

IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY



Environmental Health Criteria 240 Principles and Methods for the Risk Assessment of Chemicals in Food

CUMULATIVE INDEX



A joint publication of the Food and Agriculture Organization
of the United Nations and the World Health Organization



Food and Agriculture
Organization of
the United Nations



World Health
Organization

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization or the World Health Organization.

Environmental Health Criteria 240

PRINCIPLES AND METHODS FOR THE RISK ASSESSMENT OF CHEMICALS IN FOOD

A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



**Food and Agriculture
Organization of the
United Nations**



**World Health
Organization**

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data

Principles and methods for the risk assessment of chemicals in food.

(Environmental health criteria ; 240)

1. Risk assessment. 2. Hazard assessment. 3. Exposure assessment. 4. Dose-response assessment. 5. Chemicals. 6. Food safety. 7. Food additives. 8. Contaminants. 9. Pesticide residues. 10. Veterinary drug residues. I. World Health Organization. II. Food and Agriculture Organization of the United Nations.

ISBN 978 92 4 157240 8
ISSN 0250-863X

(NLM classification: WA 712)

© World Health Organization 2009

All rights reserved. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to WHO Press, at the above address (fax: +41 22 791 4806; e-mail: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This document was technically and linguistically edited by Marla Sheffer, Ottawa, Canada.

Printed by Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Germany.

INDEX

A

- Absorption, distribution, metabolism and excretion (ADME) study, xvii, 4-11–4-12
- absorption, 4-20–4-23. *See also* Absorption, of a substance
 - basic, 4-19
 - distribution, 4-23–4-26
 - elimination of radioactive compound and metabolite, 4-33
 - excretion, 4-28–4-29
 - metabolism, 4-26–4-28
 - role in the design of animal toxicity tests, 4-30–4-31
 - role in the interpretation of data from animal toxicity tests, 4-31–4-37
 - route-to-route extrapolation, 4-37–4-38
- Absorption, of a substance, lii, 3-6, 3-20, 4-20–4-24, 4-28, 4-36, 4-41, 4-46, 4-133, 4-138, 4-141–4-143, 4-149, 4-151, 4-154, 5-4–5-5, 5-51, 8-28, 9-25, 9-29, 9-31
- Acceptable, enzyme preparations, lxxviii, 9-18–9-20
- Acceptable daily intake (ADI), liii–lvi, 4-33. *See also* Tolerable daily intake (TDI)
- effect on the human gut microflora, 5-39–5-40
 - for enzymes, 9-20
 - for food additives, 5-20, 5-21, 5-33–5-35
 - health-based guidance values, 5-33–5-42
 - in vitro MIC data, 5-40–5-41
 - JECFA specifications for food additives, 3-5–3-6, 9-12
 - microbiological, lvii, 4-155, 5-39–5-40
 - “not specified,” lvi, lvii, 5-34, 5-37, 9-20
 - for pesticides, 5-35–5-37
 - for veterinary drugs, lxxv–lxxvi, 5-37–5-42
- Accumulation, assessment of, 4-15, 4-35
- Accuracy, 3-3, 3-11, 3-16–3-17, 3-20, 4-114, 4-147, 5-20, 6-13, 6-19, 6-27, 6-33, 6-52, 6-61, 7-6, 8-31, 8-34, 9-23
- Acetylcholinesterase (AChE), 4-102–4-103, 5-52, 6-72, 7-9
- Acid-release carbon disulfide, 3-19
- Active transport processes, 4-21, 4-24
- Acute dietary exposure assessments, 6-68–6-71
- Acute exposure, 1-10, 4-52, 5-45, 5-47, 5-50, 5-55, 6-2, 6-15, 6-69, 6-71, 6-92
- Acute reference dose (ARfD), xlix, 1-15, 3-12, 4-22. *See also* Acceptable daily intake (ADI); Health-based guidance values; Provisional maximum tolerable daily intake (PMTDI);

