrations (Mouse Bone Marrow)	49,000	10–15
In Vivo Chromosome Aberrations (Rat Bone Marrow)	50,000	60
In Vitro Unscheduled DNA Synthesis (UDS)	15,000	5
In Vivo/In Vitro UDS	48,000	25–50
In Vitro SHE Cell Transformation (Syrian Hamster Embryo Cells)	20,000	25–30
Mouse Micronucleus	11,000 (males) 22,000 (males and females)	10–15
In Vitro Sister Chromatid Exchange (SCE)	12,000	5
In Vivo SCE (Mouse)	33,000	15

[a] Based on 2007 costs. Costs generally increase by 4%–7% per year at a minimum.

Table 207 Aquatic/Ecotoxicology Tests—Cost and Material Requirements

Study Type	Typical Costs [a] ($)	Estimated Material Requirements (g)
Fish Static Acute (96 hr)	4,500	10
Fish Early Life Stage	44,000	350
Daphnid Static Acute (48 hr)	4,200	5
Daphnid 21-Day Chronic Reproduction	20,000	100
Algal Static Acute (96 hr)	5,000	5
Algal Static 14-Day	13,000	5
Fish Bioconcentration	78,000	200
Earthworm (48 hr — Filter Paper)	5,000	5
Earthworm (14-Day — Soil)	6,500	30

[a] Based on 2007 costs. Costs generally increase by 4%–7% per year at a minimum.

Table 208 Chemical Functional Groups

Acetamido (acetylamino)	$CH_3CONH–$
Acetimido (acetylimino)	$CH_3C(=NH)–$
Acetoacetamido	$CH_3COCH_2CONH–$
Acetoacetyl	$CH_3COCH_2CO–$
Acetonyl	CH_3COCH_2
Acetonylidene	$CH_3COCH=$
Acetyl	$CH_3CO–$
Acrylyl	$CH_2=CHCO–$
Adipyl (from adipic acid)	$–OC(CH_2)_4CO–$
Alanyl (from alanine)	$CH_3CH(NH_2)CO–$
β-Alanyl	$H\ N(CH_2)_2CO–$
Allophanoyl	$H_2NCONHCO–$
Allyl (2-propenyl)	$CH_2=CHCH_2–$
Allylidene (2-propenylidene)	$CH_2=CHCH=$
Amidino (aminoiminomethyl)	$H_2NC(=NH)–$
Amino	$H_2N–$

Table 208 Chemical Functional Groups (Continued)

Amyl (pentyl)	$CH_3(CH_2)_4$–
Anilino (phenylamino)	C_6H_5NH–
Anisidino	$CH_3OC_6H_4NH$–
Anisyl (from anisic acid)	$CH_3OC_6H_4CO$–
Anthranoyl (2-aminobenzoyl)	2-$H_2NC_6H_4CO$–
Arsino	AsH_2–
Azelaoyl (from azelaic acid)	–$OC(CH_2)_7CO$–
Azido	N_3–
Azino	=NN=
Azo	–N=N–
Azoxy	–N(O)N–
Benzal	C_6H_5CH=
Benzamido (benzylamino)	C_6H_5CONH–
Benzhydryl (diphenylmethyl)	$(C_6H_5)_2CH$–
Benzimido (benzylimino)	$C_6H_5C(=NH)$–
Benzoxy (benzoyloxy)	C_6H_5COO–
Benzoyl	C_6H_5CO–
Benzyl	$C_6H_5CH_2$–
Benzylidine	C_6H_5CH=
Benzyldyne	$C_6H_5C\equiv$
Biphenylyl	$C_6H_5C_6H_5$–
Biphenylene	–$C_6H_4C_6H_4$–
Butoxy	C_4H_9O–
sec-Butoxy	$C_2H_5CH(CH_3)O$–
tert-Butoxy	$(CH_3)_3CO$–
Butyl	$CH_3(CH_2)_3$–
iso-Butyl (3-methylpropyl)	$(CH_3)_2(CH_2)_2$–
sec-Butyl (1-methylpropyl)	$C_2H_5CH(CH_3)$–
tert-Butyl (1,1, dimethylethyl)	$(CH_3)_3C$–
Butyryl	C_3H_7CO–
Caproyl (from caproic acid)	$CH_3(CH_2)_4CO$–
Capryl (from capric acid)	$CH_3(CH_2)_6CO$–
Caprylyl (from caprylic acid)	$CH_3(CH_2)_6CO$–
Carbamido	H_2NCONH–
Carbamoyl (aminocarbonyl)	H_2NCO–
Carbamyl (aminocarbonyl)	H_2NCO–

Table 208 Chemical Functional Groups (Continued)

Carbazoyl (hydrazinocarbonyl)	$H_2NNHCO–$
Carbethoxy	$C_2H_5O_2C–$
Carbobenzoxy	$C_6H_5CH_2O_2C–$
Carbonyl	–C=O–
Carboxy	HOOC–
Cetyl	$CH_3(CH_2)_{15}–$
Chloroformyl (chlorocarbonyl)	CLCO–
Cinnamyl (3-phenyl-2-propenyl)	$C_6H_5CH=CHCH_2–$
Cinnamoyl	$C_6H_5CH=CHCO–$
Cinnamylidene	$C_6H_5CH=CHCH=$
Cresyl (hydroxymethylphenyl)	$HO(CH_3)C_6H_4–$
Crotoxyl	$CH_3CH=CHCO–$
Crotoyl (2-butenyl)	$CH_3CH=CHCH_2$
Cyanamido (cyanoamino)	NCNH–
Cyanato	NCO–
Cyano	NC–
Decanedioyl	$–OC(CH_2)_6CO–$
Decanoly	$CH_3(CH_2)_6CO–$
Diazo	$N_2=$
Diazoamino	–NHN=N–
Disilanyl	$H_2SiSiH_2–$
Disiloxanoxy	$H_3SiOSiH_2O)–$
Disulfinyl	–S(O)S(O)–
Dithio	–SS–
Enanthyl	$CH_3(CH_2)_5CO–$
Epoxy	–O–
Ethenyl (vinyl)	$CH_2=CH–$
Ethinyl	HC≡C–
Ethoxy	$C_2H_5O–$
Ethyl	$CH_3CH_2–$
Ethylthio	C_2H_5S
Formamido (formylamino)	HCONH–
Formyl	HCO–
Fumaroyl (from fumaric acid)	–OCCH=CHCO–
Furfuryl (2-furanylmethyl)	$OC_4H_3CH_2–$
Furfurylidene (2-furanylmethylene)	$OC_4H_3CH=$
Furyl (furanyl)	$OC_4H_3–$
Glutamyl (from glutamic acid)	$–OC(CH_2)_2CH(NH_2)CO–$

Table 208 Chemical Functional Groups (Continued)

Glutaryl (from glutaric acid)	$-OC(CH_2)CO-$
Glycidyl (oxiranylmethyl)	CH_2-CHCH_2-
Glycinamido	H_2NCH_2CONH-
Glycolyl (hydroxyacetyl)	$HOCH_2CO-$
Glycyl (aminoacetyl)	H_2NCH_2CO-
Glyoxylyl (oxoacetyl)	$HCOCO-$
Guanidino	$H_2NC(=NH)NH-$
Guanyl	$H_2NC(=NH)-$
Heptadecanoyl	$CH_3(CH_2)_{15}CO-$
Heptanamido	$CH_3(CH_2)_{15}CONH-$
Heptanedioyl	$-OC(CH_2)_5CO-$
Heptanoyl	$CH_3(CH_2)_5CO-$
Hexadecanoyl	$CH_3(CH_2)_4CO-$
Hexamethylene	$-(CH_2)_6-$
Hexanedioyl	$-OC(CH_2)_4CO-$
Hippuryl (*N*-benzoylglycyl)	$C_6H_5CONHCH_2CO-$
Hydantoyl	$H_2NCONHCH_2CO-$
Hydrazino	N_2NNH-
Hydrazo	$-HNNH-$
Hydrocinnamoyl	$C_6H_5(CH_2)_2CO-$
Hydroperoxy	$HOO-$
Hydroxamino	$HONH-$
Hydroxy	$HO-$
Imino	$HN=$
Iodoso	$OI-$
Isoamyl (isopentyl)	$(CH_3)_2CH(CH_2)_2-$
Isobutenyl (2-methyl-1-propenyl)	$(CH_3)_2C=CH-$
Isobutoxy	$(CH_3)_2CHCHO-$
Isobutyl	$(CH_3)_2CHCH_2-$
Isobutylidene	$(CH_3)_2CHCH=$
Isobutyryl	$(CH_3)_2CHCO-$
Isocyanato	$OCN-$
Isocyano	$CN-$
Isohexyl	$(CH_3)_2CH(CH_2)_3-$
Isoleucyl (from isoleucine)	$C_2H_3CH(CH_3)CH(NH_4)CO-$
Isonitroso	$HON=$
Isopentyl	$(CH_3)_2CH(CH_2)_2-$
Isopentylidene	$(CH_3)_2CHCH_2CH=$
Isopropenyl	$H_2C=C(CH_3)-$

Table 208 Chemical Functional Groups (Continued)

Isopropoxy	$(CH_3)_2CHO–$
Isopropyl	$(CH_3)_2CH–$
Isopropylidene	$(CH_3)_2C=$
Isothiocyanato (isothiocyano)	SCN–
Isovaleryl (from isovaleric acid)	$(CH_3)_2CHCH_2CO–$
Keto (oxo)	O=
Lactyl (from lactic acid)	$CH_3CH(OH)CO–$
Lauroyl (from lauric acid)	$CH_3(CH_2)_{10}CO–$
Laucyl (from leucine)	$(CH_3)_2CHCH_2CH(NH_2)CO–$
Levulinyl (from levulinic acid)	$CH_3CO(CH_2)_2CO–$
Malonyl (from malonic acid)	$–OCCH_2CO–$
Mandelyl (from mandelic acid	$C_6H_5CH(OH)CO–$
Mercapto	HS–
Methacrylyl (from methacrylic acid)	$CH_2=C(CH_3)CO–$
Methallyl	$CH_2=C(CH_3)CH_2–$
Methionyl (from methionine)	$CH_3SCH_2CH_2CH(NH_2)CO–$
Methoxy	$CH_3O–$
Methyl	$H_3C–$
Methylene	$H_2C=$
Methylenedioxy	$–OCH_2O–$
Methylenedisulfonyl	$–O_2SCH_2SO_2–$
Methylol	$HOCH_2–$
Methylthio	$CH_2S–$
Myristyl (from myristic acid)	$CH_3(CH_2)_{12}CO–$
Naphthal	$(C_{10}H_7)CH=$
Naphthobenzyl	$(C_{10}H_7)CH_2–$
Naphthoxy	$(C_{10}H_7)O–$
Naphthyl	$(C_{10}H_7)–$
Naphthylidene	$(C_{10}H_6)=$
Neopentyl	$(CH_3)_3CCH_2–$
Nitramino	$O_2NNH–$
Nitro	$O_2N–$
Nitrosamino	ONNH–
Nitrosimino	ONN=
Nitroso	ON–
Nonanoyl (from nonanoic acid)	$CH_3(CH_2)_7CO–$

Table 208 Chemical Functional Groups (Continued)

Oleyl (from oleic acid)	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO–$
Oxalyl (from oxalic acid)	–OCCO–
Oxamido	$H_2NCOCONH–$
Oxo (keto)	O=
Palmityl (from palmitic acid)	$CH_3(CH_2)_{14}CO–$
Pelargonyl (from pelargonic acid)	$CH_3(CH_2)_7CO–$
Pentamethylene	$–(CH_2)_5–$
Pentyl	$CH_3(CH_2)_4–$
Phenacyl	$C_6H_5COCH_2–$
Phenacylidene	$C_6H_5COCH{=}$
Phenanthryl	$(C_{14}H_9)–$
Phenethyl	$C_6H_5CH_2CH_2–$
Phenoxy	$C_6H_5O–$
Phenyl	$C_6H_5–$
Phenylene	$–C_6H_4–$
Phenylenedioxy	$–OC_6H_4O–$
Phosphino	$H_2P–$
Phosphinyl	$H_2P(O)–$
Phospho	$O_2P–$
Phosphono	$(HO)_2P(O)–$
Phthalyl (from phthalic acid)	$1,2\text{-}C_6H_4(CO–)_2$
Picryl (2,4,6-trinitrophenyl)	$2,4,6\text{-}(NO_2)_2C_6H_2–$
Pimelyl (from pimelic acid)	$–OC(CH_2)_5CO–$
Piperidino	$C_5H_{10}N–$
Piperidyl (piperidinyl)	$(C_5H_{10}N)–$
Piperonyl	$3,4\text{-}(CH_2O_2)C_6H_3CH_2–$
Pivalyl (from pivalic acid)	$(CH_3)_3CCO–$
Prenyl (3-methyl-2-butenyl)	$(CH_3)_2C{=}CHCH_2–$
Propargyl (2-propynyl)	$HC{\equiv}CCH_2–$
Propenyl	$CH_2{=}CHCH_2–$
iso-Propenyl	$(CH_3)_2C{=}$
Propionyl	$CH_3CH_2CO–$
Propoxy	$CH_3CH_2CH_2O–$
Propyl	$CH_3CH_2CH_2–$
iso-Propyl	$(CH_3)_2CH–$
Propylidene	$CH_3CH_2CH{=}$
Pyridino	$C_5H_5N–$
Pyridyl (pyridinyl)	$(C_5H_4N)–$
Pyrryl (pyrrolyl)	$(C_3H_4N)–$

Table 208 Chemical Functional Groups (Continued)

Salicyl (2-hydroxybenzoyl)	$2\text{-}HOC_6H_4CO–$
Selenyl	HSe–
Seryl (from serine)	$HOCH_2CH(NH_2)CO–$
Siloxy	$H_3SiO–$
Silyl	$H_3Si–$
Silylene	$H_2Si=$
Sorbyl (from sorbic acid)	$CH_3CH=CHCH=CHCO–$
Stearyl (from stearic acid)	$CH_3(CH_2)_{16}CO–$
Styryl	$C_6H_5CH=CH–$
Suberyl (from suberic acid)	$–OC(CH_2)_6CO–$
Succinamyl	$H_2NCOCH_2CH_2CO–$
Succinyl (from succinic acid)	$–OCCH_2CH_2CO–$
Sulfamino	$HOSO_2NH–$
Sulfamyl	$H_2NSO–$
Sulfanilyl	$4\text{-}H_2NC_6H_4SO_2–$
Sulfeno	HOS–
Sulfhydryl (mercapto)	HS–
Sulfinyl	OS=
Sulfo	$HO_3S–$
Sulfonyl	$–SO_2–$
Terephthalyl	$1,4\text{-}C_6H_4(CO–)_2$
Tetramethylene	$–(CH_2)_4–$
Thenyl	$(C_4H_3S)CH–$
Thienyl	$(C_4H_3S)–$
Thiobenzoyl	$C_6H_5CS–$
Thiocarbamyl	$H_2NCS–$
Thiocarbonyl	–CS–
Thiocarboxy	HOSC–
Thiocyanato	NCS–
Thionyl (sulfinyl)	–SO–
Thiophenacyl	$C_6H_5CSCH_2–$
Thiuram (aminothioxomethyl)	$H_2NCS–$
Threonyl (from threonine)	$CH_3CH(OH)CH(NH_2)CO–$
Toluidino	$CH_3C_6H_4NH–$
Toluyl	$CH_3C_6H_4CO–$
Tolyl (methylphenyl)	$CH_3C_6H_4–$
α-Tolyl	$C_6H_5CH_2–$
Tolylene (methylphenylene)	$(CH_3C_6H_3)=$
α-Tolylene	$C_6H_5CH=$

Table 208 Chemical Functional Groups (Continued)

Tosyl [(4-methylphenyl) sulfonyl)]	$4\text{-}CH_3C_6H_4SO_2–$
Triazano	$H_2NNHNH–$
Trimethylene	$–(CH_2)_3–$
Triphenylmethyl (trityl)	$(C_6H_5)_3C–$
Tyrosyl (from tyrosine)	$4\text{-}HOC_6H_4CH_2CH(NH_2)CO–$
Ureído	$H_2NCONH–$
Valeryl (from valeric acid)	C_4H_9CO
Valyl (from valine)	$(CH_3)_2CHCH(NH_2)CO–$
Vinyl	$CH_2=CH–$
Vinylidene	$CH_2=C=$
Xenyl (biphenylyl)	$C_6H_5C_6H_4–$
Xylidino	$(CH_3)_2C_6H_3NH–$
Xylyl (dimethylphenyl)	$(CH_3)_2C_6H_3–$
Xylylene	$–CH_2C_6H_4CH_2–$

Source: From Lide, D.R. (1992).

Table 209 Standard Atomic Weights

(Scaled to A_r (^{12}C) = 12)

The atomic weights of many elements are not invariant but depend on the origin and treatment of the material. The footnotes to this table elaborate the types of variation to be expected for individual elements. The values of A_r (E) and uncertainty U_r (E) given here apply to elements as they exist naturally on earth.

Name	Sym.	Atomic Number	Atomic Weight	Footnotes			
Actinium*	Ac	89					A
Aluminum	Al	13	26.981539(5)				
Americium*	Am	95					A
Antimony (Stibium)	Sb	51	121.75(3)				
Argon	Ar	18	39.948(1)	g		r	
Arsenic	As	33	74.92159(2)				
Astatine*	At	85					A
Barium	Ba	56	137.327(7)				
Berkelium*	Bk	97					A
Beryllium	Be	4	9.012182(3)				
Bismuth	Bi	83	208.98037(3)				
Boron	B	5	10.811(5)	g	m	r	
Bromine	Br	35	79.904(1)				
Cadmium	Cd	48	112.411(8)	g			
Cesium	Cs	55	132.90543(5)				
Calcium	Ca	20	40.078(4)	g			
Californium*	Cf	98					A
Carbon	C	6	12.011(1)			r	
Cerium	Ce	58	140.115(4)	g			
Chlorine	Cl	17	35.4527(9)				
Chromium	Cr	24	51.9961(6)				
Cobalt	Co	27	58.93320(1)				
Copper	Cu	29	63.546(3)			r	
Curium*	Cm	96					A
Dysprosium	Dy	66	162.50(3)	g			
Einsteinium*	Es	99					A
Erbium	Er	68	167.26(3)	g			
Europium	Eu	63	151.965(9)	g			
Fermium*	Fm	100					A
Fluorine	F	9	18.9984032(9)				
Francium*	Fr	87					A

Table 209 Standard Atomic Weights (Continued)

Name	Sym.	Atomic Number	Atomic Weight	Footnotes			
Gadolinium	Gd	64	157.25(3)	g			
Gallium	Ga	31	69.723(1)				
Germanium	Ge	32	72.61(2)				
Gold	Au	79	196.96654(3)				
Hafnium	Hf	72	178.49(2)				
Helium	He	2	4.002602(2)	g		r	
Holmium	Ho	67	164.93032(3)				
Hydrogen	H	1	1.00794(7)	g	m	r	
Indium	In	49	114.82(1)				
Iodine	I	53	126.90447(3)				
Iridium	Ir	77	192.22(3)				
Iron	Fe	26	55.847(3)				
Krypton	Kr	36	83.80(1)	g	m		
Lanthanum	La	57	138.9055(2)	g			
Lawrencium*	Lr	103					A
Lead	Pb	82	207.2(1)	g		r	
Lithium	Li	3	6.941(2)	g	m	r	
Lutetium	Lu	71	174.967(1)	g			
Magnesium	Mg	12	24.3050(6)				
Manganese	Mn	25	54.93805(1)				
Mendelevium*	Md	101					A
Mercury	Hg	80	200.59(3)				
Molybdenum	Mo	42	95.94(1)				
Neodymium	Nd	60	144.24(3)	g			
Neon	Ne	10	20.1797(6)	g	m		
Neptunium*	Np	93					A
Nickel	Ni	28	58.69(1)				
Niobium	Nb	41	92.90638(2)				
Nitrogen	N	7	14.00674(7)	g		r	
Nobelium*	No	102					A
Osmium	Os	76	190.2(1)	g			
Oxygen	O	8	15.9994(3)	g		r	
Palladium	Pd	46	105.42(1)	g			
Phosphorus	P	15	30.973762(4)				
Platinum	Pt	78	195.08(3)				
Plutonium*	Pu	94					A
Polonium*	Po	84					A

Table 209 Standard Atomic Weights (Continued)

Name	Sym.	Atomic Number	Atomic Weight	Footnotes			
Potassium (Kalium)	K	19	39.0983(1)				
Praseodymium	Pr	59	140.90765(3)				
Promethium*	Pm	61					A
Protactinium*	Pa	91					
Radium*	Ra	88					A
Radon*	Rn	86					A
Rhenium	Re	75	186.207(1)				
Rhodium	Rh	45	102.90550(3)				
Rubidium	Rb	37	85.4678(3)	g			
Ruthenium	Ru	44	101.07(2)	g			
Samarium	Sm	62	150.36(3)	g			
Scandium	Sc	21	44.955910(9)				
Selenium	Se	34	78.96(3)				
Silicon	Si	14	28.0855(3)			r	
Silver	Ag	47	107.8682(2)	g			
Sodium (Natrium)	Na	11	22.989768(6)				
Strontium	Sr	38	87.62(1)	g		r	
Sulfur	S	16	32.066(6)			r	
Tantalum	Ta	73	180.9479(1)				
Technetium*	Tc	43					A
Tellurium	Te	52	127.60(3)	g			
Terbium	Tb	65	158.92534(3)				
Thallium	Tl	81	204.3833(2)				
Thorium*	Th	90	232.038(1)	g			Z
Thulium	Tm	69	168.93421(3)				
Tin	Sn	50	118.710(7)	g			
Titanium	Ti	22	47.88(3)				
Tungsten (Wolfram)	W	74	183.85(3)				
Unnilquadium	Unq	104					A
Unnilpentium	Unp	105					A
Unnihexium	Unh	106					A
Unnilseptium	Uns	107					A
Uranium*	U	92	238.0289(1)	g	m		Z
Vanadium	V	23	50.9415(1)				
Xenon	Xe	54	131.29(2)	g	m		

Table 209 Standard Atomic Weights (Continued)

Name	Sym.	Atomic Number	Atomic Weight	Footnotes
Ytterbium	Yb	70	173.04(3)	g
Yttrium	Y	39	88.90585(2)	
Zinc	Zn	30	65.39(2)	
Zirconium	Zr	40	91.224(2)	g

g = Geological specimens are known in which the element has an isotopic composition outside the limits for normal material. The difference between the atomic weight of the element in such specimens and that given in the table may exceed the implied uncertainty.

m = Modified isotopic compositions may be found in commercially available material because it has been subjected to an undisclosed or inadvertent isotopic separation. Substantial deviations in atomic weight of the element from that given in the table can occur.

r = Range in isotopic composition of normal terrestrial material prevents a more precise A_r (E) being given: the tabulated A_r (E) value should be applicable to any normal material.