- Tolerable daily intake (TDI)
 - biological and toxicological considerations, 5-47–5-48
 - general considerations, 5-44–5-45
 - guidelines for derivation of, 4-136–4-137, 5-55
 - human data, use of, 5-54–5-55
 - intake considerations, 5-55
 - JMPR guidelines, 6-69
 - population subgroups, 5-54
 - practical cut-off values, 5-45–5-47
 - risk assessment, 7-3, 7-16
 - stepwise process for setting, 5-48–5-49
 - toxicological end-points relevant for, 5-49–5-51
 - uncertainty factors for, 5-51–5-54
 - for a veterinary drug residue, 6-71
- Acute risk assessment, 4-13
- Acute toxicity study, 1-15–1-16, 4-13, 4-49–4-52
- Additives, food, exposure assessment of. *See* Food additives, safety evaluations for
- Adjustment factors, 4-18, 5-24, 5-49, 6-13. *See also* Chemical-specific adjustment factor (CSAF); Safety factor; Uncertainty factors
- ADME. *See* Absorption, distribution, metabolism and excretion (ADME) study
- Adverse effects, 4-125, 4-147, 6-67, 7-13, 9-2
 - biomarker of potential, lii, 4-16, 4-138, 4-142–4-144, 4-149, 9-33
 - definition, 2-4, 5-6, 5-22
 - dose–response assessment, 5-6
 - on embryos, 5-50
 - on the endocrine system, 5-50
 - in enzymic inhibition, 4-103, 4-142
 - evaluation of, 4-96
 - genetic toxicological studies, 4-52
 - in high-dose animal studies, 4-7
 - identification of, 9-33
 - in immune system, 4-113
 - intakes of approved food substances, 4-145–4-146
 - neurotoxicity, 4-93, 4-96, 4-99
 - of nutrients and related substances, 9-30–9-34
 - and nutritional status, 9-24–9-26
 - from pesticides, 3-12
 - reproductive and developmental toxicity, 4-78, 4-80–4-82, 4-86–4-87, 4-89
 - and setting of an ARfD, 5-45, 5-54
 - threshold, lxi
 - in tissue-associated lymphoid tissues, 4-108

- in toxicological studies, xlvi, xlvi, 4-5, 4-16, 4-27, 4-36. *See also*
Toxicological and human studies
- ULs for nutrients, 9-28–9-30
- of veterinary antimicrobial drug residues on the human intestinal
microflora, 4-154–4-156
- Aflatoxins, 6-15, 6-20, 7-2, 7-4, 9-5–9-6
- Aggregate exposure, lxi, 6-72, 6-74. *See also* Combined exposure;
Cumulative exposure
- Alanine aminotransferase (ALT), 4-45
- ALARA. *See* As low as reasonably achievable (ALARA)
- Allergenicity, li, 4-123–4-124, 6-71, 8-16, 9-32, 9-39, 9-41, 9-43
assessment of, 4-129–4-132
- Allergic reactions to foods. *See* Food allergy and other food
hypersensitivities, study
- Analytical methods, xliv–xlvi, lviii, lxx, 6-27, 9-22
contaminants, 3-23
for determining residues in food animal tissues, 8-10–8-11
dietary exposure assessments, 6-10–6-11, 6-13, 6-18–6-19, 6-21
for the establishment of MRLs, 8-13–8-15, 8-42, 8-47
food additive specifications, 3-10–3-11
JECFA and JMPR review of, 3-2–3-4
pesticide characterization, 3-16–3-19
in plant metabolism studies, 8-29–8-30
in stored analytical samples, 8-31–8-36
used in a TDS, 6-13
used in the supervised trials and processing studies, 8-4
used in toxicokinetic studies, 5-4–5-5
veterinary drug residues, 3-21–3-22, 5-42
- Analytical recoveries, 3-16–3-19, 8-31–8-33, 8-37–8-38
- Anaphylaxis, 4-121–4-122, 4-124
- Aneugenicity, xlix, 4-56, 4-72
- Animal food allergens, 4-123
- Animal models, xlvi. *See also* Transgenic mouse models
- Animal studies, xlvi, lii, 1-11, 4-7, 4-11, 4-13–4-17, 4-19, 4-137–4-138,
4-153, 5-4–5-5, 5-22, 5-29, 5-33, 5-39, 5-46, 5-52. *See also*
Laboratory animal studies
- Animal testing, xlvii, 4-9, 9-7
- Animal treatments, lxiv, 3-17, 3-20, 4-51, 8-6, 8-25, 8-27, 8-36–8-39,
8-42–8-44
- Antagonism, lxii, 7-10
- Antibacterial activity, 4-153–4-154
- Anticaking agents, 3-8
- Antifoaming agents, 3-7
- Apparent volume of distribution (V), 4-32

Area under the concentration–time curve (AUC), 4-31–4-32
ARfD. *See* Acute reference dose (ARfD)
D-Ascorbic acid, 4-57
As low as reasonably achievable (ALARA), 7-2, 7-13
Aspartate aminotransferase (AST), 4-45
Assessment factor, 5-24, 5-49, 5-54. *See also* Safety factor; Uncertainty factor
AUC. *See* Area under the concentration–time curve (AUC)
Autoimmunity, 4-105, 4-111

B

Benchmark dose (BMD), xlviii, lvi, 4-17, 5-8, 5-10, 5-30–5-33, 9-35
Benchmark dose lower limit (BMDL), liv, lviii, lxiii, 4-128, 5-10, 5-21, 5-25–5-26, 5-31–5-32, 5-51, 7-14, 7-16, 9-36
Benign neoplasms, 4-70
Bias, 3-23, 4-42, 4-146, 4-147, 6-19, 6-24, 6-26, 6-31
Biliary excretion, 4-22, 4-28–4-29
Bioavailability, of a substance, 4-21–4-23, 4-32, 4-35–4-36, 8-22, 8-25, 9-31, 9-37
Biological disposition, of a chemical, 4-19
Biological fate, of a compound, 4-19–4-20, 4-32
Biologically based dose–response models, 5-17–5-18
Biological tests, 3-9, 3-24, 9-23
Biomarkers of exposure, lii, 4-142–4-144, 4-149, 6-74–6-77
 benefits, 6-77
 of body burden, 5-4
 challenges with, 6-74–6-75
 GEMS/Food, 6-76
 human milk, 6-76
 of internal exposure into an external dose, conversion, 5-5
 of nutrient risk assessment, 9-34
 relevance in toxicity studies, 4-16
 of a toxic response, 7-11
Biomarkers of effect, 4-143, 4-144. *See also* Biomarkers of exposure
Biotransformation. *See* Metabolism studies
Blood–brain barrier, 4-24
BMD. *See* Benchmark dose (BMD)
BMDL. *See* Benchmark dose lower limit (BMDL)
BMDL for a 10% incidence (BMDL₁₀), 5-11
Body weight, 4-44
 ADI expressed in terms of, lv, 5-20–5-21
 in ArfDs, 5-46, 5-48, 5-51, 5-53
 as basis for total organ's solid content (TOS), 9-19, 9-22

- clearance of substance per unit time in terms of, 4-32, 4-37
 - in clinical laboratory studies, 4-145
 - constant dosage regime expressed in, 4-36
 - consumption values in relation to, 5-46, 6-29, 6-38, 6-41, 6-49–6-50
 - in deriving UL, 9-38
 - in dietary exposure assessment, 6-3, 6-42, 6-47–6-49, 6-62–6-63, 6-93
 - in dose–response assessment, 4-42, 5-5, 5-7, 5-12, 5-17
 - as end-points, 4-80
 - and feed intake data, 4-44
 - gain in, 4-44, 4-64, 4-90, 5-51, 5-53
 - JECFA standard, 5-41
 - lethality of a substance expressed in, 4-14
 - in neurotoxicity studies, 4-97
 - NOAEL expressed in terms of, 4-37
 - organ weight, 4-47
 - reduction in, 4-42, 4-44, 4-82, 4-88, 4-90
 - in reproductive and developmental toxicity study, 4-82, 4-88, 4-90
 - in standard toxicology studies, 4-97
 - threshold of toxicological concern (TTC) in terms of, 9-2
 - in toxicity studies, 4-42
- Bound residues, 8-10, 8-20, 8-22–8-23
- Brain sparing, 4-97
- Budget method, lx, 6-45–6-50
- Bulk sweeteners, safety assessment of, lxxviii, 5-44, 9-21
- Butyrylcholinesterase, 4-103