A = Radioactive element that lacks a characteristic terrestrial isotopic composition.

Z = An element, without stable nuclides, exhibiting a range of trial compositions of long-lived radionuclides such that a meaningful atomic weight can be given.

* Element has no stable nuclides.

Source: From Pankow, J.F. (1991).

Table 210 Frequently Encountered Acronyms

AAALAC	Association for the Assessment and Accreditation of Laboratory Animal Care
AADA	Abbreviated Antibiotic Drug Application
AALAS	American Association for Laboratory Animal Science
AAPCO	Association of American Pesticide Control Officials
ACB	Analytical Chemistry Branch (re: OPP)
ACC	American Chemistry Council
ACP	Associates of Clinical Pharmacology
ACS	American Chemical Society
ACT	American College of Toxicology
ACUP	Animal Care and Use Procedure
ADE	Adverse Drug Experience/Effect/Event
ADI	Acceptable Daily Intake (see also RfD)
ADME	Absorption Distribution, Metabolism, Excretion
ADR	Adverse Drug Reaction
AE	Adverse Experience/Event
AERS	Adverse Event Reporting System
AHI	Animal Health Institute
ai/A	Active Ingredient per Acre
AI	Active Ingredient
ALISS	"A — List" Inventory Support System (re: SRRD)
ALJ	Administrative Law Judge
ANADA	Abbreviated New Animal Drug Application
ANDA	Abbreviated New Drug Application
ANSI	American National Standards Institute
AOAC	Association of Official Analytical Chemists
ARAR	Applicable, Relevant and Appropriate Requirements (re: Superfund)
APB	Antimicrobial Program Branch
ARB	Accelerated Reregistration Branch (re: SRRD of OPP)
ARS	Agricultural Research Service (re: USDA)
ARTS	Accelerated Reregistration Tracking System (re: SRRD of OPP)
ASAP	Administrative System Automations Project
ASQC	American Society of Quality Control
ASR	Analytical Summary Report
ASTHO	Association of State and Territorial Health Officials
ASTM	Association of Standard Test Methods
AWA	Animal Welfare Act
BAB	Biological Analysis Branch (re: BEAD of OPP)
BARQA	The British Association of Research Quality Assurance
BDAT	Best Demonstrated Available Technology
BEAD	Biological and Economic Analysis Division (re: OPP)

Table 210 Frequently Encountered Acronyms (Continued)

CANADAs	Computer Assisted New Drug Applications
CANADA	Computer Assisted New Animal Drug Application
CAP	Compliance Audit Program
CAPER	Computer Assisted Preclinical Electronic Review
CAPLA	Computer Assisted Product License Application (Re: Biologics)
CB	Communications Branch (re: OPP)
CB I & II	Chemistry Branch I and II (re: OPP)
CBER	Center for Biologics Evaluation and Research (re: FDA)
CBI	Confidential Business Information
CDC	Centers for Disease Control (see also USCDC)
CDER	Center for Drug Evaluation and Research (re: FDA)
CDRH	Center for Devices and Radiological Health (re: FDA)
CEQ	Council on Environmental Quality
CERCLA	Comprehensive, Environmental, Response, Compensation, and Liability Act
CFD	Call For Data
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practices (see also GMP)
CLIA	Clinical Laboratory Improvement Act
CMA	Chemical Manufacturers Association
CMC	Chemistry Manufacturing and Controls
CNAEL	Committee on National Accreditation for Environmental Laboratories
CORT	toxicology studies set: Chronic feeding; Oncogenicity; Reproduction; Teratology
CPDA	Chemical Producers and Distributors Association
CPG	Compliance Policy Guide
CPGM	Compliance Program Guidance Manuals (re: Bioresearch Monitoring Program)
CPSC	Consumer Product Safety Commission
CRA	Clinical Research Associate
CRADA	Cooperative Research and Development Agreement
CRF	Case Report Form
CRO	Contract Research Organization
CRP	Child Resistant Packaging
CSA	Clinical & Scientific Affairs
CSF	Confidential Statement of Formula
CSMA	Chemical Specialties Manufacturers Association
CSO	Consumer Safety Officer (re: FDA)
CSRS	Cooperative State Research Service
CTB	Certification and Training Branch (re: FOD of OPP)
CV	Curriculum Vitae

Table 210 Frequently Encountered Acronyms (Continued)

CVM	Center for Veterinary Medicine (re: FDA)
CWA	Clean Water Act
DAMOS	Drug Application Methodology with Optical Storage (re: EC)
DCI	Data Call-In notice (re: RD or SRRD of OPP)
DEA	Drug Enforcement Agency
DEB	Dietary Exposure Branch (see also CB I and II)
DFE	Design for the Environment
DI	Department of Interior (see also USDI)
DIA	Drug Information Association
DIS	Drug Information System
DISLODG	Dislodgeable Foliar Residue (re: EPA)
DMF	Drug Master File
DOE	Department of Energy (see also USDOE)
DOT	Department of Transportation
DQOs	Data Quality Objectives (re: EPA work)
DRES	Dietary Risk Evaluation System (re: OPP)
EAB	Economic Analysis Branch (re: OPP)
EC	Emulsifiable Concentrate
EC	European Community (see also EEC)
EDF	Environmental Defense Fund
EEB	Ecological Effects Branch (re: OPP)
EEC	European Economic Community (see also EC)
EFED	Environmental Fate and Effects Division (re: OPP)
EFGWB	Environmental Fate and Groundwater Branch (re: OPP)
EIR	Establishment Inspection Report
ELA	Establishment License Report (re: Biologics)
ELGIN	Environmental Liaison Group International
ELI	Environmental Law Institute
EMO	Experimental Manufacturing Order
EP	End Use Product
EPA	Environmental Protection Agency (see also USEPA)
EPCRA	Emergency Planning and Community Right to Know Act
EPRS	Establishment/Product Registration System
ESA	Entomological Society of America
EUP	Experimental Use Permit (re: EPA FIFRA)
FACTS	Field Accomplishments and Compliance Tracking System
FDA	Food and Drug Administration (see also USFDA)
FDB	Field Data Book
FD&C	Federal Food, Drug and Cosmetic Act (see also FFDCA, FDCL)
FDCL	Food, Drug Cosmetic Law (see also FD&C, FFDCA)

Table 210 Frequently Encountered Acronyms (Continued)

FDLI	Food & Drug Law Institute
FFDCA	Federal Food, Drug and Cosmetic Act (see also FD&C, FDCL)
FHB	Fungicide-Herbicide Branch (re: RD of OPP)
FHSA	Federal Health and Safety Act
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FOD	Field Operations Division (re: OPP)
FOI	Freedom of Information (see also FOIA)
FOIA	Freedom of Information Act (see also FOI)
FPLA	Fair Packaging & Labeling Act
FR	Federal Register
FRD	Field Research Director
FTC	Federal Trade Commission
FWS	Fish and Wildlife Service (see also USFWS)
GALP	Good Automated Laboratory Practices
GARPs	Good Academic Research Practices (draft 1992)
GAO	General Accounting Office
GATT	General Agreement on Tariffs and Trade
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GLPS	Good Laboratory Practice Standards
GMP	Good Manufacturing Practices
GH_2O	Groundwater Studies (re: EPA)
GRAE	Generally Recognized As Effective
GRAS	Generally Recognized As Safe
HDT	Highest Dose Tested (re: EPA)
HED	Health Effects Division (re: OPP)
HEI	Health Effects Institute
HES	Health and Environmental Safety
HHS	Health and Human Services
HIMA	Health Industry Manufacturers Association
HPB	Health Protection Branch (re: Canada)
HPVSIDS	High Production Volume Screening Info Data Set (re: OECD)
HRS	Hazard Ranking System (re: Superfund)
IACUC	Institutional Animal Care and Use Committee
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICR	Information Collection Request
IDB	Investigational Drug Brochure
IDE	Investigational Device Exemption
IG	Inspector General (see also OIG)

Table 210 Frequently Encountered Acronyms (Continued)

INAD	Investigational New Animal Drug
IND	Investigational New Drug
IPM	Integrated Pest Management (re: OPP)
IR-4	Interregional Research Project #4 for Minor Crops (re: USDA)
IRB	Insecticide and Rodenticide Branch (re: RD of OPP)
IRB	Institutional Review Board
IS	Information Standards
ISA	Information Systems Architecture
ISB	Information Services Branch (re: PMSD of OPP)
ISQA	International Society of Quality Assurance
ITC	Interagency Testing Committee (re: TSCA)
LAC	Laboratory Accreditation Committee
LADD	Lifetime Average Daily Dose (re: OPP)
LADD	Lowest Acceptable Daily Dose (re: OPP)
LC_{50}	Lethal Concentration for 50% of test population
LD_{50}	Lethal Dose for 50% of test population
LDT	Lowest Dose Tested
LEL	Lowest Effective Level
LRD	Laboratory Research Director
LUIS	Label Use Information System (re: OPP)
MARSQA	Mid-Atlantic Region Society of Quality Assurance
MCA	Medicines Control Agency (U.K. equivalent of FDA)
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDDI	Medical Devices, Diagnostics and Instrumentation
MNVP	Medically Necessary Veterinary Product (re: FDACVM)
MOE	Margin of Exposure
MOS	Margin of Safety
MOU	Memorandum of Understanding
MP	Manufacturing Use Product (re: OPP, see also MUP)
MPI	Maximum Permitted Intake
MRID #	Master Record Identification Number
MS	Master Schedule
MSS	Master Schedule Sheet
MSDS	Material Safety Data Sheet
MTL	Master Testing List
MUP	Manufacturing Use Product (re: OPP, see also MP)
MURS	MultiUser Regulatory Submission (International MultiAgency Project)
NACA	National Agricultural Chemical Association
NADA	New Animal Drug Application

Table 210 Frequently Encountered Acronyms (Continued)

NADE	New Animal Drug Evaluation, office of (re: FDACVM)
NAF	Notice of Adverse Findings
NAI	No Action Indicated
NAICC	National Alliance of Independent Crop Consultants
NARA	National Agrichemical Retailers Association
NAS	National Academy of Sciences
NASDA	National Association of State Departments of Agriculture
NCAMP	National Coalition Against the Misuse of Pesticides
NCE	New Chemical Entity
NCP	National Contingency Plan (re: Superfund)
NBS	National Bureau of Standards (now called NIST)
NDA	New Drug Application
NDS	New Drug Submission
NEIC	National Enforcement Investigation Center (re: USEPA)
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology (formerly NBS)
NPCA	National Pest Control Association
NPDES	National Pollutant Discharge Elimination System
NPIRS	National Pesticide Information Retrieval System
NPL	National Priority List (re: Superfund)
NPTN	National Pesticide Telecommunications Network
NRDC	Natural Resources Defense Council
NTIS	National Technical Information Service
OAI	Official Action Indicated
OASIS	Operational and Administrative System for Import Support
ODW	Office of Drinking Water
OECD	Organization for Economic Cooperation and Development
OECA	Office of Enforcement and Compliance Assurance
OES	Office of Endangered Species (re: FWS of DI)
OGD	Office of Generic Drugs (re: FDA)
OIG	Office of the Inspector General (see also IG)
OLTS	OnLine Tracking System
OMB	Office of Management and Budget
OPM	Office of Personnel Management
OPP	Office of Pesticide Programs (re: EPA)
OPPT	Office of Pollution Prevention and Toxics (formerly OTS; re. TSCA)
OPPTS	Office of Prevention, Pesticides and Toxic Substances
OREB	Occupational and Residential Exposure Branch (re: HED of OPP)

Table 210 Frequently Encountered Acronyms (Continued)

OSB	Occupational Safety Branch (re: FOD of OPP)
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste (re: EPA)
OSWER	Office of Solid Waste and Emergency Response
OTA	Office of Technology Assessment (re: Congress)
OTC	Over the Counter
OTS	Office of Toxic Substances (now called OPPT)
OWPE	Office of Waste Programs Enforcement
PAG	Pesticide Assessment Guidelines
PAI	Pure Active Ingredient
PBA	Preliminary Benefit Analysis
PCO	Pest Control Operator
PDA	Parenteral Drug Association
PDMS	Pesticide Document Management System
PDR	Physician's Desk Reference
PDUFA	Prescription Drug User Fee Act
PES	Planning and Evaluation Staff
PHED	Pesticide Handlers Exposure Database (re: EPA)
PHI	PreHarvest Interval
PHI	PostHarvest Interval
PIMS	Pesticide Incident Monitoring System
PLA	Product License Application (re: Biologics)
PM	Product Manager
PMA	Pharmaceutical Manufacturers Association
PMN	Premanufacturers Notification (re: TSCA)
PMSD	Program Management and Support Division (re: OPP)
P&P guide	Policy and Procedures guide (re: FDACVM)
PPIS	Pesticide Product Information Systems
PR#	Pesticide Clearance Request Number
PR notice	Pesticide Registration Notice
PRATS	Pesticide Registration Activity Tracking System
PRCSQA	Pacific Regional Chapter of the Society of Quality Assurance
PRP	Potentially Responsible Party (re: Superfund)
PSA	Product Safety Assurance
QA	Quality Assurance
QAAS	Quality Assurance Advisory Subcommittee
QAO	Quality Assurance Officer
QAP	Quality Assurance Project Plan
QAU	Quality Assurance Unit
QC	Quality Control

Table 210 Frequently Encountered Acronyms (Continued)

QMP	Quality Management Plan
QUA	Qualitative Use Assessment
R&D	Research and Development
R&E	Research and Experimental
RAC	Raw Agricultural Commodity (see also RACPC)
RAC	Risk Assessment Council
RACPC	Raw Agricultural Commodity Processing (re: EPA)
RAF	Risk Assessment Forum
RAPS	Regulatory Affairs Professional Society
RB	Reregistration Branch
RCFs	Refractory Ceramic Fibers
RCRA	Resource Conservation and Recovery Act
RD	Registration Division (re: OPP)
RDRA	Remedial Design/Remedial Action (re: Superfund)
RED	Reregistration Eligibility Document
REI	Reentry Interval (re: OPP)
RFC	Regional Field Coordinator
RfD	Reference Dose
RFD	Recommended for Development
RI/FS	Remedial Investigation/Feasibility Study (re: Superfund)
RLC	Regional Laboratory Coordinator
RM	Review Manager (re: OPP)
RM-1	Risk Management–1 (re: EPA)
RM-2	Risk Management–2 (re: EPA)
RMEB	Resource Management and Evaluation Branch (re: PMSD of OPP)
ROD	Record of Decision (re: Superfund)
RPAR	Rebuttable Presumption Against Registration (re: OPP; see also SR)
RRC	Regulatory Review Committee of the Society of Quality Assurance
RRD	Residue Research Director
RS	Registration Standard (re: OPP)
RSB	Registration Support Branch
RTECS	Registry of Toxic Effects of Chemical Substances
RUP	Restricted Use Pesticide
SAB	Scientific Advisory Board (re: EPA)
SACB	Science Analysis and Coordination Branch (re: HED of OPP)
SACS	Science Analysis and Coordination Staff (re: EFED of OPP)
SAES	State Agricultural Experiment Stations
SAP	Scientific Advisory Panel (re: FIFRA)
SARA	Superfund Amendments and Reauthorization Act
SB	Systems Branch (re: PMSD of OPP)

Table 210 Frequently Encountered Acronyms (Continued)

SD	Study Director
SDLC	Software Development Life Cycles
SDWA	Safe Drinking Water Act
SETAC	Society of Environmental Toxicology & Chemistry
SFIREG	State FIFRA Issues, Research and Evaluation Group
SGML	Standard General Markup Language (Computer Language)
SITE	Superfund Innovative Technology Evaluation Program
SMART	Submission Management and Review Tracking
SMARTS	Simple Maintenance of ARTS (see also ARTS)
SOP	Standard Operating Procedure
SOT	Society of Toxicology
SPI	Standard Practice Instructions
SQA	Society of Quality Assurance
SR	Special Review (re: OPP; formerly RPAR)
SRB	Special Review Branch (re: SRRD of OPP)
SRRD	Special Review and Reregistration Division (re: OPP)
STARS	Submission Tracking And Reporting System
STP	Society of Toxicologic Pathologists
TCLP	Toxicity Characteristic Leaching Procedure, RCRA
TEP	Typical End use Product
TFM	Testing Facility Management
TGAI	Technical Grade Active Ingredient
TMRC	Theoretical Maximum Residue Contribution (re: OPP)
TOSCA	Toxic Substances Control Act (see also TSCA)
TQ	Total Quality
TQM	Total Quality Management
TQSS	Total Quality Specialty Section of the Society of Quality Assurance
TRI	Toxics Release Inventory (re: EPCRA)
TSCA	Toxic Substances Control Act (see also TOSCA)
TSCATS	TSCA Test Submissions
TVOCs	Total Volatile Organic Compounds
UN	United Nations
USC	United States Code
USCDC	United States Centers for Disease Control (see also CDC)
USDA	United States Department of Agriculture
USDOE	United States Department of Energy (see also DOE)
USDI	United States Department of Interior (see also DI)
USEPA	United States Environmental Protection Agency (see also EPA)
USFDA	United States Food and Drug Administration (see also FDA)
USFWS	United States Fish and Wildlife Service (see also FWS)

Table 210 Frequently Encountered Acronyms (Continued)

VAI	Voluntary Action Indicated
WEXWPS	Worker Exposure Studies—Worker Protection Standards (re: EPA)
WHO	World Health Organization
WP	Wettable Powders
WSS	Weed Science Society

Source: From Society of Quality Assurance. With permission.

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Section 16
Glossary—by Subject

Carcinogenesis

Adduct: The covalent linkage or addiction product between an alkylating agent and cellular macromolecules such as protein, RNA, and DNA.

Alkylating agent: A chemical compound that has positively charged (electron-deficient) groups that can form covalent linkages with negatively charged portions of biological molecules such as DNA. The covalent linkage is referred to as an adduct and may have mutagenic or carcinogenic effects on the organism. The alkyl species is the radical that results when an aliphatic hydrocarbon loses one hydrogen atom to become electron-deficient. Alkylating agents react primarily with guanine, adding their alkyl group to N7 of the purine ring.

Altered focus: A histologically identifiable clone of cells within an organ that differs phenotypically from the normal parenchyma. Foci of altered cells usually result from increased cellular proliferation, represent clonal expansions of initiated cells, and are frequently observed in multistage animal models of carcinogenesis. Foci of cellular alteration are most commonly observed in the liver of carcinogen-treated rodents and are believed by some to represent preneoplastic lesions.

Benign: A classification of anticipated biological behavior of neoplasms in which the prognosis for survival is good. Benign neoplasms grow slowly, remain localized, and usually cause little harm to the patient.

Choristoma: A mass of well-differentiated cells from one organ included within another organ, e.g., adrenal tissue present in the lung.

Chromosomal aberration: A numerical or structural chromosomal abnormality.

Cocarcinogen: An agent not carcinogenic alone but that potentiates the effect of a known carcinogen.

Cocarcinogenesis: The augmentation of neoplasm formation by simultaneous administration of a genotoxic carcinogen and an additional agent (cocarcinogen) that has no inherent carcinogenic activity by itself.

Direct carcinogen: Carcinogens that have the necessary structure to directly interact with cellular constituents and cause neoplasia. Direct-acting carcinogens do not require metabolic conversion by the host to be active. They are considered genotoxic because they typically undergo covalent binding to DNA.

Dysplasia: Disordered tissue formation characterized by changes in size, shape, and orientational relationships of adult types of cells. Primarily seen in epithelial cells.

Epigenetic: Change in phenotype without a change in DNA structure. One of two main mechanisms of carcinogen action, epigenetic carcinogens are nongenotoxic, i.e., they do not form reactive intermediates that interact with genetic material in the process of producing or enhancing neoplasm formation.

Genotoxic carcinogen: An agent that interacts with cellular DNA either directly in its parent form (direct carcinogen) or after metabolic biotransformation.

Hyperplasia: A numerical increase in the number of phenotypically normal cells within a tissue or organ.

Hypertrophy: Increase in the size of an organelle, cell, tissue, or organ within a living organism. To be distinguished from hyperplasia, hypertrophy refers to an increase in size rather than an increase in number. Excessive hyperplasia in a tissue may produce hypertrophy of the organ in which that tissue occurs.

Initiation: The first step in carcinogenesis whereby limited exposure to a carcinogenic agent produces a latent but heritable alteration in a cell, permitting its subsequent proliferation and development into a neoplasm after exposure to a promoter.

Initiator: A chemical, physical, or biological agent that is capable of irreversibly altering the genetic component (DNA) of the cell. Although initiators are generally considered to be carcinogens, they are typically used at low noncarcinogenic doses in two-stage initiation–promotion animal model systems. Frequently referred to as a "tumor initiator."

In situ carcinoma: A localized intraepithelial form of epithelial cell malignancy. The cells possess morphological criteria of malignancy but have not yet gone beyond the limiting basement membrane.

Malignant: A classification of anticipated biological behavior of neoplasms in which the prognosis for survival is poor. Malignant neoplasms grow rapidly, invade, and destroy, and are usually fatal.

Metaplasis: The substitution in a given area of one type of fully differentiated cell for the fully differentiated cell type normally present in that area, e.g., squamous epithelium replacing ciliated epithelium in the respiratory airways.

Metastasis: The dissemination of cells from a primary neoplasm to a noncontiguous site and their growth therein. Metastases arise by dissemination of cells from the primary neoplasm via the vascular or lymphatic system and are an unequivocal hallmark of malignancy.

Mitogenesis: The generation of cell division or cell proliferation.

MTD: Maximum tolerated dose. Refers to the maximum amount of an agent that can be administered to an animal in a carcinogenicity test without adversely affecting the animal because of toxicity other than carcinogenicity. Examples of having exceeded the MTD include excessive early mortality, excessive loss of body weight, production of anemia, production of tissue necrosis, and overloading of the metabolic capacity of the organism.

Mutation: A structural alteration of DNA that is hereditary and gives rise to an abnormal phenotype. A mutation is always a change in the DNA base sequence and includes substitutions, additions, rearrangements, or deletions of one or more nucleotide bases.

Oncogene: The activated form of a protooncogene. Oncogenes are associated with development of neoplasia.

Preneoplastic lesion: A lesion usually indicative that the organism has been exposed to a carcinogen. Presence of preneoplastic lesions indicates that there is enhanced probability for development of neoplasia in the affected organ. Preneoplastic lesions are believed to have a high propensity to progress to neoplasia.

Procarcinogen: An agent that requires bioactivation in order to give rise to a direct acting carcinogen. Without metabolic activation these agents are not carcinogenic.

Progression: Processes associated with the development of an initiated cell to a biologically malignant neoplasm. Sometimes used in a more limited sense to describe the process whereby a neoplasm develops from a benign to a malignant proliferation or from a low-grade to a high-grade malignancy. Progression is that

stage of neoplastic development characterized by demonstrable changes associated with increased growth rate, increased invasiveness, metastases, and alterations in biochemical and morphologic characteristics of a neoplasm.

Promoter: *Use in multistage carcinogenesis*—An agent that is not carcinogenic itself but when administered after an initiator of carcinogenesis stimulates the clonal expansion of the initiated cell to produce a neoplasm. *Use in molecular biology*—A DNA sequence that initiates the process of transcription and is located near the beginning of the first exon of a structural gene.

Promotion: The enhancement of neoplasm formation by the administration of a carcinogen followed by an additional agent (promoter) that has no intrinsic carcinogenic activity by itself.

Protooncogene: A normal cellular structural gene that, when activated by mutations, amplifications, rearrangements, or viral transduction, functions as an oncogene and is associated with development of neoplasia. Protooncogenes regulate functions related to normal growth and differentiation of tissues.

Regulatory gene: A gene that controls the activity of a structural gene or another regulatory gene. Regulatory genes usually do not undergo transcription into messenger RNA.

Sister chromatid exchange: The morphological reflection of an interchange between DNA molecules at homologous loci within a replicating chromosome.

Somatic cell: A normal diploid cell of an organism as opposed to a germ cell, which is haploid. Most neoplasms are believed to begin when a somatic cell is mutated.

Transformation: Typically refers to tissue culture systems where there is conversion of normal cells into cells with altered phenotypes and growth properties. If such cells are shown to produce invasive neoplasms in animals, malignant transformation is considered to have occurred.

Ultimate carcinogen: The form of the carcinogen that actually interacts with cellular constituents to cause the neoplastic transformation. The final product of metabolism of the procarcinogen.

Clinical Pathology

Activated partial thromboplastin time: A measure of the relative activity of factors in the intrinsic clotting sequence and the common pathway necessary in normal blood coagulation.

Alanine aminotransferase (ALT): An enzyme, primarily of liver origin, whose blood levels can rise in response to hepatocellular toxicity. Also known as SGPT (serum glutamic pyruvic transaminase).

Albumin: The most abundant blood protein synthesized by the liver.

Alkaline phosphatase: An enzyme whose blood levels can rise in response to hepatobiliary disease or increased osteoblastic (bone cell) activity. Serum alkaline phosphatase activity can be reduced in fasted rats because the intestinal isozyme is an important component of serum enzyme activity.

Anemia: Any conditions in which RBC count, hemoglobin concentration, and hematocrit are reduced.

Anisocytosis: Variations in the size of red blood cells.

Aspartate aminotransferase (AST): An enzyme whose blood levels can rise in response to hepatotoxicity, muscle damage, or hemolysis. Also known as SGOT (serum glutamic oxaloacetic transaminase).

Azotemia: An increase in serum urea nitrogen and/or creatinine levels.

Blood urea nitrogen (BUN): The end product of protein catabolism. Blood levels can rise after renal (glomerular) injury.

Creatine kinase (CK): An enzyme that is concentrated in skeletal muscle, brain, and heart tissue.

Creatinine: The end product of creatine metabolism in muscle. Elevated blood levels can indicate renal (glomerular) injury.

Fibrinogen: A glycoprotein that is involved in the formation of fibrin.

Gamma glutamyltransferase (γGT): An enzyme of liver origin, whose blood concentration can be elevated in hepatobiliary disease.

Globulin: A group of blood proteins synthesized by lymphatic tissue in the liver.

Hemolysis: The destruction of red blood cells, resulting in liberation of hemoglobin into plasma.

Icteric: Relating to a jaundiced condition, typically as a result of elevated serum bilirubin levels.

Lactate dehydrogenase: An enzyme found in several organs, including liver, kidney, heart, and skeletal muscle.

Mean corpuscular hemoglobin: The average amount of hemoglobin per red blood cell.

Mean corpuscular hemoglobin concentration: The average hemoglobin concentration per red blood cell.

Mean corpuscular volume: The average size of the red blood cell.
Methemoglobin: Oxidized hemoglobin incapable of carrying oxygen.
Packed cell volume: The percentage of blood that contains RBC components; synonymous with hematocrit.
Poikilocytosis: Variations in the shape of red blood cells.
Polychromasia: Increased basophilic staining of erythrocytes.
Polycythemia: An increase in the number of red blood cells.
Prothrombin time: A measure of the relative activity of factors in the extrinsic clotting sequence and the common pathway necessary in normal blood coagulation.
Reticulocyte: An immature (polychromatic) erythrocyte.
Reticulocytosis: Increased numbers of reticulocytes in the circulation, typically seen in response to regenerative anemia.
Sorbitol dehydrogenase (SDH): An enzyme of liver origin, whose blood concentration rises in response to hepatocellular injury.
Triglycerides: Synthesized primarily in the liver and intestine; the major form of lipid storage.

Dermal Toxicology

Acanthosis: Hypertrophy of the stratum spinosum and granulosum.
Blanching: To take color from, to bleach. Characterized by a white or pale discoloration of the exposure area due to decreased blood flow to the skin (ischemia).
Contact dermatitis: A delayed type of induced sensitivity (allergy) of the skin with varying degrees of erythema, edema, and vesiculation, resulting from cutaneous contact with a specific allergen.
Contact urticaria: Wheal-and-flare response elicited within 30 to 60 min after cutaneous exposure to test substance. May be IgE mediated or nonimmunologically mediated.
Corrosion: Direct chemical action on normal living skin that results in its disintegration, an irreversible alteration at the site of contact. Corrosion is manifested by ulceration and necrosis with subsequent scar formation.
Cumulative irritation: Primary irritation resulting from repeated exposures to materials that do not in themselves cause acute primary irritation.

Dermatitis: Inflammation of the skin.

Desquamation: The shedding of the cuticle in scales or the outer layer of any surface. To shred, peel, or scale off, as the casting off of the epidermis in scales or shred, or the shedding of the outer layer of any surface.

Eczema: Inflammatory condition in which the skin becomes red and small vesicles, crusts, and scales develop.

Edema: An excessive accumulation of serous fluid or water in cells, tissues, or serous cavities.

Erythema: An inflammatory redness of the skin, as caused by chemical poisoning or sunburn, usually a result of congestion of the capillaries.

Eschar: A dry scab, thick coagulated crust, or slough formed on the skin as a result of a thermal burn or by the action of a corrosive or caustic substance.

Exfoliation: To remove in flakes or scales, peel. To cast off in scales, flakes, etc. To come off or separate, as scales, flakes, sheets, or layers. Detachment and shedding of superficial cells of an epithelium or from any tissue surface. Scaling or desquamation of the horny layer of epidermis, which varies in amount from minute quantities to shedding the entire integument.

Hyperkeratosis: Hypertrophy and thickening of the stratum corneum.

Irritant: A substance that causes inflammation and other evidence of irritation, particularly of the skin, on first contact or exposure; a reaction of irritation not dependent on a mechanism of sensitization.

Irritation: A local reversible inflammatory response of normal living skin to direct injury caused by a single application of a toxic substance, without the involvement of an immunologic mechanism.

Necrosis: Pathological death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage.

Nonocclusive: Site of application of test substance is open to the air.

Occlusive covering: A bandage or dressing that covers the skin and excludes it from air. Prevents loss of a test substance by evaporation and by increasing tissue penetration.

Photoallergy: An increased reactivity of the skin to UV and/or visible radiation produced by a chemical agent on an immunologic basis. Previous allergy sensitized by exposure to the chemical agent and appropriate radiation is necessary. The main role of light in photoallergy appears to be in the conversion of the hapten to a complete allergen.

Photoirritation: Irritation resulting from light-induced molecular changes in the structure of chemicals applied to the skin.

Photosensitization: Sensitization of the skin to ultraviolet (UV) light, usually due to the action of certain drugs, plants, or other substances, may occur shortly after administration of the substance, or may occur only after latent period of days to months. The processes whereby foreign substances, either absorbed locally into the skin or systemically, may be subjected to photochemical reactions within the skin, leading to either chemically induced photosensitivity reactions or alteration of the "normal" pathologic effects of light. UV-A is usually responsible for most photosensitivity reactions.

Semiocclusive covering: Site of application of test substance is covered; however, movement of air through covering is not restricted.

Sensitization (allergic contact dermatitis): An immunologically mediated cutaneous reaction to a substance.

Superficial sloughing: Characterized by dead tissue separated from a living structure. Any outer layer or covering that is shed. Necrosed tissue separated from the living structure.

Ulceration: The development of an inflammatory, often suppurating, lesion on the skin or an internal mucous surface of the body caused by superficial loss of tissue, resulting in necrosis of the tissue.

Ecotoxicology

Bioaccumulation: General term describing a process by which chemicals are taken up by aquatic organisms directly from water as well as from exposure through other routes, such as consumption of food and sediment containing chemicals.

Bioaccumulation factor (BAF): The ratio of tissue chemical residue to chemical concentration in an external environmental phase (i.e., water, sediment, or food). BAF is measured as steady state in situations where organisms are exposed from multiple sources (i.e., water, sediment, and food), unless noted otherwise.

Biochemical oxygen demand (BOD): Sometimes called *biological oxygen demand*, a measure of the rate at which molecular oxygen is consumed by microorganisms during oxidation of organic matter. The standard test is the 5-day BOD test, in which the amount of dissolved oxygen required for oxidation

over a 5-day period is measured. The results are measured in mg of oxygen/L (mg/L) or parts per million (ppm).

Bioconcentration: A process by which there is a net accumulation of a chemical directly from water into aquatic organisms, resulting from simultaneous uptake (e.g., by gill or epithelial tissue) and elimination.

Bioconcentration factor (BCF): A term describing the degree to which a chemical can be concentrated in the tissues of an organism in the aquatic environment as a result of exposure to a waterborne chemical. At steady state during the uptake phase of a bioconcentration test, the BCF is a value that is equal to the concentration of a chemical in one or more tissues of the exposed aquatic organisms divided by the average exposure water concentration of the chemical in the test.

Biodegradation: The transformation of a material resulting from the complex enzymatic action of microorganisms (e.g., bacteria, fungi). It usually leads to disappearance of the parent chemical structure and to the formation of smaller chemical species, some of which are used for cell anabolism. Although typically used with reference to microbial activity, it may also refer to general metabolic breakdown of a substance by any living organism.

Chemical oxygen demand (COD): COD is measured instead of BOD when organic materials are not easily degraded by microorganisms. Strong oxidizing agents (e.g., potassium permanganate) are used to enhance oxidation. COD values will be larger than BOD values.

EC_{50} (median effective concentration): The concentration of chemical in water to which test organisms are exposed is estimated to be effective in producing some sublethal response in 50% of the test organisms. The EC_{50} is usually expressed as a time-dependent value (e.g., 24 h or 96 h EC_{50}). The sublethal response elicited from the test organisms as a result of exposure to the chemical must be clearly defined (e.g., test organisms may be immobilized, lose equilibrium, or undergo physiological or behavioral changes).

Fate: Disposition of a material in various environmental compartments (e.g., soil or sediment, water, air, and biota) as a result of transport, transformation, and degradation.

LC_{50} (median lethal concentration): The concentration of chemical in water to which test organisms are exposed is estimated to be lethal to 50% of the

test organisms. The LC_{50} is often expressed as a time-dependent value (e.g., 24 hr or 96 hr LC_{50}).

Maximal acceptable toxicant concentration (MATC): The hypothetical toxic threshold concentration lying in a range bounded at the lower end by the highest tested concentration having no observed effect (NOEC) and at the higher end by the lowest concentration having a statistically significant toxic effect (LOEC) in a life cycle (full chronic) or a partial life cycle (partial chronic) test. This can be represented by NOEC < MATC < LOEC.

Octanol–water partition coefficient (*Kow*): The ratio of the solubility of a chemical in n-octanol and water at steady state; also expressed as *P*. The logarithm of *P* or *Kow* (i.e., log *P* or *Kow*) is used as an indication of the propensity of a chemical for bioconcentration by aquatic organisms.

TLm or TL_{50} (median tolerance limit): The concentration of material in water at which 50% of the test organisms survive after a specified time of exposure. The TLm (or TL_{50}) is usually expressed as a time-dependent value (e.g., 24 hr or 96 hr TL_{50}).

Genetic Toxicology

Aneuploidy: An abnormal number of chromosomes in a cell or organism that is not an exact multiple of the haploid number.

Base substitution: The substitution of one or more bases for another in the nucleotide sequence.

Clastogen: An agent that produces structural changes of chromosomes.

Frameshift mutation: A mutation in the genetic code in which one base or two adjacent bases are inserted into or deleted from the nucleotide sequence of a gene.

Gene mutation: A detectable permanent change (point mutation, insertion, or deletion) within a single gene or its regulating sequences.

Micronucleus: A microscopically detectable particle in a cell that contains nuclear DNA, usually one twentieth to one fifth the size of the main nucleus. It may be composed of a broken centric or acentric part of a chromosome or a whole chromosome.

Mitotic index: The ratio of the number of cells in a population in various stages of mitosis to the number of cells in the population not in mitosis.

Plasmid: An autonomously replicating DNA molecule distinct from the normal genome. A plasmid may insert into the host chromosome or form an extra chromosomal element.

Point mutation: Change in the genetic code, usually confined to a single base pair.

Unscheduled DNA synthesis (UDS): DNA synthesis that occurs at some stage in the cell cycle other than S-phase in response to DNA damage and is usually associated with DNA excision repair.

IMMUNOTOXICOLOGY

ADCC (antibody-dependent cell-mediated cytotoxicity): A specific form of cell-mediated immunity in which an antibody binds a target and a cytotoxic cell (either a macrophage or lymphocyte), linking the two together before lysis of the target cell.

Adjuvant: A material that enhances an immune response. It generally refers to a mixture of oil and mycobacterial cell fragments (complete adjuvant).

Allogenic: From a different genetic background. In the context of immunotoxicology, this usually refers to the use of genetically dissimilar cells in *in vitro* assays to elicit a cell-mediated immune reaction.

Antibody: Complex macromolecules produced by plasma cells that recognize specific antigens. Antibodies are also referred to as immunoglobulins (Ig). They consist of two basic units: the antigen-binding fragment (Fab) contains variable regions coding for antigen recognition; and the constant fragment (Fc), which determines the function of the antibody. An Fc is designated as IgA, IgD, IgE, IgG, and IgM. Cross-linking of antibody molecules on the surface of a cell leads to activation of complement, resulting in destruction of the target by lytic cells, or in phagocytosis by macrophages.

Antibody-forming cell (AFC)/Plaque-forming cell (PFC) assay: The AFC assay measures the ability of animals to produce either IgM or IgG antibodies against a T-dependent or T-independent antigen following *in vivo* sensitization. Due to the involvement of multiple cell populations in mounting an antibody response, the AFC assay actually evaluates several immune parameters simultaneously. It is considered to be one of the most sensitive indicator systems for immunotoxicology studies.

Antigen: A molecule that is the subject of a specific immune reaction. Antigens are recognized in a cognate fashion by either immunoglobulins or the antigen receptor on the surface of T-cells. Antigens are usually proteinaceous in nature.

Antigen-presenting cell (APC): Cells that are responsible for making antigens accessible to immune effector and regulatory cells. Following internalization and degradation of the antigen (e.g., by phagocytes), a fragment of the antigen molecule is presented on the APC cell surface in association with histocompatibility molecules. The resulting complex is subsequently recognized by either B-cells via surface-bound Ig molecules, or by T-cells via the T-cell antigen receptor. Induction of a specific immune response then proceeds. Representative APCs include macrophages, dendritic cells, and certain B-cells.

B-cell/B lymphocytes: Lymphocytes that recognize antigen via surface-bound Ig. B-cells that have been exposed to cognate antigen subsequently proliferate and differentiate into plasma cells, which are responsible for producing specific antibody. B-cells differentiate in the bone marrow in mammals and in an organ known as the *bursa* in birds.

CD (cluster of differentiation): The CD series is used to denote cell surface markers (e.g., CD4, CD8). These markers, used experimentally as a means of identifying cell types, also serve physiological roles.

Cell-mediated immunity (CMI): Antigen-specific reactivity mediated primarily by T-lymphocytes. CMI may take the form of immunoregulatory activity (mediated by CD4 helper T-cells) or immune effector activity (mediated by CD8 killer T-cells). Other forms of direct cellular activity in host defense (e.g., NK cells, macrophages) are not antigen specific and are more accurately referred to as natural immunity.

Complement: A group of approximately 20 protein precursor molecules that interact in a cascading fashion. Following activation, the various complement precursor molecules assemble into a complex that intercalates into the membrane of a cell, resulting in osmotic lysis of the target cell.

Cytokine: Small peptides produced primarily by cells of the immune system, particularly helper T-cells. Cytokines are roughly grouped into nonexclusive categories including interleukins, tumor necrosis factors, interferons, colony-stimulating factors, and various miscellaneous cytokines. Related molecules include peptide growth factors, transforming growth factors, and chemokines.

Cytokines form an interactive network with both hormones and neuropeptides. Cytokines may be referred to in the older literature as lymphokines.

Cytotoxic T-lymphocyte (CTL): A subset of CD8 T-cells that are able to kill target cells following the induction of a specific immune response. The mechanism of lysis appears to be a combination of direct lysis by extravasation of lytic molecules, as well as the induction or apoptosis in the target cell. Measurement of CTL activity is a sensitive indicator of cell-mediated immunity.

Delayed-type hypersensitivity (DTH): A form of cell-mediated immunity in which recall exposure to an antigen results in an inflammatory reaction mediated by T-lymphocytes. Usually expressed as contact hypersensitivity.

ELISA (Enzyme-Linked ImmunoSorbent Assay): A type of immunoassay in which specific antibodies are used to both capture and detect antigens of interest. The most popular type is the "sandwich" ELISA in which antibodies are bound to a substrate such as a plastic culture plate. These antibodies bind antigenic determinants on molecules (or alternatively on whole cells). Unrelated material is washed away, and the plates are exposed to an antibody of a different specificity; this antibody is coupled to a detector molecule.

Gut-associated lymphoid tissue (GALT): Lymphoid cells and tissues lining the mucosa that serve as the first point of contact with antigen encountered via this route. GALT comprises Peyer's patches, the appendix, tonsils, and mesenteric lymph nodes.

Hapten: Low-molecular-weight molecules that are not antigenic by themselves, but which are recognized as antigens when bound to larger molecules, usually proteins.

Humoral-mediated immunity (HMI): Specific immune responses that are mediated primarily by humoral factors, including antibodies and complement. The induction of HMI generally, although not exclusively, requires the cooperation of cellular immune mechanisms.

Hybridoma: A genetically-engineered cell clone that produced antibodies of a single type (i.e., monoclonal antibodies). Monoclonal antibodies are highly specific for their cognate antigen and make highly useful tools for immunotoxicological studies.

Hypersensitivity: A vigorous and often inappropriate immune response to seemingly innocuous antigens. Hypersensitivity is classified into subtypes, depending on the mechanisms of action and the target cells or tissues.

Immune reserve: The concept that the immune response exhibits multiple redundancies that are capable of accommodating acute reductions in isolated immune functions. This reserve would theoretically prevent a severe reduction in host resistance, following a temporary immunosuppression of selected immune functions.

Macrophage: A bone-marrow-derived cell that is present in the peripheral tissue; macrophages found in the circulation are referred to as monocytes. Macrophages serve a wide variety of host defense needs, acting as both nonspecific killer cells and as regulators of other immune, and nonimmune host resistance mechanisms.

Major histocompatibility complex (MHC): Murine cell surface molecules of which two major classes are recognized: Class I (present on all nucleated cells) and Class II (present on B-cells, T-cells, and macrophages). MHC molecules appear to direct the course of immune reactivity and are presented in association with antigen by antigen-presenting cells. The human equivalent is termed HLA (human leukocyte antigen).

Mitogen: Molecules capable of inducing cellular activation and may include sugars or peptides. The ability of a cell to respond to stimulation with a mitogen (generally assessed by cellular proliferation) is thought to give an indication of the cell's immune responsiveness. Mitogens most commonly employed in immunotoxicology assays include the T-cell mitogens, Concanavalin A (ConA), and phytohemagglutinin (PHA). Mitogens routinely used for assessing B-cell proliferation include pokeweed mitogen (PWM) and *E. coli* lipopolysaccharide (LPS).

Natural (nonspecific) immunity: Host defense mechanisms that do not require prior exposure to antigen. Nonspecific immunity is mediated by NK cells, macrophages, neutrophils, and complement.

Natural killer (NK) cells: A population of lymphocytes separate from T- and B-lymphocytes, also referred to as large granular lymphocytes (LGL). NK cells exhibit cytotoxicity against virally infected cells and certain tumor cells. They are notable in that they do not require prior exposure to antigen to express cytotoxicity towards their targets. Assessment of NK activity provides a measurement of nonspecific host resistance.

RES (reticuloendothelial system): The system composed of all phagocytic cells of the body, including monocytes and tissue macrophages. This system is now more commonly known as the mononuclear phagocytic system.

T-cell/T-lymphocyte: Lymphocytes that recognize specific antigens via a complex of molecules known collectively as the T-cell antigen receptor. T-cells are primarily responsible for the induction and maintenance of cell-mediated immunity, although they also regulate humoral-mediated immunity and some nonimmune effector mechanisms. A variety of T-cell populations exist, including T-helper cells, T-cytotoxic cells, T-inducer cells, and T-regulator cells. T-cells mature in the thymus.

Xenobiotic: Any substance that is foreign to an organism. In the context of immunotoxicology, this term generally refers to nonbiological chemicals and drugs.

Inhalation Toxicology

Dust: The airborne state of a chemical that is solid at room temperature but is dispensed into a particulate atmosphere.

Fume: The airborne state of a chemical that is liquid or solid at room temperature and pressure but is heated and allowed to condense into a particulate atmosphere.

Gas: The airborne state of a chemical that boils at or below room temperature and pressure.

Geometric standard deviation (GSD): The relative dispersion of the MMAD, such that a value approaching one indicates a monodisperse atmosphere.

Head-only exposure: A system for exposing test animals via inhalation in which they are restrained in a tube in such a way that only their heads are exposed directly to the test material.

Intratracheal dosing: A method of delivering, via a syringe and blunt needle, test material directly into the trachea of a test animal.

Liquid aerosol: The airborne state of a chemical that is liquid at room temperature and pressure but is nebulized into a particulate atmosphere.

Mass median aerodynamic diameter (MMAD): The median-size particle based on mass measurement relative to a unit density sphere.

Nose-only exposure: A system for exposing test animals via inhalation in which they are restrained in a tube in such a way that only their nose or snout is exposed directly to the test material.

Smoke: The airborne state of a chemical that is combusted and allowed to condense into a particulate matter.

Vapor: The airborne state of a chemical that is liquid at room temperature and pressure but is volatile.

Whole-body exposure: A system for exposing test animals via inhalation in which they are placed in a chamber in such a way that their entire bodies are exposed directly to the test material.

Medical Devices

Biomaterial: A material that has direct or indirect patient contact. A biomaterial (also termed a *biomedical material*) may be composed of any synthetic or natural rubber or fiber, polymeric or elastomeric formulation, alloy, ceramic, bonding agent, ink, or other nonviable substance, including tissue rendered nonviable, used as a device or any part thereof.

Class testing: The testing of plastics for biological reactivity according to predetermined testing requirements defined by the United States Pharmacopeial.

Combination (medical device) product: A product containing both a drug and device component that are physically, chemically, or otherwise combined to result in a medical product that is used therapeutically as a single entity. The medical device component must be evaluated for safety according to device requirements, the drug component evaluated for safety as per drug requirements, and the safety of the finished combined product also must be evaluated.

Direct contact: When the materials of a medical device are in direct (i.e., intimate) contact with the surface or tissues of the body (e.g., adhesive bandages, pacemaker leads).

Extract: A solution produced by the incubation of a material/medical device in an appropriate vehicle. After incubation, the vehicle contains the soluble chemicals (or leachables) that have dissolved out of, or off of, the material/medical device.

Indirect contact: When materials of a medical device do not contact the surface or tissues of the body, but the materials of the device may influence the body. In this case, a solution or other material that contacts the device may become contaminated with leachables from the device, which in turn contacts tissues of the body (e.g., intravenous infusion bag).

ISO: International Standards Organization.

Medical device: Any instrument, apparatus, appliance, material, or other article, including software, whether used alone or in combination, intended by the manufacturer for use by human beings solely or principally for the purpose of diagnosis, prevention, monitoring, or treatment; alleviation of disease, injury, or handicap; investigation, replacement, or modification of the anatomy or of a physiological process; control of conception; and that which does not achieve its principal intended action of the body by pharmaceutical, immunological, or metabolic means but may be assisted in its function by such means.

Predicate device: A previously marketed medical device that is substantially equivalent to a proposed device. The predicate device is used as a comparison to the proposed device to establish safety and efficacy.

Processing aid: A material that contacts a medical device product during the manufacturing process and, therefore, has a potential for affecting product quality and/or may elicit a biological response following the use of a medical device. Solvents, cleaning products, lubricants, and mold-release agents are examples of processing aids.

USP Negative Control Plastic RS: A standardized plastic produced by the USP for use as a control material in some biocompatibility assays.

Neurotoxicology

Akenesia: Absence or the loss of power of voluntary motion; immobility.

Ataxia: Incoordination; the inability to coordinate the muscles in the execution of voluntary movement.

Catalepsy: Condition in which there is waxy rigidity of the limbs that may be placed in various positions that will be maintained for a time.

Clonic convulsion: A convulsion in which the muscles alternately relax and contract.

Clonus: A form of movement characterized by contractions and relaxations of a muscle.

Convulsion: A violent spasm of the face, trunk, or extremities.

Dysarthria: Disturbance of articulation due to emotional stress or paralysis, incoordination, or spasticity of muscles used in vocalizing.

Dyskinesia: Difficulty in performing voluntary movements; a movement disorder characterized by insuppressible, stereotyped, automatic movements.

Dystonia: Abnormal tonicity (hyper- or hypo-) in any tissues.
Fasiculations: Involuntary contractions, or twitching , of groups of muscle fibers.
Hyperkinesia: Excessive muscular activity.
Myoclonus: Brief, involuntary twitching of a muscle or a group of muscles.
Myotonia: Delayed relaxation of a muscle after an initial contraction.
Paraesthesia: An abnormal sensation such as burning, prickling, tickling, or tingling.
Stereotypy: The constant repetition of gestures or movements that appears to be excessive or purposeless.
Tonic convulsion: A convulsion in which muscle contraction is sustained.

Ocular Toxicology

Anterior chamber: The aqueous-containing cavity of the eye, bounded by the cornea anteriorly, the chamber angle structures peripherally, and the iris and lens posteriorly.
Blepharitis: Inflammation of the eyelids.
Blepharospasm: Involuntary spasm of the eyelids.
Cataract: An opacity of the lens or its capsule.
Chemosis: Intense edema of the conjunctiva. The conjunctiva is loose fibrovascular connective tissue that is relatively rich in lymphatics and responds to noxious stimuli by swelling to the point of prolapse between the lids.
Choroid: The vascular middle coat between the retina and sclera.
Ciliary body: Portion of the uveal tract between the iris and the choroid, consisting of ciliary processes and the ciliary muscle.
Conjunctiva: Mucous membrane that lines the posterior aspect of the eyelids (palpebral conjunctiva) and the anterior sclera (bulbar conjunctiva).
Conjunctivitis: Inflammation of the conjunctiva.
Cornea: Transparent portion of the outer coat of the eyeball forming the anterior wall of the anterior chamber.
Exophthalmos: Abnormal protrusion of the eyeball.
Fluorescein (fluorescein sodium): A fluorescent dye, the simplest of the fluorane dyes and the mother substance of eosin, that is commonly used intravenously to determine the state of adequacy of circulation in the retina and to a lesser degree in the chorioid and iris. Another important use is to detect

epithelial lesions of the cornea and conjunctiva. Peak excitation occurs with light at a wavelength between 485 and 500 nm and peak emission occurs between 520 and 530 nm.

Fovea: Depression in the macula adapted for most acute vision.

Fundus: The posterior portion of the eye visible through an ophthalmoscope.

Hyperemia: Excess of blood in a part due to local or general relaxation of the arterioles. Blood vessels become congested and give the area involved a reddish or red–blue color.

Injection: Congestion of blood vessels.

Iris: The circular pigmented membrane behind the cornea and immediately in front of the lens; the most anterior portion of the vascular tunic of the eye. It is composed of the dilator and sphincter muscles, and the two-layered posterior epithelium, and mesodermal components that form the iris stroma.

Iritis: Inflammation of the iris, manifested by vascular congestion (hyperemia). An outpouring of serum proteins into the aqueous (flare) may accompany the inflammatory reaction.

Keratitis: Inflammation of the cornea.

Lens: A transparent biconvex structure suspended in the eyeball between the aqueous and the vitreous. Its function is to bring rays of light to a focus on the retina. Accommodation is produced by variations in the magnitude of this effect.

Miotic: A drug causing pupillary constriction.

Mydriatic: A drug causing pupillary dilatation.

Nystagmus: An involuntary, rapid movement of the eyeball that may be horizontal, vertical, rotatory, or mixed.

Optic disk: Ophthalmoscopically visible portion of the optic nerve.

Palpebral: Pertaining to the eyelid.

Pannus: Vascularization and connective-tissue deposition beneath the epithelium of the cornea.

Posterior chamber: Space filled with aqueous anterior to the lens and posterior to the iris.

Ptosis: Drooping of the upper eyelid.

Pupil: The round opening at the center of the iris, which allows transmission of light to the posterior of the eyeball.

Retina: The innermost nervous tunic of the eye, which is derived from the optic cup (the outer layer develops into the complex sensory layer).

Sclera: The white tough covering of the eye that, with the cornea, forms the external protective coat of the eye.

Vitreous: Transparent, colorless, mass of soft, gelatinous material filling the space in the eyeball posterior to the lens and anterior to the retina.

PHARMACEUTICALS

Abbreviated New Drug Application (ANDA): An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called *abbreviated* because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the innovator drug). Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low-cost alternative to the American public.

Active ingredient: Any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or affects the structure or any function of the body of humans or animals.

ADME: Absorption, distribution, metabolism, and excretion.

Biologic license application (BLA): Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm, who manufactures a biologic for sale in interstate commerce, to hold a license for the product. A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and the medical effects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued, allowing the firm to market the product.

Biologic product: A biologic product is any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries. Biologic products are a subset of "drug products" distinguished by their

manufacturing processes (biological process versus chemical process). In general, the term "drugs" includes biologic products.

CBER: FDA's Center for Biologics Evaluation and Research—The division charged with regulating biological products.

CDER: FDA's Center for Drug Evaluation and Research—The division charged with developing and enforcing policy with regard to the safety, effectiveness, and labeling of all drug products for human use.

Drug: A substance recognized by an official pharmacopoeia or formulary. A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. A substance (other than food) intended to affect the structure or any function of the body. A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biologic products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

Human equivalent dose: A dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose. In drug development, the term HED is usually used to refer to the human equivalent dose of the NOAEL.

Drug label: The FDA-approved label is the official description of a drug product, which includes indication (what the drug is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children, and other populations; and safety information for the patient. Labels are often found inside drug product packaging.

Identification threshold: A limit (%) above which an impurity or degradation product should be identified.

IND: Investigational New Drug Application—a request to initiate a clinical study of a new drug product.

Maximum recommended starting dose (MRSD): The highest dose recommended as the initial dose of a drug in a clinical trial. The MRSD is predicted to cause no adverse reactions.

New Drug Application (NDA): When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a New Drug Application. The application must contain data from

specific technical viewpoints for review, including chemistry, pharmacology, medicine, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDAs are assigned an NDA number.

Pharmacologically active dose (PAD): The lowest dose tested in an animal species with the intended pharmacologic activity.

PLA: Product license application for a biologic.

Qualification threshold: A limit (%) above which an impurity or degradation product should be qualified.

Qualification: For pharmaceuticals, the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or degradation product or a given impurity or degradation profile at the levels specified.

Reporting threshold: A limit (%) above which an impurity or degradation product should be reported.

Reproductive/Developmental Toxicology

Aberration: A minor structural change. It may be a retardation (a provisional delay in morphogenesis), a variation (external appearance controlled by genetic and extragenetic factors), or a deviation (resulting from altered differentiation).

Ablepharia: Absence or reduction of the eyelids.

Abrachius: Without arms, forelimbs.

Acardia: Absence of the heart.

Acaudia (anury): Agenesis of the tail.

Accessory spleen: An additional spleen.

Acephaly: Congenital absence of the head.

Achondroplasia: A hereditary defect in the formation of epiphysial cartilage, resulting in a form of dwarfism with short limbs, normal trunk, small face, normal vault, etc.

Acrania: Partial or complete absence of the skull.

Acystia: Absence of the urinary bladder.

Adactyly: Absence of digits.

Agastria: Absence of the stomach.

Agenesis: Absence of an organ or part of an organ.

Agenesis of the kidney: Absence of the kidneys.

Agenesis of the lung (lobe): Complete absence of a lobe of the lung.
Aglossia: Absence of the tongue.
Agnathia: Absence of the lower jaw (mandible).
Anal atresia: Congenital absence of the anus.
Anencephaly: Congenital absence of the cranial vault with missing or small brain mass.
Anomaly or abnormality: A morphologic or functional deviation from normal limit. It can be a malformation or a variation.
Anophthalmia: Absence of eyes.
Anorchism: Congenital absence of one or both testes.
Anotia: Absence of the external ears.
Aphalangia: Absence of a finger or a toe; corresponding metacarpals not affected.
Aplasia: Lack of development of an organ; frequently used to designate complete suppression or failure of development of a structure from the embryonic primordium.
Aplasia of the lung: The trachea shows rudimentary bronchi, but pulmonary and vascular structures are absent.
Apodia: Absence of one or both feet.
Aproctia: Imperforation or absence of the anus.
Arrhinia: Absence of the nose.
Arthrogryposis: Persistent flexure or contracture of a joint; flexed paw (bent at wrist) is most common form of arthrogryposis.
Aspermia: No ejaculate.
Astomia: Absence of oral orifice.
Asthenozoospermia: More than 50% spermatozoa with poor (< 2 grade) forward progression.
Azoospermia: No spermatozoa in the ejaculate.
Brachydactyly: Shortened digits.
Brachyury (short tail): Tail that is reduced in length.
Bulbous rib: Having a bulge or balloon-like enlargement somewhere along its length.
Cardiomegaly: Hypertrophy (enlargement) of the heart.
Cardiovascular situs inversus: Mirror-image transposition of the heart and vessels to the other side of the body.
Cephalocele: A protrusion of a part of the cranial contents, not necessarily neural tissue.

Conceptus: The sum of derivatives of a fertilized ovum at any stage of development from fertilization until birth.

Corpus luteum: The yellow endocrine body formed in the ovary at the site of the ruptured graafian follicle.

Craniorhachischisis: Exencephaly and holorrachischisis (fissure of the spinal cord).

Cranioschisis: Abnormal fissure of the cranium; may be associated with meningocele or encephalocele.

Cryptorchidism (undescended testes, ectopic testes): Failure of the testes to descend into the scrotum (can be unilateral).

Cyclopia: One central orbital fossa with none, one, or two lobes.

Deflection: A turning, or state of being turned, aside.

Deformity: Distortion of any part or general disfigurement of the body.

Deviation: Variation from the regular standard or course.

Dextrocardia: Location of the heart in the right side of the thorax; a developmental disorder that is associated with total or partial situs inversus (transposition of the great vessels and other thoraco–abdominal organs) or occurs as an isolated anomaly.

Dextrogastria: Having the stomach on the right side of the body.

Displaced rib: Out of normal position.

Dysgenesis: Defective development; malformation.

Dysmelia: Absence of a portion of one or several limbs.

Dysplasia: (a) abnormal development of tissues; (b) alteration in size, shape, or organization of adult cells.

Dystocia: Abnormal labor.

Ectocardia: Displacement of the heart inside or outside the thorax.

Ectopic: Out of the normal place.

Ectopic esophagus: Displacement of the esophagus (description of position should be included).

Ectopic pinna: Displaced external ear.

Ectrodactyly: Absence of all or of only a part of a digit (partial ectrodactyly).

Ectromelia: Aplasia or hypoplasia of one or more bones of one or more limbs (this term includes amelia, hemimelia, and phocomelia).

Encephalocele: A partial protrusion of brain through an abnormal cranial opening; not as severe as exencephaly.

Estrus: Phase of the sexual cycle of female mammals characterized by willingness to mate.

Exencephaly: Brain outside of the skull as a result of a large cranial defect.

Exomphalos: Congenital herniation of abdominal viscera into umbilical cord.

Exophthalmos: Protrusion of the eyeball ("pop" eye).

Fecundity: Ability to produce offspring rapidly and in large numbers.

Feticide: The destruction of the fetus in the uterus.

Gamete: A male (spermatozoa) or female (ovum) reproductive cell.

Gastroschisis: Fissure of the abdominal wall (median line) not involving the umbilicus, usually accompanied by protrusion of the small part of the large intestine, not covered by membranous sac.

Hemivertebra: Presence of only one-half of a vertebral body.

Hepatic lobe agenesis: Absence of a lobe of the liver.

Hepatomegaly: Abnormal enlargement of the liver.

Hydrocephaly: Enlargement of the head caused by abnormal accumulation of cerebrospinal fluid in subarachnoid cavity (external hydrocephaly) or ventricular system (internal hydrocephaly).

Hydronephrosis: Dilatation of the renal pelvis usually combined with destruction of renal parenchyma and often with dilation of the ureters (bilateral, unilateral). Note: This is a pathology term and should have histological confirmation.

Hypoplasia of the lung: Bronchial tree is poorly developed, and pulmonary tissue shows an abnormal histologic picture (total or partial); incomplete development, smaller.

Hypospadias: Urethra opening on the underside of the penis or on the perineum (males), or into the vagina (females).

Imperforate: Not open; abnormally closed.

Incomplete ossification (delayed, retarded): Extent of ossification is less than what would be expected for that developmental age, not necessarily associated with reduced fetal or pup weight.

Levocardia: Displacement of the heart in the extreme left hemithorax.

Lordosis: Anterior concavity in the curvature of the cervical and lumbar spine as viewed from the side.

Macrobrachia: Abnormal size or length of the arm.

Macrodactylia: Excessive size of one or more digits.

Macroglossia: Enlarged tongue, usually protruding.

Macrophthalmia: Enlarged eyes.

Malformation: A permanent alteration (anomaly) in which there is a morphological defect of an organ or a larger region of the body, resulting from an abnormal developmental process. A malformation will adversely affect survival, growth, or development of functional competence.

Meiosis: Cell division occurring in maturation of the sex cell (gametes) by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species.

Microcephaly: Small head.

Micrognathia: Shortened lower jaw (mandible), tongue may protrude.

Microphthalmia: Small eyes.

Microstomia: Small mouth opening.

Microtia: Small external ear.

Monocardium: Possessing a heart with only one atrium and one ventricle.

Multigravida: A female pregnant for the second (or more) time.

Naris (nostril) atresia: Absence or closure of nares.

Nasal agenesis: Absence of the nasal cavity and external nose.

Normozoospermia: Normal semen sample.

Nulliparous: A female that never has born viable offspring.

Oligodactyly: Fewer than normal number of digits.

Oligohydramnios (oligoamnios): Reduction in the amount of amniotic fluid.

Oligozoospermia: A subnormal sperm concentration in ejaculate.

Omphalocele: Midline defect in the abdominal wall at the umbilicus, through which the intestines and often other viscera (stomach, spleen, and portions of the liver) protrude. These are always covered by a membranous sac. As a rule, the umbilical cord emerges from the top of the sac.

Pachynsis: Abnormal thickening.

Patent ductus arteriosus (ductus botalli): An open channel of communication between the main pulmonary artery and the aorta, may occur as an isolated abnormality or in combination with other heart defects.

Polydactyly: Extra digits.

Polysomia: A fetal malformation consisting of two or more imperfect and partially fused bodies.

Pseudopregnancy: (a) False pregnancy: condition occurring in animals in which anatomical and physiological changes occur similar to those of pregnancy; (b) The premenstrual stage of the endometrium: so called because it resembles the endometrium just before implantation of the blastocyst.

Rachischisis: Absence of vertebral arches in limited area (partial rachischisis) or entirely (rachischisis totalis).

Renal hypoplasia: Incomplete development of the kidney.

Resorption: A conceptus which, having implanted in the uterus, subsequently died and is being, or has been, resorbed.

Rhinocephaly: A developmental anomaly characterized by the presence of a proboscis-like nose above the eyes, partially or completely fused into one.

Rudimentary rib: Imperfectly developed riblike structure.

Schistoglossia: Cleft tongue.

Seminiferous epithelium: The normal cellular components within the seminiferous tubule consisting of Sertoli cells, spermatogonia, primary spermatocytes, secondary spermatocytes, and spermatids.

Septal agenesis: Absence of nasal septum.

Sertoli cells: Cells in the testicular tubules providing support, protection, and nutrition for the spermatids.

Spermatocytogenesis: The first stage of spermatogenesis in which spermatogonia develop into spermatocytes and then into spermatids.

Spermiation: The second stage of spermatogenesis in which the spermatids transform into spermatozoa.

Spina bifida: Defect in closure of bony spinal cavity.

Sympodia: Fusion of the lower extremities.

Syndactyly: Partially or entirely fused digits.

Teratology of Fallot: An abnormality of the heart that includes pulmonary stenosis, ventricular septal defect, dextraposition of the aorta overriding the ventricular septum and receiving blood from both ventricles, and right ventricular hypertrophy.

Teratozoospermia: Fewer than 30% spermatozoa with normal morphology.

Thoracogastroschisis: Midline fissure in the thorax and abdomen.

Totalis or partialis: Total or partial transposition of viscera (due to incomplete rotation) to the other side of the body; heart most commonly affected (dextrocardia).

Tracheal stenosis: Constriction or narrowing of the tracheal lumen.

Unilobular lung: In the rat fetus, a condition in which the right lung consists of one lobe instead of four separate lobes.

Vaginal plug: A mass of coagulated semen that forms in the vagina of animals after coitus; also called copulation plug or bouchon vaginal.

Variation: An alteration that represents a retardation in development, a transitory alteration or a permanent alteration not believed to adversely affect survival, growth, development, or functional competence.

Risk Assessment/General Toxicology

Absorbed dose: The amount of a substance penetrating across the exchange boundaries of an organism and into body fluids, and tissues after exposure.

Acceptable Daily Intake (ADI): A value used for noncarcinogenic effects that represents a daily dose that is very likely to be safe over an extended period of time. An ADI is similar to an RfD (defined below) but less strictly defined.

Administered dose: The amount of a substance given to a human or test animal in determining dose–response relationships, especially through ingestion or inhalation (see *applied dose*). Administered dose is actually a measure of exposure, because even though the substance is "inside" the organism once ingested or inhaled, administered dose does not account for absorption (see absorbed dose).

Aggregate risk: The sum of individual increased risks of an adverse health effect in an exposed population.

Applied dose: The amount of a substance given to a human or test animal in determining dose–response relationships, especially through dermal contact. Applied dose is actually a measure of exposure, because it does not take absorption into account (see *absorbed dose*).

Biological significant effect: A response in an organism or other biological system that is considered to have a substantial or noteworthy effect (positive or negative) on the well-being of the biological system. Used to distinguish from statistically significant effects or changes, which may or may not be meaningful to the general state of health of the system.

Cancer potency factor (CPF): The statistical 95% upper confidence limit on the slope of the dose–response relationship at low doses for a carcinogen.

Values are in units of lifetime risk per unit dose (mg/kg/d). A plausible upper bound risk is derived by multiplying the extended lifetime average daily dose (LADD) by the CPF.

Case-control study: A retrospective epidemiologic study in which individuals with the disease under study (cases) are compared with individuals without the disease (controls) in order to contrast the extent of exposure in the diseased group with the extent of exposure in the controls.

Ceiling limit: A concentration limit in the work place that should not be exceeded, even for a short time, to protect workers against frank health effects.

CFR: Code of Federal Regulations (United States).

Cohort study: A study of a group of persons sharing a common experience (e.g., exposure to a substance) within a defined time period; the experiment is used to determine if an increased risk of a health effect (disease) is associated with that exposure.

Confidence limit: The confidence interval is a range of values that has a specified probability (e.g., 95%) of containing a given parameter or characteristic. The confidence limit often refers to the upper value of the range (e.g. upper confidence limit).

Critical endpoint: A chemical may elicit more than one toxic effect (endpoint), even in one test animal, in tests of the same or different duration (acute, subchronic, and chronic exposure studies). The doses that cause these effects may differ. The critical endpoint used in the dose–response assessment is the one that occurs at the lowest dose. In the event that data from multiple species are available, it is often the most sensitive species that determines the critical endpoint. This term is applied in the derivation of risk reference doses (RfDs).

Cross-sectional study: An epidemiologic study assessing the prevalence of a disease in a population. These studies are most useful for conditions or diseases that are not expected to have a long latent period and do not cause death or withdrawal from the study population. Potential bias in case ascertainment and exposure duration must be addressed when considering cross-sectional studies.

De minimus risk: From the legal maxim *de minimus non curat lex* or the "law is not concerned with trifles." As relates to risk assessment of carcinogens, it is commonly interpreted to mean that a lifetime risk of 1×10^{-6} is a *de minimus*

level of cancer risk (i.e., insignificant and therefore acceptable) and is of no public health consequence.

Dispersion model: A mathematical model or computer simulation used to predict the movement of airborne or waterborne contaminants. Models take into account a variety of mixing mechanisms that dilute effluents and transport them away from the point of emission.

Dose: The amount of substance administered to an animal or human, generally expressed as the weight or volume of the substance per unit of body weight (e.g., mg/kg, mL/kg).

Dose–response relationship: A relationship between the dose, often actually based on "administered dose" (i.e., exposure) rather than absorbed dose, and the extent of toxic injury produced by that chemical. Response can be expressed either as the severity of injury or proportion of exposed subjects affected. A dose–response assessment is one of the steps in a risk assessment.

Duration of exposure: Generally referred to in toxicology as acute (one-time), subacute (repeated over several weeks), subchronic (repeated for a fraction of a lifetime), and chronic (repeated for nearly a lifetime).

Endemic: Present in a community or among a group of people; said of a disease prevailing continually in a region.

Environmental fate: The destiny of a chemical or biological pollutant after release into the environment. Environmental fate involves temporal and spatial considerations of transport, transfer, storage, and transformation.

Exposure: Contact of an organism with a chemical, physical, or biological agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, and digestive tract) and available for absorption.

Exposure frequency: The number of times an exposure occurs in a given period. The exposures may be continuous, discontinuous but regular (e.g., once daily), or intermittent.

Extrapolation: An estimate of response or quantity at a point outside the range of the experimental data. Also refers to the estimation of a measured response in a different species or by a different route than that used in the experimental study of interest (i.e., species-to-species, route-to-route, acute-to-chronic, high-to-low).

Fence line concentration: Modeled or measured concentrations of pollutants found at the boundaries of a property on which a pollution source is located. Usually assumed to be the nearest location at which an exposure of the general population could occur.

Frank effect level (FEL): Related to biological responses to chemical exposures (compare with NOAEL and LOEL); the exposure level that produces an unmistakable adverse health effect (such as inflammation, severe convulsions, or death).

Hazard: The inherent ability of a substance to cause an adverse effect under defined conditions of exposure.

Hazard index: The ratio of the maximum daily dose (MDD) to the acceptable daily intake (ADI) used to evaluate the risk of noncarcinogens. A value of less than one indicates the risk from the exposure is likely insignificant; a value greater than one indicates a potentially significant risk.

Human equivalent dose: The human dose of an agent expected to induce the same type and severity of toxic effect that an animal dose has induced.

Immediately dangerous to life and health (IDLH): A concentration representing the maximum level of a pollutant from which an individual could escape within 30 min without escape-impairing symptoms or irreversible health effects.

Incidence: The number of new cases of a disease within a specified time period. It is frequently presented as the number of new cases per 1,000, 10,000, or 100,000. The incidence rate is a direct estimate of the probability or risk of developing a disease during a specified time period.

Involuntary risk: A risk that impinges on an individual without his or her awareness or consent.

Latency: The period of time between exposure to an injurious agent and the manifestation of a response.

LC_{LO} (lethal concentration low): The lowest concentration of a chemical required to cause death in some of the population after exposure for a specified period of time and observed for a specified period of time after exposure. Refers to inhalation time exposure in the context of air toxics (may refer to water concentration for tests of aquatic organisms).

LC_{50} (median lethal concentration): The concentration of a chemical required to cause death in 50% of the exposed population when exposed for a specified time period, and observed for a specified period of time after exposure.

Refers to inhalation exposure concentration in the context of air toxics (may refer to water concentration for tests of aquatic organisms).

LD_{LO} (lethal dose low): The lowest dose of a chemical required to cause death in some of the population after noninhalation exposure (e.g., injection, ingestion), for a specified observation period after exposure.

LD_{50} (median lethal dose): The dose of a chemical required to cause death in 50% of the exposed population after noninhalation exposure (e.g., injection, ingestion), for a specified observation period after exposure.

Lifetime average daily dose (LADD): The total dose received over a lifetime multiplied by the fraction of a lifetime during which exposure occurs, expressed in mg/kg body weight/day.

Lifetime risk: A risk that results from lifetime exposure.

Lowest-observed-adverse-effect level (LOAEL): The lowest dose or exposure level of a chemical in a study at which there is a statistically or biologically significant increase in the frequency or severity of an *adverse* effect in the exposed population as compared with an appropriate, unexposed control group.

Lowest-observed effect level (LOEL): In a study, the lowest dose or exposure level of a chemical at which a statistically or biologically significant effect is observed in the exposed population compared with an appropriate unexposed control group. The effect is generally considered not to have an *adverse* effect on the health and survival of the animal. This term is occasionally misused in place of a LOAEL.

Margin of exposure (MOE): The ratio of the no-observed-adverse-effect level (NOAEL) to the estimated human exposure. The MOE was formerly referred to as the margin of safety (MOS).

Maximum contaminant level (MCL): The maximum level of a contaminant permissible in water as defined by regulations promulgated under the Safe Drinking Water Act.

Maximum daily dose (MDD): Maximum dose received on any given day during a period of exposure generally expressed in mg/kg body weight/d.

Maximum tolerated dose (MTD): The highest dose of a toxicant that causes toxic effects without causing death during a chronic exposure and that does not decrease the body weight by more than 10%.

Modifying factor (MF): A factor that is greater than zero and less than or equal to 10; used in the operational derivation of a reference dose. Its magnitude

depends upon an assessment of the scientific uncertainties of the toxicological database not explicitly treated with standard uncertainty factors (e.g., number of animals tested). The default value for the MF is 1.

Multistage model: A mathematical function used to extrapolate the probability of incidence of disease from a bioassay in animals using high doses, to that expected to be observed at the low doses that are likely to be found in chronic human exposure. This model is commonly used in quantitative carcinogenic risk assessments where the chemical agent is assumed to be a complete carcinogen and the risk is assumed to be proportional to the dose in the low region.

Nonthreshold toxicant: An agent considered to produce a toxic effect from any dose; any level of exposure is deemed to involve some risk. Usually only in regard to carcinogenesis.

No-observed-adverse-effect level (NOAEL): The highest experimental dose at which there is no statistically or biologically significant increases in frequency or severity of *adverse* health effects, as seen in the exposed population compared with an appropriate, unexposed population. Effects may be produced at this level, but they are not considered to be adverse.

No-observed-effect level (NOEL): The highest experimental dose at which there is no statistically or biologically significant increases in the frequency or severity of effects seen in the exposed compared with an appropriate unexposed population.

Occupational exposure limit (OEL): A generic term denoting a variety of values and standards, generally time-weighted average concentrations of airborne substances, to which a worker can be safely exposed during defined work periods.

Permissible exposure limit (PEL): Similar to an occupational exposure limit.

Potency: A comparative expression of chemical or drug activity measured in terms of the relationship between the incidence or intensity of a particular effect and the associated dose of a chemical, to a given or implied standard of reference. Can be used for ranking the toxicity of chemicals.

ppb: Parts per billion.

ppm: Parts per million.

Prevalence: The percentage of a population that is affected with a particular disease at a given time.

q1*: The symbol used to denote the 95% upper bound estimate of the linearized slope of the dose–response curve in the low dose region as determined by the multistage model.

Reference dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude or more) of the daily exposure to the human population (including sensitive subpopulations) that is likely to be without deleterious effects during a lifetime. The RfD is reported in units of mg of substance/kg body weight/d for oral exposures, or mg/substance/m^3 of air breathed for inhalation exposures (RfC).

Risk: The probability that an adverse effect will occur under a particular condition of exposure.

Risk assessment: The scientific activity of evaluating the toxic properties of a chemical and the conditions of human exposure to it to ascertain both the likelihood that exposed humans will be adversely affected, and to characterize the nature of the effects they may experience. May contain some or all of the following four steps.

- **Hazard identification**: The determination of whether a particular chemical is or is not causally linked to particular health effects.
- **Dose–response assessment**: The determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.
- **Exposure assessment**: The determination of the extent of human exposure.
- **Risk characterization**: The description of the nature and often the magnitude of human risk, including attendant uncertainty.

Risk management: The decision-making process that uses the results of risk assessment to produce a decision about environmental action. Risk management includes consideration of technical, scientific, social, economic, and political information.

Short-term exposure limit (STEL): A time-weighted average occupational exposure level (OEL) that the American Conference of Government and Industrial Hygienists (ACGIH) indicates should not be exceeded any time during the workday. Exposures at the STEL should not be longer than 15 min and should not be repeated more than 4 times per day. There should be at least 60 min between successive exposures at the STEL.

Slope factor: See cancer potency factor.

SNUR: Significant New Use Rule.

Standardized mortality ratio: The number of deaths, either total or cause-specific, in a given group expressed as a percentage of the number of deaths that could have been expected if the group had the same age- and sex-specific rates as the general population. Used in epidemiologic studies to adjust mortality rates to a common standard so that comparisons can be made among groups.

STEL: See short-term exposure limit.

Surface area scaling factor: The intra- and interspecies scaling factor most commonly used for cancer risk assessment by the U.S. EPA to convert an animal dose to a human equivalent dose: milligrams per square meter surface area per day. Body surface area is proportional to basal metabolic rate; the ratio of surface area to metabolic rate tends to be constant from one species to another. Because body surface area is approximately proportional to an animal's body weight to the 2/3 power, the scaling factor can be reduced to milligrams per body weight$^{2/3}$.

TC_{LO} (toxic concentration low): The lowest concentration of a substance in air required to cause a toxic effect in some of the exposed population.

TD_{LO} (toxic dose low): The lowest dose of a substance required to cause a toxic effect in some of the exposed population.

Threshold limit value (TLV): The time-weighted average concentration of a substance below that no adverse health effects are expected to occur for workers assuming exposure for 8 hr per day, 40 hr per week. TLVs are published by the American Conference of Governmental Industrial Hygienists (ACGIH).

Time-weighted average (TWA): An approach to calculating the average exposure over a specified time period.

Uncertainty factor (UF): One of several, generally 10-fold factors, applied to a NOAEL or a LOAEL to derive a reference dose (RfD) from experimental data. UFs are intended to account for: (a) the variation in the sensitivity among the members of the human population; (b) the uncertainty in extrapolating animal data to human; (c) the uncertainty in extrapolating from data obtained in a less-than-lifetime exposure study to chronic exposure; and (d) the uncertainty in using a LOAEL rather than a NOAEL for estimating the threshold region.

Unit cancer risk: A measure of the probability of an individual's developing cancer as a result of exposure to a specified unit ambient concentration. For example, an inhalation unit cancer risk of 3.0 × 10-4 near a point source implies that if 10,000 people breathe a given concentration of a carcinogenic agent (e.g., 1 ($\mu g/m^3$) for 70 years, 3 of the 10,000 will develop cancer as a result of this exposure. In water the exposure unit is usually 1 μg/L), whereas in air it is 1 ($\mu g/m^3$).

Upper-bound cancer-risk assessment: A qualifying statement indicating that the cancer risk estimate is not a true value in that the dose–response modeling used provides a value that is not likely to be an underestimate of the true value. The true value may be lower than the upper-bound cancer risk estimate, and it may even be close to zero. This results from the use of a statistical upper confidence limit and from the use of conservative assumptions in deriving the cancer risk estimate.

Upper 95% confidence limit: Assuming random and normal distribution, this is the range of values below which a value will fall 95% of the time.

Voluntary risk: Risk that an individual has consciously decided to accept.

Safety Pharmacology

Action potential amplitude (APA): The amplitude of the cardiac action potential in millivolts (mV) and is a measure of the total amplitude of the action potential from initial resting level to peak depolarization. APA is determined by the combined activity of cardiac channels and transient potassium channels.

Action potential duration (APD): The duration of the cardiac action potential in milliseconds, measured from the initial upstroke to the point of return to either 60% (APD_{60}) or 90% (APD_{90}) of the initial resting potential. APD prolongation corresponds to an increase in the electrocardiographic QT interval.

Basic cycle length (BCL): In cardiac electrophysiology, is the basic cycle length of repetitive stimulation and is the inverse of stimulation frequency. BCL = 2, 1, and 0.5 s, respectively, corresponds to bradycardic (30 beats/min), normocardic (60 beats/min), and tachycardic (120 beats/min) heart rates.

hERG: Refers to both the gene that encodes the pore-forming subunit of the human cardiac ether-a-go-go related potassium channel and the protein subunit

itself. hERG channels are responsible for the delayed rectifier potassium current (I_{Kr}) that regulates action potential repolarization.

IC_{50}: Refers to the concentration or dose of test article that produces 50% inhibitory response in a test system assay.

Purkinje cells: Modified cardiac muscle cells specialized for conduction of electrical excitation from the atrioventricular node through the ventricular septum and throughout the walls of the ventricle. Purkinje cells are organized into fiber bundles that can be readily dissected from the working myocardium and studied *in vitro* using electrophysiological recording methods.

Purkinje fiber stimulation frequency: The repetition rate for application of brief electric shocks to a Purkinje fiber preparation. A frequency rate of 1 Hz corresponds to 1 shock/s and represents the normal heart rate of 1 beat/s. Frequencies of 0.5 Hz and 2 Hz correspond to bradiocardic and tachycardic heart rates.

QT interval: The time interval in the electrocardiogram extending from the start of the QRS complex to the end of the T wave, and is the measure of the duration of ventricular depolarization and repolarization. The QRS complex corresponds to the upstroke of the cardiac action potential, and the end of the T wave corresponds to the return of the action potential baseline.

Resting membrane potential (RMP): In cardiac electrophysiology, RMP is the resting membrane potential in millivolts (mV) and is obtained from the membrane voltage measured immediately before the action potential upstroke. RMP is controlled primarily by inwardly rectifying potassium channels. A decrease in RMP may indicate inhibition of the inward rectifier current.

V_{max}: In cardiac electrophysiology, this is the maximum rate of depolarization measured in volts/second obtained by taking the first derivative of the rising phase of the action potential. V_{max} amplitude is determined primarily by the activity of cardiac sodium channels. A decrease in V_{max} indicates sodium channel blockade, and corresponds to a broadening of the electrographic QRS interval and, potentially, a slowing of conduction velocity in the intact heart.

Section 17
Glossary—Alphabetical

Abbreviated New Drug Application (ANDA): An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called *abbreviated* because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the innovator drug). Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low-cost alternative to the American public.

Aberration: In developmental toxicology, a minor structural change. It may be a retardation (a provisional delay in morphogenesis), a variation (external appearance controlled by genetic and extragenetic factors), or a deviation (resulting from altered differentiation).

Ablepharia: Absence or reduction of the eyelids.

Abrachius: Without arms, forelimbs.

Absorbed dose: The amount of a substance penetrating across the exchange boundaries of an organism and into body fluids, and tissues after exposure.

Acanthosis: In dermatology, hypertrophy of the stratum spinosum and granulosum.

Acardia: Absence of the heart.

Acaudia (anury): Agenesis of the tail.

Acceptable Daily Intake (ADI): A value used for noncarcinogenic effects that represents a daily dose that is very likely to be safe over an extended period of time. An ADI is similar to an RfD (see *RfD*) but less strictly defined.

Accessory spleen: An additional spleen.

Acephaly: Congenital absence of the head.

Achondroplasia: A hereditary defect in the formation of epiphysial cartilage, resulting in a form of dwarfism with short limbs, normal trunk, small face, normal vault, etc.

Acrania: Partial or complete absence of the skull.

Action potential amplitude (APA): The amplitude of the cardiac action potential in millivolts (mV) and is a measure of the total amplitude of the action potential from initial resting level to peak depolarization. APA is determined by the combined activity of cardiac channels and transient potassium channels.

Action potential duration (APD): The duration of the cardiac action potential in milliseconds, measured from the initial upstroke to the point of return to either 60% (APD_{60}) or 90% (APD_{90}) of the initial resting potential. APD prolongation corresponds to an increase in the electrocardiographic QT interval.

Activated partial thromboplastin time: A measure of the relative activity of factors in the intrinsic clotting sequence and the common pathway necessary in normal blood coagulation.

Active ingredient: Any component of a drug that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or affects the structure or any function of the body of humans or animals.

Acystia: Absence of the urinary bladder.

Adactyly: Absence of digits.

ADCC (antibody-dependent cell-mediated cytotoxicity): A specific form of cell-mediated immunity in which an antibody binds a target and a cytotoxic cell (either a macrophage or lymphocyte), linking the two together before lysis of the target cell.

Adduct: The covalent linkage or addiction product between an alkylating agent and cellular macromolecules such as protein, RNA, and DNA.

Adjuvant: A material that enhances an immune response. It generally refers to a mixture of oil and mycobacterial cell fragments (complete adjuvant).

ADME: Absorption, distribution, metabolism, and excretion.

Administered dose: The amount of a substance given to a human or test animal in determining dose–response relationships, especially through ingestion or inhalation (see *applied dose).* Administered dose is actually a measure of exposure, because even though the substance is "inside" the organism once ingested or inhaled, administered dose does not account for absorption (see *absorbed dose).*

Agastria: Absence of the stomach.

Agenesis of the kidney: Absence of the kidneys.

Agenesis of the lung (lobe): Complete absence of a lobe of the lung.

Agenesis: Absence of an organ or part of an organ.

Aggregate risk: The sum of individual increased risks of an adverse health effect in an exposed population.

Aglossia: Absence of the tongue.

Agnathia: Absence of the lower jaw (mandible).

Akenesia: Absence or the loss of power of voluntary motion; immobility.

Alanine aminotransferase (ALT): An enzyme, primarily of liver origin, whose blood levels can rise in response to hepatocellular toxicity. Also known as SGPT (serum glutamic pyruvic transaminase).

Albumin: The most abundant blood protein synthesized by the liver.

Alkaline phosphatase: An enzyme whose blood levels can rise in response to hepatobiliary disease or increased osteoblastic (bone cell) activity. Serum alkaline phosphatase activity can be reduced in fasted rats because the intestinal isozyme is an important component of serum enzyme activity.

Alkylating agent: A chemical compound that has positively charged (electron-deficient) groups that can form covalent linkages with negatively charged portions of biological molecules such as DNA. The covalent linkage is referred to as an adduct and may have mutagenic or carcinogenic effects on the organism. The alkyl species is the radical that results when an aliphatic hydrocarbon loses one hydrogen atom to become electron-deficient. Alkylating agents react primarily with guanine, adding their alkyl group to N7 of the purine ring.

Allogenic: From a different genetic background. In the context of immunotoxicology, this usually refers to the use of genetically dissimilar cells in in vitro assays to elicit a cell-mediated immune reaction.

Altered focus: A histological identifiable clone of cells within an organ that differs phenotypically from the normal parenchyma. Foci of altered cells usually result from increased cellular proliferation, represent clonal expansions of initiated cells, and are frequently observed in multistage animal models of carcinogenesis. Foci of cellular alteration are most commonly observed in the liver of carcinogen-treated rodents and are believed by some to represent preneoplastic lesions.

Anal atresia: Congenital absence of the anus.

Anemia: Any conditions in which RBC count, hemoglobin concentration, and hematocrit are reduced.

Anencephaly: Congenital absence of the cranial vault with missing or small brain mass.

Aneuploidy: An abnormal number of chromosomes in a cell or organism that is not an exact multiple of the haploid number.

Anisocytosis: Variations in the size of red blood cells.

Anomaly or abnormality: In developmental toxicology, a morphologic or functional deviation from normal limit. It can be a malformation or a variation.

Anophthalmia: Absence of eyes.

Anorchism: Congenital absence of one or both testes.

Anotia: Absence of the external ears.

Anterior chamber: The aqueous-containing cavity of the eye, bounded by the cornea anteriorly, the chamber angle structures peripherally, and the iris and lens posteriorly.

Antibody: Complex macromolecules produced by plasma cells that recognize specific antigens. Antibodies are also referred to as immunoglobulins (Ig). They consist of two basic units: the antigen-binding fragment (Fab) contains variable regions coding for antigen recognition; and the constant fragment (Fc), which determines the function of the antibody. An Fc is designated as IgA, IgD, IgE, IgG, and IgM. Cross-linking of antibody molecules on the surface of a cell leads to activation of complement, resulting in destruction of the target by lytic cells, or in phagocytosis by macrophages.

Antibody-dependent cell-mediated cytotoxicity (ADCC): A specific form of cell-mediated immunity in which an antibody binds a target and a cytotoxic cell (either a macrophage or lymphocyte), linking the two together prior to lysis of the target cell.

Antibody-forming cell (AFC)/Plaque-forming cell (PFC) assay: The AFC assay measures the ability of animals to produce either IgM or IgG antibodies against a T-dependent or T-independent antigen following in vivo sensitization. Due to the involvement of multiple cell populations in mounting an antibody response, the AFC assay actually evaluates several immune parameters simultaneously. It is considered to be one of the most sensitive indicator systems for immunotoxicology studies.

Antigen: A molecule that is the subject of a specific immune reaction. Antigens are recognized in a cognate fashion by either immunoglobulins or the antigen receptor on the surface of T-cells. Antigens are usually proteinaceous in nature.

Antigen-presenting cell (APC): Cells that are responsible for making antigens accessible to immune effector and regulatory cells. Following internalization and degradation of the antigen (e.g., by phagocytes), a fragment of the antigen molecule is presented on the APC cell surface in association with histocompatibility molecules. The resulting complex is subsequently recognized by either B-cells via surface-bound Ig molecules, or by T-cells via the T-cell antigen receptor. Induction of a specific immune response then proceeds. Representative APCs include macrophages, dendritic cells, and certain B-cells.

Aphalangia: Absence of a finger or a toe; corresponding metacarpals not affected.

Aplasia: Lack of development of an organ; frequently used to designate complete suppression or failure of development of a structure from the embryonic primordium.

Aplasia of the lung: The trachea shows rudimentary bronchi, but pulmonary and vascular structures are absent.

Apodia: Absence of one or both feet.

Applied dose: The amount of a substance given to a human or test animal in determining dose–response relationships, especially through dermal contact. Applied dose is actually a measure of exposure, because it does not take absorption into account (see *absorbed dose).*

Aproctia: Imperforation or absence of the anus.

Arrhinia: Absence of the nose.

Arthrogryposis: Persistent flexure or contracture of a joint; flexed paw (bent at wrist) is the most common form of arthrogryposis.

Aspartate aminotransferase (AST): An enzyme whose blood levels can rise in response to hepatotoxicity, muscle damage, or hemolysis. Also known as SGOT (serum glutamic oxaloacetic transaminase).

Aspermia: No ejaculate.

Asthenozoospermia: More than 50% spermatozoa with poor (< 2 grade) forward progression.

Astomia: Absence of oral orifice.

Ataxia: Incoordination; the inability to coordinate the muscles in the execution of voluntary movement.

Azoospermia: No spermatozoa in the ejaculate.

Azotemia: An increase in serum urea nitrogen and/or creatinine levels.

Base substitution: The substitution of one or more bases for another in the nucleotide sequence.

Basic cycle length (BCL): In cardiac electrophysiology, is the basic cycle length of repetitive stimulation and is the inverse of stimulation frequency. BCL = 2, 1, and 0.5 s, respectively, corresponds to bradycardic (30 beats/min), normocardic (60 beats/min), and tachycardic (120 beats/min) heart rates.

B-cell/B lymphocytes: Lymphocytes that recognize antigen via surface-bound Ig. B-cells that have been exposed to cognate antigen subsequently proliferate and differentiate into plasma cells, which are responsible for producing specific antibody. B-cells differentiate in the bone marrow in mammals and in an organ known as the *bursa* in birds.

Benign: A classification of anticipated biological behavior of neoplasms in which the prognosis for survival is good. Benign neoplasms grow slowly, remain localized, and usually cause little harm to the patient.

Bioaccumulation factor (BAF): The ratio of tissue chemical residue to chemical concentration in an external environmental phase (i.e., water, sediment, or food). BAF is measured as steady state in situations where organisms are exposed from multiple sources (i.e., water, sediment, and food), unless noted otherwise.

Bioaccumulation: General ecotoxicology term describing a process by which chemicals are taken up by aquatic organisms directly from water as well as from exposure through other routes, such as consumption of food and sediment containing chemicals.

Biochemical oxygen demand (BOD): Sometimes called *biological oxygen demand*, a measure of the rate at which molecular oxygen is consumed by microorganisms during oxidation of organic matter. The standard test is the 5-day BOD test, in which the amount of dissolved oxygen required for oxidation over a 5-day period is measured. The results are measured in mg of oxygen/L (mg/L) or parts per million (ppm).

Bioconcentration factor (BCF): A term describing the degree to which a chemical can be concentrated in the tissues of an organism in the aquatic

environment as a result of exposure to a waterborne chemical. At steady state during the uptake phase of a bioconcentration test, the BCF is a value that is equal to the concentration of a chemical in one or more tissues of the exposed aquatic organisms divided by the average exposure water concentration of the chemical in the test.

Bioconcentration: A process by which there is a net accumulation of a chemical directly from water into aquatic organisms, resulting from simultaneous uptake (e.g., by gill or epithelial tissue) and elimination.

Biodegradation: The transformation of a material resulting from the complex enzymatic action of microorganisms (e.g., bacteria, fungi). It usually leads to disappearance of the parent chemical structure and to the formation of smaller chemical species, some of which are used for cell anabolism. Although typically used with reference to microbial activity, it may also refer to general metabolic breakdown of a substance by any living organism.

Biologic license application (BLA): Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm, who manufactures a biologic for sale in interstate commerce, to hold a license for the product. A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and the medical effects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued, allowing the firm to market the product.

Biologic product: A biologic product is any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries. Biologic products are a subset of "drug products" distinguished by their manufacturing processes (biological process versus chemical process). In general, the term "drugs" includes biologic products.

Biological significant effect: A response in an organism or other biological system that is considered to have a substantial or noteworthy effect (positive or negative) on the well-being of the biological system. Used to distinguish from statistically significant effects or changes, which may or may not be meaningful to the general state of health of the system.

Biomaterial: A material that has direct or indirect patient contact. A biomaterial (also termed a *biomedical material*) may be composed of any synthetic or

natural rubber or fiber, polymeric or elastomeric formulation, alloy, ceramic, bonding agent, ink, or other nonviable substance, including tissue rendered nonviable, used as a device or any part thereof.

Blanching: In dermal toxicology, to take color from, to bleach. Characterized by a white or pale discoloration of the exposure area due to decreased blood flow to the skin (ischemia).

Blepharitis: Inflammation of the eyelids.

Blepharospasm: Involuntary spasm of the eyelids.

Blood Urea nitrogen (BUN): The end product of protein catabolism. Blood levels can rise after renal (glomerular) injury.

Brachydactyly: Shortened digits.

Brachyury (short tail): Tail that is reduced in length.

Bulbous rib: Having a bulge or balloon-like enlargement somewhere along its length.

Cancer potency factor (CPF): The statistical 95% upper confidence limit on the slope of the dose–response relationship at low doses for a carcinogen. Values are in units of lifetime risk per unit dose (mg/kg/d). A plausible upper bound risk is derived by multiplying the extended lifetime average daily dose (LADD) by the CPF.

Cardiomegaly: Hypertrophy (enlargement) of the heart.

Cardiovascular situs inversus: Mirror-image transposition of the heart and vessels to the other side of the body.

Case-control study: A retrospective epidemiologic study in which individuals with the disease under study (cases) are compared with individuals without the disease (controls) in order to contrast the extent of exposure in the diseased group with the extent of exposure in the controls.

Catalepsy: Condition in which there is waxy rigidity of the limbs that may be placed in various positions that will be maintained for a time.

Cataract: An opacity of the lens of the eye or its capsule.

CBER: FDA's Center for Biologics Evaluation and Research—The division charged with regulating biological products.

CD (cluster of differentiation): The CD series is used to denote cell surface markers (e.g., CD4, CD8). These markers, used experimentally as a means of identifying cell types, also serve physiological roles.

CDER: FDA's Center for Drug Evaluation and Research—The division charged with developing and enforcing policy with regard to the safety, effectiveness, and labeling of all drug products for human use.

Ceiling limit: A concentration limit in the work place that should not be exceeded, even for a short time, to protect workers against frank health effects.

Cell-mediated immunity (CMI): Antigen-specific reactivity mediated primarily by T-lymphocytes. CMI may take the form of immunoregulatory activity (mediated by CD4 helper T-cells) or immune effector activity (mediated by CD8 killer T-cells). Other forms of direct cellular activity in host defense (e.g., NK cells, macrophages) are not antigen specific and are more accurately referred to as natural immunity.

Cephalocele: A protrusion of a part of the cranial contents, not necessarily neural tissue.

CFR: Code of Federal Regulations (United States).

Chemical oxygen demand (COD): COD is measured instead of BOD when organic materials are not easily degraded by microorganisms. Strong oxidizing agents (e.g., potassium permanganate) are used to enhance oxidation. COD values will be larger than BOD values.

Chemosis I: In ophthalmology, intense edema of the conjunctiva. The conjunctiva is loose fibrovascular connective tissue that is relatively rich in lymphatics and responds to noxious stimuli by swelling to the point of prolapse between the lids.

Choristoma: A mass of well-differentiated cells from one organ included within another organ, e.g., adrenal tissue present in the lung.

Choroid: The vascular middle coat between the retina and sclera of the eye.

Chromosomal aberration: A numerical or structural chromosomal abnormality.

Ciliary body: Portion of the uveal tract between the iris and the choroid of the eye, consisting of ciliary processes and the ciliary muscle.

Class testing: The testing of plastics for biological reactivity according to predetermined testing requirements defined by the United States Pharmacopeia.

Clastogen: An agent that produces structural changes of chromosomes.

Clonic convulsion: A convulsion in which the muscles alternately relax and contract.

Clonus: A form of movement characterized by contractions and relaxations of a muscle.

Cocarcinogen: An agent not carcinogenic alone but that potentiates the effect of a known carcinogen.

Cocarcinogenesis: The augmentation of neoplasm formation by simultaneous administration of a genotoxic carcinogen and an additional agent (cocarcinogen) that has no inherent carcinogenic activity by itself.

Cohort study: A study of a group of persons sharing a common experience (e.g., exposure to a substance) within a defined time period; the experiment is used to determine if an increased risk of a health effect (disease) is associated with that exposure.

Combination (medical device) product: A product containing both a drug and device component that are physically, chemically, or otherwise combined to result in a medical product that is used therapeutically as a single entity. The medical device component must be evaluated for safety according to device requirements, the drug component evaluated for safety as per drug requirements, and the safety of the finished combined product also must be evaluated.

Complement: A group of approximately 20 protein precursor molecules that interact in a cascading fashion. Following activation, the various complement precursor molecules assemble into a complex that intercalates into the membrane of a cell, resulting in osmotic lysis of the target cell.

Conceptus: The sum of derivatives of a fertilized ovum at any stage of development from fertilization until birth.

Confidence limit: The confidence interval is a range of values that has a specified probability (e.g., 95%) of containing a given parameter or characteristic. The confidence limit often refers to the upper value of the range (e.g., upper confidence limit).

Conjunctiva: Mucous membrane that lines the posterior aspect of the eyelids (palpebral conjunctiva) and the anterior sclera (bulbar conjunctiva).

Conjunctivitis: Inflammation of the conjunctiva.

Contact dermatitis: A delayed type of induced sensitivity (allergy) of the skin with varying degrees of erythema, edema, and vesiculation, resulting from cutaneous contact with a specific allergen.

Contact urticaria: Wheal-and-flare response elicited within 30 to 60 min after cutaneous exposure to test substance. May be IgE mediated or nonimmunologically mediated.

Convulsion: A violent spasm of the face, trunk, or extremities.

Cornea: Transparent portion of the outer coat of the eyeball forming the anterior wall of the anterior chamber.

Corpus luteum: The yellow endocrine body formed in the ovary at the site of the ruptured graafian follicle.

Corrosion: Direct chemical action on normal living skin that results in its disintegration, an irreversible alteration at the site of contact. Corrosion is manifested by ulceration and necrosis with subsequent scar formation.

Craniorhachischisis: Exencephaly and holorrachischisis (fissure of the spinal cord).

Cranioschisis: Abnormal fissure of the cranium; may be associated with meningocele or encephalocele.

Creatine kinase (CK): An enzyme that is concentrated in skeletal muscle, brain, and heart tissue.

Creatinine: The end product of creatine metabolism in muscle. Elevated blood levels can indicate renal (glomerular) injury.

Critical endpoint: A chemical may elicit more than one toxic effect (endpoint), even in one test animal, in tests of the same or different duration (acute, subchronic, and chronic exposure studies). The doses that cause these effects may differ. The critical endpoint used in the dose–response assessment is the one that occurs at the lowest dose. In the event that data from multiple species are available, it is often the most sensitive species that determines the critical endpoint. This term is applied in the derivation of risk reference doses (RfDs).

Cross-sectional study: An epidemiologic study assessing the prevalence of a disease in a population. These studies are most useful for conditions or diseases that are not expected to have a long latent period and do not cause death or withdrawal from the study population. Potential bias in case ascertainment and exposure duration must be addressed when considering cross-sectional studies.

Cryptorchidism (undescended testes, ectopic testes): Failure of the testes to descend into the scrotum (can be unilateral).

Cumulative irritation: In dermal toxicology, primary irritation resulting from repeated exposures to materials that do not in themselves cause acute primary irritation.

Cyclopia: In developmental toxicology, one central orbital fossa with none, one, or two lobes.

Cytokine: Small peptides produced primarily by cells of the immune system, particularly helper T-cells. Cytokines are roughly grouped into nonexclusive categories including interleukins, tumor necrosis factors, interferons, colony-stimulating factors, and various miscellaneous cytokines. Related molecules include peptide growth factors, transforming growth factors, and chemokines. Cytokines form an interactive network with both hormones and neuropeptides. Cytokines may be referred to in the older literature as lymphokines.

Cytotoxic T-lymphocyte (CTL): A subset of CD8 T-cells that are able to kill target cells following the induction of a specific immune response. The mechanism of lysis appears to be a combination of direct lysis by extravasation of lytic molecules, as well as the induction or apoptosis in the target cell. Measurement of CTL activity is a sensitive indicator of cell-mediated immunity.

De minimus risk: From the legal maxim *de minimus non curat lex* or the "law is not concerned with trifles." As relates to risk assessment of carcinogens, it is commonly interpreted to mean that a lifetime risk of 1×10^{-6} is a *de minimus* level of cancer risk (i.e., insignificant and therefore acceptable) and is of no public health consequence.

Deflection: In developmental toxicology, a turning, or state of being turned, aside.

Deformity: Distortion of any part or general disfigurement of the body.

Delayed-type hypersensitivity (DTH): A form of cell-mediated immunity in which recall exposure to an antigen results in an inflammatory reaction mediated by T-lymphocytes. Usually expressed as contact hypersensitivity.

Dermatitis: Inflammation of the skin.

Desquamation: The shedding of the cuticle in scales or the outer layer of any surface in dermal toxicology. To shred, peel, or scale off, as the casting off of the epidermis in scales or shred, or the shedding of the outer layer of any surface.

Deviation: Variation from the regular standard or course.

Dextrocardia: Location of the heart in the right side of the thorax; a developmental disorder that is associated with total or partial situs inversus

(transposition of the great vessels and other thoraco–abdominal organs) or occurs as an isolated anomaly.

Dextrogastria: Having the stomach on the right side of the body.

Direct carcinogen: Carcinogens that have the necessary structure to directly interact with cellular constituents and cause neoplasia. Direct-acting carcinogens do not require metabolic conversion by the host to be active. They are considered genotoxic because they typically undergo covalent binding to DNA.

Direct contact: When the materials of a medical device are in direct (i.e., intimate) contact with the surface or tissues of the body (e.g., adhesive bandages, pacemaker leads).

Dispersion model: A mathematical model or computer simulation used to predict the movement of airborne or waterborne contaminants. Models take into account a variety of mixing mechanisms that dilute effluents and transport them away from the point of emission.

Displaced rib: Out of normal position.

Dose: The amount of substance administered to an animal or human, generally expressed as the weight or volume of the substance per unit of body weight (e.g., mg/kg, mL/kg).

Dose–response relationship: A relationship between the dose, often actually based on "administered dose" (i.e., exposure) rather than absorbed dose, and the extent of toxic injury produced by that chemical. Response can be expressed either as the severity of injury or proportion of exposed subjects affected. A dose–response assessment is one of the steps in a risk assessment.

Drug: A substance recognized by an official pharmacopoeia or formulary. A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. A substance (other than food) intended to affect the structure or any function of the body. A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biologic products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

Drug label: The FDA-approved label is the official description of a drug product, which includes indication (what the drug is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children,

and other populations; and safety information for the patient. Labels are often found inside drug product packaging.

Duration of exposure: Generally referred to in toxicology as acute (one-time), subacute (repeated over several weeks), subchronic (repeated for a fraction of a lifetime), and chronic (repeated for nearly a lifetime).

Dust: The airborne state of a chemical that is solid at room temperature but is dispensed into a particulate atmosphere.

Dysarthria: In neurotoxicology, disturbance of articulation due to emotional stress or paralysis, incoordination, or spasticity of muscles used in vocalizing.

Dysgenesis: Defective development; malformation.

Dyskinesia: Difficulty in performing voluntary movements; a movement disorder characterized by insuppressible, stereotyped, automatic movements.

Dysmelia: Absence of a portion of one or several limbs.

Dysplasia: Disordered tissue formation characterized by changes in size, shape, and orientational relationships of adult types of cells. Primarily seen in epithelial cells.

Dystocia: Abnormal labor.

Dystonia: Abnormal tonicity (hyper- or hypo-) in any tissues.

EC_{50} (median effective concentration): The concentration of chemical in water to which test organisms are exposed is estimated to be effective in producing some sublethal response in 50% of the test organisms. The EC_{50} is usually expressed as a time-dependent value (e.g., 24 hr or 96 hr EC_{50}). The sublethal response elicited from the test organisms as a result of exposure to the chemical must be clearly defined (e.g., test organisms may be immobilized, lose equilibrium, or undergo physiological or behavioral changes).

Ectocardia: Displacement of the heart inside or outside the thorax.

Ectopic esophagus: Displacement of the esophagus (description of position should be included).

Ectopic pinna: Displaced external ear.

Ectopic: Out of the normal place.

Ectrodactyly: Absence of all or of only a part of a digit (partial ectrodactyly).

Ectromelia: Aplasia or hypoplasia of one or more bones of one or more limbs (this term includes amelia, hemimelia, and phocomelia).

Eczema: Inflammatory condition in which the skin becomes red and small vesicles, crusts, and scales develop.

Edema: An excessive accumulation of serous fluid or water in cells, tissues, or serous cavities.

ELISA (Enzyme-Linked ImmunoSorbent Assay): A type of immunoassay in which specific antibodies are used to both capture and detect antigens of interest. The most popular type is the "sandwich" ELISA in which antibodies are bound to a substrate such as a plastic culture plate. These antibodies bind antigenic determinants on molecules (or alternatively on whole cells). Unrelated material is washed away, and the plates are exposed to an antibody of a different specificity; this antibody is coupled to a detector molecule.

Encephalocele: A partial protrusion of brain through an abnormal cranial opening; not as severe as exencephaly.

Endemic: Present in a community or among a group of people; said of a disease prevailing continually in a region.

Environmental fate: The destiny of a chemical or biological pollutant after release into the environment. Environmental fate involves temporal and spatial considerations of transport, transfer, storage, and transformation.

Epigenetic: Change in phenotype without a change in DNA structure. One of two main mechanisms of carcinogen action, epigenetic carcinogens are nongenotoxic, i.e., they do not form reactive intermediates that interact with genetic material in the process of producing or enhancing neoplasm formation.

Erythema: An inflammatory redness of the skin, as caused by chemical poisoning or sunburn, usually a result of congestion of the capillaries.

Eschar: A dry scab, thick coagulated crust, or slough formed on the skin as a result of a thermal burn or by the action of a corrosive or caustic substance.

Estrus: Phase of the sexual cycle of female mammals characterized by willingness to mate.

Exencephaly: Brain outside of the skull as a result of a large cranial defect.

Exfoliation: To remove in flakes or scales, peel. To cast off in scales, flakes, etc. To come off or separate, as scales, flakes, sheets, or layers in dermal toxicology. Detachment and shedding of superficial cells of an epithelium or from any tissue surface. Scaling or desquamation of the horny layer of epidermis, which varies in amount from minute quantities to shedding the entire integument.

Exomphalos: Congenital herniation of abdominal viscera into umbilical cord.

Exophthalmos: Protrusion of the eyeball ("pop" eye).

Exposure: Contact of an organism with a chemical, physical, or biological agent. Exposure is quantified as the amount of the agent available at the exchange boundaries of the organism (e.g., skin, lungs, and digestive tract) and available for absorption.

Exposure assessment: The determination of the extent of human exposure.

Exposure frequency: The number of times an exposure occurs in a given period. The exposures may be continuous, discontinuous but regular (e.g., once daily), or intermittent.

Extract: A solution produced by the incubation of a material/medical device in an appropriate vehicle. After incubation, the vehicle contains the soluble chemicals (or leachables) that have dissolved out of, or off of, the material/medical device.

Extrapolation: An estimate of response or quantity at a point outside the range of the experimental data. Also refers to the estimation of a measured response in a different species or by a different route than that used in the experimental study of interest (i.e., species-to-species, route-to-route, acute-to-chronic, high-to-low).

Fasiculations: Involuntary contractions, or twitching, of groups of muscle fibers.

Fate: Disposition of a material in various environmental compartments (e.g., soil or sediment, water, air, and biota) as a result of transport, transformation, and degradation.

Fecundity: Ability to produce offspring rapidly and in large numbers.

Fence line concentration: Modeled or measured concentrations of pollutants found at the boundaries of a property on which a pollution source is located. Usually assumed to be the nearest location at which an exposure of the general population could occur.

Feticide: The destruction of the fetus in the uterus.

Fibrinogen: A glycoprotein that is involved in the formation of fibrin.

Fluorescein (fluorescein sodium): A fluorescent dye, the simplest of the fluorane dyes and the mother substance of eosin, that is commonly used intravenously to determine the state of adequacy of circulation in the retina and to a lesser degree in the chorioid and iris. Another important use is to detect epithelial lesions of the cornea and conjunctiva. Peak excitation occurs with

light at a wavelength between 485 and 500 nm and peak emission occurs between 520 and 530 nm.

Fovea: Depression in the macula adapted for most acute vision.

Frameshift mutation: A mutation in the genetic code in which one base or two adjacent bases are inserted into or deleted from the nucleotide sequence of a gene.

Frank effect level (FEL): Related to biological responses to chemical exposures (compare with NOAEL and LOEL); the exposure level that produces an unmistakable adverse health effect (such as inflammation, severe convulsions, or death).

Fume: The airborne state of a chemical that is liquid or solid at room temperature and pressure but is heated and allowed to condense into a particulate atmosphere.

Fundus: The posterior portion of the eye visible through an ophthalmoscope.

Gamete: A male (spermatozoa) or female (ovum) reproductive cell.

Gamma glutamyltransferase (γGT): An enzyme of liver origin, whose blood concentration can be elevated in hepatobiliary disease.

Gas: The airborne state of a chemical that boils at or below room temperature and pressure.

Gastroschisis: Fissure of the abdominal wall (median line) not involving the umbilicus, usually accompanied by protrusion of the small part of the large intestine, not covered by membranous sac.

Gene mutation: A detectable permanent change (point mutation, insertion, or deletion) within a single gene or its regulating sequences.

Genotoxic carcinogen: An agent that interacts with cellular DNA either directly in its parent form (direct carcinogen) or after metabolic biotransformation.

Geometric standard deviation (GSD): In inhalation toxicology, the relative dispersion of the MMAD, such that a value approaching one indicates a monodisperse atmosphere.

Globulin: A group of blood proteins synthesized by lymphatic tissue in the liver.

Gut-associated lymphoid tissue (GALT): Lymphoid cells and tissues lining the mucosa that serve as the first point of contact with antigen encountered via this route. GALT comprises Peyer's patches, the appendix, tonsils, and mesenteric lymph nodes.

Hapten: Low-molecular-weight molecules that are not antigenic by themselves, but which are recognized as antigens when bound to larger molecules, usually proteins.

Hazard: The inherent ability of a substance to cause an adverse effect under defined conditions of exposure.

Hazard identification: The determination of whether a particular chemical is or is not causally linked to particular health effects.

Hazard index: The ratio of the maximum daily dose (MDD) to the acceptable daily intake (ADI) used to evaluate the risk of noncarcinogens. A value of less than one indicates the risk from the exposure is likely insignificant; a value greater than one indicates a potentially significant risk.

Head-only exposure: A system for exposing test animals via inhalation in which they are restrained in a tube in such a way that only their heads are exposed directly to the test material.

Hemivertebra: Presence of only one-half of a vertebral body.

Hemolysis: The destruction of red blood cells, resulting in liberation of hemoglobin into plasma.

Hepatic lobe agenesis: Absence of a lobe of the liver.

Hepatomegaly: Abnormal enlargement of the liver.

hERG: Refers to both the gene that encodes the pore-forming subunit of human cardiac ether-a-go-go related potassium channel and the protein subunit itself. hERG channels are responsible for the delayed rectifier potassium current (I_{Kr}) that regulates action potential repolarization.

Human equivalent dose (HED): A dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose. In drug development, the term HED is usually used to refer to the human equivalent dose of the NOAEL.

Humoral-mediated immunity (HMI): Specific immune responses that are mediated primarily by humoral factors, including antibodies and complement. The induction of HMI generally, although not exclusively, requires the cooperation of cellular immune mechanisms.

Hybridoma: A genetically-engineered cell clone that produced antibodies of a single type (i.e., monoclonal antibodies). Monoclonal antibodies are highly specific for their cognate antigen and make highly useful tools for immunotoxicological studies.

Hydrocephaly: Enlargement of the head caused by abnormal accumulation of cerebrospinal fluid in subarachnoid cavity (external hydrocephaly) or ventricular system (internal hydrocephaly).

Hydronephrosis: Dilatation of the renal pelvis usually combined with destruction of renal parenchyma and often with dilation of the ureters (bilateral, unilateral). Note: This is a pathology term and should have histological confirmation.

Hyperemia: Excess of blood in a part due to local or general relaxation of the arterioles. Blood vessels become congested and give the area involved a reddish or red–blue color.

Hyperkeratosis: Hypertrophy and thickening of the stratum corneum.

Hyperkinesia: Excessive muscular activity.

Hyperplasia: A numerical increase in the number of phenotypically normal cells within a tissue or organ.

Hypersensitivity: A vigorous and often inappropriate immune response to seemingly innocuous antigens. Hypersensitivity is classified into subtypes, depending on the mechanisms of action and the target cells or tissues.

Hypertrophy: Increase in the size of an organelle, cell, tissue, or organ within a living organism. To be distinguished from hyperplasia, hypertrophy refers to an increase in size rather than an increase in number. Excessive hyperplasia in a tissue may produce hypertrophy of the organ in which that tissue occurs.

Hypoplasia of the lung: Bronchial tree is poorly developed, and pulmonary tissue shows an abnormal histologic picture (total or partial); incomplete development, smaller.

Hypospadias: Urethra opening on the underside of the penis or on the perineum (males), or into the vagina (females).

IC_{50}: Refers to the concentration or dose of test article that produces 50% inhibitory response in a test system assay.

Icteric: Relating to a jaundiced condition, typically as a result of elevated serum bilirubin levels.

Identification threshold: A limit (%) above which an impurity or degradation product of a drug should be identified.

Immediately dangerous to life and health (IDLH): A concentration representing the maximum level of a pollutant from which an individual could

escape within 30 min without escape-impairing symptoms or irreversible health effects.

Immune reserve: The concept that the immune response exhibits multiple redundancies that are capable of accommodating acute reductions in isolated immune functions. This reserve would theoretically prevent a severe reduction in host resistance, following a temporary immunosuppression of selected immune functions.

Imperforate: Not open; abnormally closed.

In situ carcinoma: A localized intraepithelial form of epithelial cell malignancy. The cells possess morphological criteria of malignancy but have not yet gone beyond the limiting basement membrane.

Incidence: The number of new cases of a disease within a specified time period. It is frequently presented as the number of new cases per 1,000, 10,000, or 100,000. The incidence rate is a direct estimate of the probability or risk of developing a disease during a specified time period.

Incomplete ossification (delayed, retarded): Extent of ossification is less than what would be expected for that developmental age, not necessarily associated with reduced fetal or pup weight.

IND: Investigational New Drug Application—a request to initiate a clinical study of a new drug product.

Indirect contact: When materials of a medical device do not contact the surface or tissues of the body, but the materials of the device may influence the body. In this case, a solution or other material that contacts the device may become contaminated with leachables from the device, which in turn contacts tissues of the body (e.g., intravenous infusion bag).

Initiation: The first step in carcinogenesis whereby limited exposure to a carcinogenic agent produces a latent but heritable alteration in a cell, permitting its subsequent proliferation and development into a neoplasm after exposure to a promoter.

Initiator: A chemical, physical, or biological agent that is capable of irreversibly altering the genetic component (DNA) of the cell. Although initiators are generally considered to be carcinogens, they are typically used at low noncarcinogenic doses in two-stage initiation–promotion animal model systems. Frequently referred to as a "tumor initiator."

Injection: In ophthalmology, congestion of blood vessels.

Intratracheal dosing: A method of delivering, via a syringe and blunt needle, test material directly into the trachea of a test animal.

Involuntary risk: A risk that impinges on an individual without his or her awareness or consent.

Iris: The circular pigmented membrane behind the cornea and immediately in front of the lens; the most anterior portion of the vascular tunic of the eye. It is composed of the dilator and sphincter muscles, and the two-layered posterior epithelium, and mesodermal components that form the iris stroma.

Iritis: Inflammation of the iris, manifested by vascular congestion (hyperemia). An outpouring of serum proteins into the aqueous (flare) may accompany the inflammatory reaction.

Irritant: A substance that causes inflammation and other evidence of irritation, particularly of the skin, on first contact or exposure; a reaction of irritation not dependent on a mechanism of sensitization.

Irritation: A local reversible inflammatory response of normal living skin to direct injury caused by a single application of a toxic substance, without the involvement of an immunologic mechanism.

ISO: International Standards Organization.

Keratitis: Inflammation of the cornea.

Lactate dehydrogenase: An enzyme found in several organs, including liver, kidney, heart, and skeletal muscle.

Latency: The period of time between exposure to an injurious agent and the manifestation of a response.

LC_{50} (Median Lethal Concentration): The concentration of a chemical required to cause death in 50% of the exposed population when exposed for a specified time period, and observed for a specified period of time after exposure. Refers to inhalation exposure concentration in the context of air toxics (may refer to water concentration for tests of aquatic organisms).

LC_{LO} (Lethal Concentration Low): The lowest concentration of a chemical required to cause death in some of the population after exposure for a specified period of time and observed for a specified period of time after exposure. Refers to inhalation time exposure in the context of air toxics (may refer to water concentration for tests of aquatic organisms).

LD_{50} (median lethal dose): The dose of a chemical required to cause death in 50% of the exposed population after noninhalation exposure (e.g., injection, ingestion), for a specified observation period after exposure.

LD_{LO} (lethal dose low): The lowest dose of a chemical required to cause death in some of the population after noninhalation exposure (e.g., injection, ingestion), for a specified observation period after exposure.

Lens: A transparent biconvex structure suspended in the eyeball between the aqueous and the vitreous. Its function is to bring rays of light to a focus on the retina. Accommodation is produced by variations in the magnitude of this effect.

Levocardia: Displacement of the heart in the extreme left hemithorax.

Lifetime average daily dose (LADD): The total dose received over a lifetime multiplied by the fraction of a lifetime during which exposure occurs, expressed in mg/kg body weight/day.

Lifetime risk: A risk that results from lifetime exposure.

Liquid aerosol: The airborne state of a chemical that is liquid at room temperature and pressure but is nebulized into a particulate atmosphere.

Lordosis: Anterior concavity in the curvature of the cervical and lumbar spine as viewed from the side.

Lowest-observed effect level (LOEL): In a study, the lowest dose or exposure level of a chemical at which a statistically or biologically significant effect is observed in the exposed population compared with an appropriate unexposed control group. The effect is generally considered not to have an adverse effect on the health and survival of the animal. This term is occasionally misused in place of a LOAEL.

Lowest-observed-adverse-effect level (LOAEL): The lowest dose or exposure level of a chemical in a study at which there is a statistically or biologically significant increase in the frequency or severity of an *adverse* effect in the exposed population as compared with an appropriate, unexposed control group.

Lung compliance: A measure of the ease with which the lung is extended usually expressed as mL/cmH_2O.

Lung resistance: The total resistance to the movement of air during the expiratory phase of the respiratory cycle expressed as $cmH_2O/mL/sec$.

Macrobrachia: Abnormal size or length of the arm.

Macrodactylia: Excessive size of one or more digits.

Macroglossia: Enlarged tongue, usually protruding.

Macrophage: A bone-marrow-derived cell that is present in the peripheral tissue; macrophages found in the circulation are referred to as monocytes. Macrophages serve a wide variety of host defense needs, acting as both nonspecific killer cells and as regulators of other immune, and nonimmune host resistance mechanisms.

Macrophthalmia: Enlarged eyes.

Major histocompatibility complex (MHC): Murine cell surface molecules of which two major classes are recognized: Class I (present on all nucleated cells) and Class II (present on B-cells, T-cells, and macrophages). MHC molecules appear to direct the course of immune reactivity and are presented in association with antigen by antigen-presenting cells. The human equivalent is termed HLA (human leukocyte antigen).

Malformation: A permanent alteration (anomaly) in which there is a morphological defect of an organ or a larger region of the body, resulting from an abnormal developmental process. A malformation will adversely affect survival, growth, or development of functional competence.

Malignant: A classification of anticipated biological behavior of neoplasms in which the prognosis for survival is poor. Malignant neoplasms grow rapidly, invade, and destroy, and are usually fatal.

Margin of exposure (MOE): The ratio of the no-observed-adverse-effect level (NOAEL) to the estimated human exposure. The MOE was formerly referred to as the margin of safety (MOS).

Mass median aerodynamic diameter (MMAD): In inhalation toxicology, the median-size particle based on mass measurement relative to a unit density sphere.

Maximal acceptable toxicant concentration (MATC): In aquatic toxicology, the hypothetical toxic threshold concentration lying in a range bounded at the lower end by the highest tested concentration having no observed effect (NOEC) and at the higher end by the lowest concentration having a statistically significant toxic effect (LOEC) in a life cycle (full chronic) or a partial life cycle (partial chronic) test. This can be represented by NOEC < MATC < LOEC.

Maximum contaminant level (MCL): The maximum level of a contaminant permissible in water as defined by regulations promulgated under the Safe Drinking Water Act.

Maximum daily dose (MDD): Maximum dose received on any given day during a period of exposure generally expressed in mg/kg body weight/day.

Maximum recommended starting dose (MRSD): The highest dose recommended as the initial dose of a drug in a clinical trial. The MRSD is predicted to cause no adverse reactions.

Maximum tolerated dose (MTD): The highest dose of a toxicant that causes toxic effects without causing death during a chronic exposure and that does not decrease the body weight by more than 10%.

Mean corpuscular hemoglobin: The average amount of hemoglobin per red blood cell.

Mean corpuscular hemoglobin concentration: The average hemoglobin concentration per red blood cell.

Mean corpuscular volume: The average size of the red blood cell.

Medical device: Any instrument, apparatus, appliance, material, or other article, including software, whether used alone or in combination, intended by the manufacturer for use by human beings solely or principally for the purpose of diagnosis, prevention, monitoring, or treatment; alleviation of disease, injury, or handicap; investigation, replacement, or modification of the anatomy or of a physiological process; control of conception; and that which does not achieve its principal intended action of the body by pharmaceutical, immunological, or metabolic means but may be assisted in its function by such means.

Meiosis: Cell division occurring in maturation of the sex cell (gametes) by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species.

Metaplasis: The substitution in a given area of one type of fully differentiated cell for the fully differentiated cell type normally present in that area, e.g., squamous epithelium replacing ciliated epithelium in the respiratory airways.

Metastasis: The dissemination of cells from a primary neoplasm to a noncontiguous site and their growth therein. Metastases arise by dissemination of cells from the primary neoplasm via the vascular or lymphatic system and are an unequivocal hallmark of malignancy.

Methemoglobin: Oxidized hemoglobin incapable of carrying oxygen.

Microcephaly: Small head.

Micrognathia: Shortened lower jaw (mandible), tongue may protrude.

Micronucleus: A microscopically detectable particle in a cell that contains nuclear DNA, usually one twentieth to one fifth the size of the main nucleus. It may be composed of a broken centric or acentric part of a chromosome or a whole chromosome.

Microphthalmia: Small eyes.

Microstomia: Small mouth opening.

Microtia: Small external ear.

Miotic: A drug causing pupillary constriction.

Mitogen: Molecules capable of inducing cellular activation and may include sugars or peptides. The ability of a cell to respond to stimulation with a mitogen (generally assessed by cellular proliferation) is thought to give an indication of the cell's immune responsiveness. Mitogens most commonly employed in immunotoxicology assays include the T-cell mitogens, Concanavalin A (ConA), and phytohemagglutinin (PHA). Mitogens routinely used for assessing B-cell proliferation include pokeweed mitogen (PWM) and *E. coli* lipopolysaccharide (LPS).

Mitogenesis: The generation of cell division or cell proliferation.

Mitotic index: The ratio of the number of cells in a population in various stages of mitosis to the number of cells in the population not in mitosis.

Modifying factor (MF): In risk assessment, a factor that is greater than zero and less than or equal to 10; used in the operational derivation of a reference dose. Its magnitude depends upon an assessment of the scientific uncertainties of the toxicological database not explicitly treated with standard uncertainty factors (e.g., number of animals tested). The default value for the MF is 1.

Monocardium: Possessing a heart with only one atrium and one ventricle.

MTD: Maximum tolerated dose. Refers to the maximum amount of an agent that can be administered to an animal in a carcinogenicity test without adversely affecting the animal because of toxicity other than carcinogenicity. Examples of having exceeded the MTD include excessive early mortality, excessive loss of body weight, production of anemia, production of tissue necrosis, and overloading of the metabolic capacity of the organism.

Multigravida: A female pregnant for the second (or more) time.

Multistage model: A mathematical function used to extrapolate the probability of incidence of disease from a bioassay in animals using high doses, to that expected to be observed at the low doses that are likely to be found in chronic human exposure. This model is commonly used in quantitative carcinogenic risk assessments where the chemical agent is assumed to be a complete carcinogen and the risk is assumed to be proportional to the dose in the low region.

Mutation: A structural alteration of DNA that is hereditary and gives rise to an abnormal phenotype. A mutation is always a change in the DNA base sequence and includes substitutions, additions, rearrangements, or deletions of one or more nucleotide bases.

Mydriatic: A drug causing pupillary dilatation.

Myoclonus: Brief, involuntary twitching of a muscle or a group of muscles.

Myotonia: Delayed relaxation of a muscle after an initial contraction.

Naris (nostril) atresia: Absence or closure of nares.

Nasal agenesis: Absence of the nasal cavity and external nose.

Natural (nonspecific) immunity: Host defense mechanisms that do not require prior exposure to antigen. Nonspecific immunity is mediated by NK cells, macrophages, neutrophils, and complement.

Natural killer (NK) cells: A population of lymphocytes separate from T- and B-lymphocytes, also referred to as large granular lymphocytes (LGL). NK cells exhibit cytotoxicity against virally infected cells and certain tumor cells. They are notable in that they do not require prior exposure to antigen to express cytotoxicity towards their targets. Assessment of NK activity provides a measurement of nonspecific host resistance.

Necrosis: Pathological death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage.

New Drug Application (NDA): When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a New Drug Application. The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medicine, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDAs are assigned an NDA number.

Nonocclusive: Site of application of test substance to the skin is open to the air.

Nonthreshold toxicant: An agent considered to produce a toxic effect from any dose; any level of exposure is deemed to involve some risk. Usually only in regard to carcinogenesis.

No-observed-adverse-effect level (NOAEL): The highest experimental dose at which there is no statistically or biologically significant increases in frequency or severity of *adverse* health effects, as seen in the exposed population compared with an appropriate, unexposed population. Effects may be produced at this level, but they are not considered to be adverse.

No-observed-effect level (NOEL): The highest experimental dose at which there is no statistically or biologically significant increases in the frequency or severity of effects seen in the exposed compared with an appropriate unexposed population.

Normozoospermia: Normal semen sample.

Nose-only exposure: A system for exposing test animals via inhalation in which they are restrained in a tube in such a way that only their nose or snout is exposed directly to the test material.

Nulliparous: A female that never has born viable offspring.

Nystagmus: An involuntary, rapid movement of the eyeball that may be horizontal, vertical, rotatory, or mixed.

Occlusive covering: A bandage or dressing that covers the skin and excludes it from air. Prevents loss of a test substance by evaporation and by increasing tissue penetration.

Occupational exposure limit (OEL): A generic term denoting a variety of values and standards, generally time-weighted average concentrations of airborne substances, to which a worker can be safely exposed during defined work periods.

Octanol–water partition coefficient (K_{ow}): The ratio of the solubility of a chemical in n-octanol and water at steady state; also expressed as *P*. The logarithm of *P* or K_{ow} (i.e., log *P* or K_{ow}) is used as an indication of the propensity of a chemical for bioconcentration by aquatic organisms.

Oligodactyly: Fewer than normal number of digits.

Oligohydramnios (oligoamnios): Reduction in the amount of amniotic fluid.

Oligozoospermia: A subnormal sperm concentration in ejaculate.

Omphalocele: Midline defect in the abdominal wall at the umbilicus, through which the intestines and often other viscera (stomach, spleen, and portions of the liver) protrude. These are always covered by a membranous sac. As a rule, the umbilical cord emerges from the top of the sac.

Oncogene: The activated form of a protooncogene. Oncogenes are associated with development of neoplasia.

Optic disk: Ophthalmoscopically visible portion of the optic nerve.

Pachynsis: Abnormal thickening.

Packed cell volume: The percentage of blood that contains RBC components; synonymous with hematocrit.

Palpebral: Pertaining to the eyelid.

Pannus: Vascularization and connective-tissue deposition beneath the epithelium of the cornea of the eye.

Paraesthesia: An abnormal sensation such as burning, prickling, tickling, or tingling.

Patent ductus arteriosus (ductus botalli): An open channel of communication between the main pulmonary artery and the aorta, may occur as an isolated abnormality or in combination with other heart defects.

Permissible exposure limit (PEL): Similar to an occupational exposure limit.

Pharmacologically active dose (PAD): The lowest dose tested in an animal species with the intended pharmacologic activity.

Photoallergy: An increased reactivity of the skin to UV and/or visible radiation produced by a chemical agent on an immunologic basis. Previous allergy sensitized by exposure to the chemical agent and appropriate radiation is necessary. The main role of light in photoallergy appears to be in the conversion of the hapten to a complete allergen.

Photoirritation: Irritation resulting from light-induced molecular changes in the structure of chemicals applied to the skin.

Photosensitization: Sensitization of the skin to ultraviolet (UV) light, usually due to the action of certain drugs, plants, or other substances, may occur shortly after administration of the substance, or may occur only after latent period of days to months. The processes whereby foreign substances, either absorbed locally into the skin or systemically, may be subjected to photochemical reactions within the skin, leading to either chemically induced

photosensitivity reactions or alteration of the "normal" pathologic effects of light. UV-A is usually responsible for most photosensitivity reactions.

PLA: Product license application for a biologic.

Plasmid: An autonomously replicating DNA molecule distinct from the normal genome. A plasmid may insert into the host chromosome or form an extra chromosomal element.

Poikilocytosis: Variations in the shape of red blood cells.

Point mutation: Change in the genetic code, usually confined to a single base pair.

Polychromasia: Increased basophilic staining of erythrocytes.

Polycythemia: An increase in the number of red blood cells.

Polydactyly: Extra digits.

Polysomia: A fetal malformation consisting of two or more imperfect and partially fused bodies.

Posterior chamber: Space filled with aqueous anterior to the lens and posterior to the iris.

Potency: A comparative expression of chemical or drug activity measured in terms of the relationship between the incidence or intensity of a particular effect and the associated dose of a chemical, to a given or implied standard of reference. Can be used for ranking the toxicity of chemicals.

ppb: Parts per billion.

ppm: Parts per million.

Predicate device: A previously marketed medical device that is substantially equivalent to a proposed device. The predicate device is used as a comparison to the proposed device to establish safety and efficacy.

Preneoplastic lesion: A lesion usually indicative that the organism has been exposed to a carcinogen. Presence of preneoplastic lesions indicates that there is enhanced probability for development of neoplasia in the affected organ. Preneoplastic lesions are believed to have a high propensity to progress to neoplasia.

Prevalence: The percentage of a population that is affected with a particular disease at a given time.

Procarcinogen: An agent that requires bioactivation in order to give rise to a direct acting carcinogen. Without metabolic activation these agents are not carcinogenic.

Processing aid: A material that contacts a medical device product during the manufacturing process and, therefore, has a potential for affecting product quality and/or may elicit a biological response following the use of a medical device. Solvents, cleaning products, lubricants, and mold-release agents are examples of processing aids.

Progression: Processes associated with the development of an initiated cell to a biologically malignant neoplasm. Sometimes used in a more limited sense to describe the process whereby a neoplasm develops from a benign to a malignant proliferation or from a low-grade to a high-grade malignancy. Progression is that stage of neoplastic development characterized by demonstrable changes associated with increased growth rate, increased invasiveness, metastases, and alterations in biochemical and morphologic characteristics of a neoplasm.

Promoter: *Use in multistage carcinogenesis*—An agent that is not carcinogenic itself but when administered after an initiator of carcinogenesis stimulates the clonal expansion of the initiated cell to produce a neoplasm. *Use in molecular biology*—A DNA sequence that initiates the process of transcription and is located near the beginning of the first exon of a structural gene.

Promotion: The enhancement of neoplasm formation by the administration of a carcinogen followed by an additional agent (promoter) that has no intrinsic carcinogenic activity by itself.

Prothrombin time: A measure of the relative activity of factors in the extrinsic clotting sequence and the common pathway necessary in normal blood coagulation.

Protooncogene: A normal cellular structural gene that, when activated by mutations, amplifications, rearrangements, or viral transduction, functions as an oncogene and is associated with development of neoplasia. Protooncogenes regulate functions related to normal growth and differentiation of tissues.

Pseudopregnancy: (a) False pregnancy: condition occurring in animals in which anatomical and physiological changes occur similar to those of pregnancy; (b) The premenstrual stage of the endometrium: so called because it resembles the endometrium just before implantation of the blastocyst.

Ptosis: Drooping of the upper eyelid.

Pupil: The round opening at the center of the iris, which allows transmission of light to the posterior of the eyeball.

Purkinje cells: Modified cardiac muscle cells specialized for conduction of electrical excitation from the atrioventricular node through the ventricular septum and throughout the walls of the ventricle. Purkinje cells are organized into fiber bundles that can be readily dissected from the working myocardium and studied in vitro using electrophysiological recording methods.

Purkinje fiber stimulation frequency: The repetition rate for application of brief electric shocks to a Purkinje fiber preparation. A frequency rate of 1 Hz corresponds to 1 shock/s and represents the normal heart rate of 1 beat /s. Frequencies of 0.5 Hz and 2 Hz correspond to bradiocardic and tachycardic heart rates.

q1*: The symbol used to denote the 95% upper bound estimate of the linearized slope of the dose–response curve in the low dose region as determined by the multistage model.

QT interval: The time interval in the electrocardiogram extending from the start of the QRS complex to the end of the T wave, and is measure of the duration of ventricular depolarization and repolarization. The QRS complex corresponds to the upstroke of the cardiac action potential, and the end of the T wave corresponds to the return of the action potential baseline.

Qualification: For pharmaceuticals, the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or degradation product or a given impurity or degradation profile at the levels specified.

Qualification threshold: A limit (%) above which an impurity or degradation product of a drug should be qualified.

Rachischisis: Absence of vertebral arches in limited area (partial rachischisis) or entirely (rachischisis totalis).

Reference dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude or more) of the daily exposure to the human population (including sensitive subpopulations) that is likely to be without deleterious effects during a lifetime. The RfD is reported in units of mg of substance/kg body weight/d for oral exposures, or mg/substance/m^3 of air breathed for inhalation exposures (RfC).

Regulatory gene: A gene that controls the activity of a structural gene or another regulatory gene. Regulatory genes usually do not undergo transcription into messenger RNA.

Renal hypoplasia: Incomplete development of the kidney.

Reporting threshold: A limit (%) above which an impurity or degradation product of a drug should be reported.

RES (reticuloendothelial system): The system composed of all phagocytic cells of the body, including monocytes and tissue macrophages. This system is now more commonly known as the mononuclear phagocytic system.

Resorption: A conceptus which, having implanted in the uterus, subsequently died and is being, or has been resorbed.

Resting membrane potential (RMP): In cardiac electrophysiology, RMP is the resting membrane potential in millivolts (mV) and is obtained from the membrane voltage measured immediately before the action potential upstroke. RMP is controlled primarily by inwardly rectifying potassium channels. A decrease in RMP may indicate inhibition of the inward rectifier current.

Reticulocyte: An immature (polychromatic) erythrocyte.

Reticulocytosis: Increased numbers of reticulocytes in the circulation, typically seen in response to regenerative anemia.

Retina: The innermost or nervous tunic of the eye, which is derived from the optic cup (the outer layer develops into the complex sensory layer).

Rhinocephaly: A developmental anomaly characterized by the presence of a proboscis-like nose above the eyes, partially or completely fused into one.

Risk: The probability that an adverse effect will occur under a particular condition of exposure.

Risk assessment: The scientific activity of evaluating the toxic properties of a chemical and the conditions of human exposure to it to ascertain both the likelihood that exposed humans will be adversely affected, and to characterize the nature of the effects they may experience.

Risk characterization: The description of the nature and often the magnitude of human risk, including attendant uncertainty.

Risk management: The decision-making process that uses the results of risk assessment to produce a decision about environmental action. Risk management includes consideration of technical, scientific, social, economic, and political information.

Rudimentary rib: Imperfectly developed riblike structure.

Schistoglossia: Cleft tongue.

Sclera: The white tough covering of the eye that, with the cornea, forms the external protective coat of the eye.

Seminiferous epithelium: The normal cellular components within the seminiferous tubule consisting of Sertoli cells, spermatogonia, primary spermatocytes, secondary spermatocytes, and spermatids.

Semiocclusive coverage: The site of dermal application of test substance is covered; however, movement of air through covering is not restricted.

Sensitization (allergic contact dermatitis): An immunologically mediated cutaneous reaction to a substance.

Septal agenesis: Absence of nasal septum.

Sertoli cells: Cells in the testicular tubules providing support, protection, and nutrition for the spermatids.

Short-term exposure limit (STEL): A time-weighted average occupational exposure level (OEL) that the American Conference of Government and Industrial Hygienists (ACGIH) indicates should not be exceeded any time during the workday. Exposures at the STEL should not be longer than 15 min and should not be repeated more than 4 times per day. There should be at least 60 min between successive exposures at the STEL.

Sister chromatid exchange: The morphological reflection of an interchange between DNA molecules at homologous loci within a replicating chromosome.

Slope factor: See *cancer potency factor.*

Smoke: The airborne state of a chemical that is combusted and allowed to condense into a particulate matter.

SNUR: Significant New Use Rule.

Somatic cell: A normal diploid cell of an organism as opposed to a germ cell, which is haploid. Most neoplasms are believed to begin when a somatic cell is mutated.

Sorbitol dehydrogenase (SDH): An enzyme of liver origin, whose blood concentration rises in response to hepatocellular injury.

Spermatocytogenesis: The first stage of spermatogenesis in which spermatogonia develop into spermatocytes and then into spermatids.

Spermiation: The second stage of spermatogenesis in which the spermatids transform into spermatozoa.

Spina bifida: Defect in closure of bony spinal cavity.

Standardized mortality ratio: The number of deaths, either total or cause-specific, in a given group expressed as a percentage of the number of deaths that could have been expected if the group had the same age- and sex-specific rates as the general population. Used in epidemiologic studies to

adjust mortality rates to a common standard so that comparisons can be made among groups.

STEL: See *short-term exposure limit.*

Stereotypy: The constant repetition of gestures or movements that appears to be excessive or purposeless.

Superficial sloughing: Characterized by dead tissue separated from a living structure. Any outer layer or covering that is shed. Necrosed tissue separated from the living structure. Term is typically used in dermal toxicology.

Surface area scaling factor: The intra- and interspecies scaling factor most commonly used for cancer risk assessment by the U.S. EPA to convert an animal dose to a human equivalent dose: milligrams per square meter surface area per day. Body surface area is proportional to basal metabolic rate; the ratio of surface area to metabolic rate tends to be constant from one species to another. Because body surface area is approximately proportional to an animal's body weight to the 2/3 power, the scaling factor can be reduced to milligrams per body weight$^{2/3}$.

Sympodia: Fusion of the lower extremities.

Syndactyly: Partially or entirely fused digits.

T-cell/T-lymphocyte: Lymphocytes that recognize specific antigens via a complex of molecules known collectively as the T-cell antigen receptor. T-cells are primarily responsible for the induction and maintenance of cell-mediated immunity, although they also regulate humoral-mediated immunity and some nonimmune effector mechanisms. A variety of T-cell populations exist, including T-helper cells, T-cytotoxic cells, T-inducer cells, and T-regulator cells. T-cells mature in the thymus.

TC_{LO} (toxic concentration low): The lowest concentration of a substance in air required to cause a toxic effect in some of the exposed population.

TD_{LO} (toxic dose low): The lowest dose of a substance required to cause a toxic effect in some of the exposed population.

Teratology of Fallot: An abnormality of the heart that includes pulmonary stenosis, ventricular septal defect, dextraposition of the aorta overriding the ventricular septum and receiving blood from both ventricles, and right ventricular hypertrophy.

Teratozoospermia: Fewer than 30% spermatozoa with normal morphology.

Thoracogastroschisis: Midline fissure in the thorax and abdomen.

Threshold limit value (TLV): The time-weighted average concentration of a substance below that no adverse health effects are expected to occur for workers assuming exposure for 8 hr per day, 40 hr per week. TLVs are published by the American Conference of Governmental Industrial Hygienists (ACGIH).

Time-weighted average (TWA): An approach to calculating the average exposure over a specified time period.

TLm or TL_{50} (median tolerance limit): In aquatic toxicology, the concentration of material in water at which 50% of the test organisms survive after a specified time of exposure. The TL_m (or TL_{50}) is usually expressed as a time-dependent value (e.g., 24 hr or 96 hr TL_{50}).

Tonic convulsion: A convulsion in which muscle contraction is sustained.

Totalis or partialis: Total or partial transposition of viscera (due to incomplete rotation) to the other side of the body; heart most commonly affected (dextrocardia).

Tracheal stenosis: Constriction or narrowing of the tracheal lumen.

Transformation: Typically refers to tissue culture systems where there is conversion of normal cells into cells with altered phenotypes and growth properties. If such cells are shown to produce invasive neoplasms in animals, malignant transformation is considered to have occurred.

Triglycerides: Synthesized primarily in the liver and intestine; the major form of lipid storage.

Ulceration: The development of an inflammatory, often suppurating, lesion on the skin or an internal mucous surface of the body caused by superficial loss of tissue, resulting in necrosis of the tissue.

Ultimate carcinogen: The form of the carcinogen that actually interacts with cellular constituents to cause the neoplastic transformation. The final product of metabolism of the procarcinogen.

Uncertainty factor (UF): One of several, generally 10-fold factors, applied to a NOAEL or a LOAEL to derive a reference dose (RfD) from experimental data. UFs are intended to account for (a) the variation in the sensitivity among the members of the human population; (b) the uncertainty in extrapolating animal data to human; (c) the uncertainty in extrapolating from data obtained in a less-than-lifetime exposure study to chronic exposure; and (d) the uncertainty in using a LOAEL rather than a NOAEL for estimating the threshold region.

Unilobular lung: In the rat fetus, a condition in which the right lung consists of one lobe instead of four separate lobes.

Unit cancer risk: A measure of the probability of an individual's developing cancer as a result of exposure to a specified unit ambient concentration. For example, an inhalation unit cancer risk of 3.0×10^{-4} near a point source implies that if 10,000 people breathe a given concentration of a carcinogenic agent (e.g., 1 $\mu g/m^3$) for 70 years, 3 of the 10,000 will develop cancer as a result of this exposure. In water the exposure unit is usually 1 µg/L, whereas in air it is 1 $\mu g/m^3$).

Unscheduled DNA synthesis (UDS): DNA synthesis that occurs at some stage in the cell cycle other than S-phase in response to DNA damage and is usually associated with DNA excision repair.

Upper 95% confidence limit: Assuming random and normal distribution, this is the range of values below which a value will fall 95% of the time.

Upper-bound cancer-risk assessment: A qualifying statement indicating that the cancer risk estimate is not a true value in that the dose–response modeling used provides a value that is not likely to be an underestimate of the true value. The true value may be lower than the upper-bound cancer risk estimate, and it may even be close to zero. This results from the use of a statistical upper confidence limit and from the use of conservative assumptions in deriving the cancer risk estimate.

USP Negative Control Plastic RS: A standardized plastic produced by the United States Pharmacopeia (USP) for use as a control material in some biocompatibility assays.

Vaginal plug: A mass of coagulated semen that forms in the vagina of animals after coitus; also called copulation plug or bouchon vaginal.

Vapor: The airborne state of a chemical that is liquid at room temperature and pressure but is volatile.

Variation: An alteration that represents a retardation in development, a transitory alteration or a permanent alteration not believed to adversely affect survival, growth, development, or functional competence.

Vitreous: Transparent, colorless, mass of soft, gelatinous material filling the space in the eyeball posterior to the lens and anterior to the retina.

V_{max}: In cardiac electrophysiology, this is the maximum rate of depolarization measured in volts/sec obtained by taking the first derivative of the rising

phase of the action potential. V_{max} amplitude is determined primarily by the activity of cardiac sodium channels. A decrease in V_{max} indicates sodium channel blockade, and corresponds to a broadening of the electrographic QRS interval and, potentially, a slowing of conduction velocity in the intact heart.

Voluntary risk: Risk that an individual has consciously decided to accept.

Whole-body exposure: A system for exposing test animals via inhalation in which they are placed in a chamber in such a way that their entire bodies are exposed directly to the test material.

Xenobiotic: Any substance that is foreign to an organism. In the context of immunotoxicology, this term generally refers to nonbiological chemicals and drugs.

Notes

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