C

- CAC. *See* Codex Alimentarius Commission (CAC)
- Cancer bioassay, l, 4-14, 4-62, 4-64–4-65, 4-69, 5-7, 7-13–7-15
- Canthaxanthin, 4-45
- Captive populations, lxxix, 9-42
- Carcinogenicity studies, xlvihi, l, 1-9, 4-14, 4-36, 4-39, 4-49, 5-39, 7-12–7-13, 9-3–9-4, 9-16
- alternative tests for, 4-65–4-69
 - assessment of response, 4-74–4-78
 - benign and malignant neoplasms, 4-70
 - characterization of effects, 4-71–4-74
 - chronic bioassays for the identification and characterization of cancer risk, 4-64–4-65
 - concept of initiation and promotion, 4-63
 - criteria in evaluation of positive findings, 4-65
 - DNA-reactive carcinogens, 4-63
 - endogenous spontaneous rodent mechanism, 4-69–4-70

- end-points, 4-69–4-71
- historical control data, 4-76–4-78
- initiation and promotion models, 4-65–4-66
- interpretation of bioassay results, 4-65
- mechanism and mode of action, 4-62–4-64
- mechanisms not relevant to humans, 4-72–4-74
- mechanisms relevant to humans, 4-71–4-72
- mode of action for a carcinogenic response, 4-75–4-76
- nature of test substance, 4-74
- neonatal mouse models, 4-66
- non-genotoxic mechanisms of carcinogenesis, 4-63–4-64
- pathological classification of neoplasms, 4-70
- preneoplastic lesions, 4-70–4-71
- purpose, 4-62
- relevance of study design, 4-74–4-75
- statistical analysis of multidose cancer bioassays, 4-64–4-65
- transgenic mouse models, 4-66–4-69
- tumour response, statistical significance of, 4-75
- and general toxicity, 4-58–4-61
- β -Carotene, 4-21
- Carrier solvents, 9-17–9-18
- Case-control studies, lii, 4-143, 4-147, 4-148
- Case-series, 4-125, 4-138, 4-143, 4-147, 4-148
- CCPR. *See* Codex Committee on Pesticide Residues (CCPR)
- Cell-mediated immunity, 4-111–4-112
- Cellular function, markers of, 4-45
- Center for the Evaluation of Risks to Human Reproduction (CERHR), 4-88–4-89
- Central nervous system toxicity, 4-44
- Central tendency, of a probability distribution, 5-6, 6-23
- Chemical Abstracts Service (CAS), 3-11
- Chemical accumulation, 4-15
- Chemical carcinogenesis, I, 4-61–4-62, 4-71, 5-12
- Chemical characterization
 - contaminants, xlvi, 3-22–3-23
 - criteria for laboratory testing and analytical methods, 3-2–3-4
 - food additives, xlv, 3-5–3-11
 - high-consumption substances, xlvi, 3-23–3-25, 9-22–9-23
 - multilaboratory and collaborative studies of methods, significance of, 3-4–3-5
 - pesticide characterization, xlv, 3-11–3-19
 - rationale for, 3-2
 - veterinary drug residues, xlv–xlvi, 3-19–3-22

- Chemical-specific adjustment factor (CSAF), lvi, 4-12, 4-37, 4-76, 4-137, 4-149, 5-26–5-28, 5-43, 5-51, 5-54, 9-36
- Chemical substances, risk assessments, xlv, 9-5, 9-20
- chemical information required for, xlv–xlvi
 - for contaminant. *See* Contaminants
 - dietary exposure, 6-67, 6-73
 - for food additives, xlv, 3-6. *See also* Food additives, safety evaluations for
 - four steps, 2-5–2-9
 - on high-consumption substances. *See* High-consumption substances, assessment of
 - human-made and naturally occurring, 7-8
 - for pesticides. *See* Pesticides
 - residues from edible tissues or animal-derived foods, xlv–xlvi, 3-20
 - screening procedure criteria, 6-6, 6-45–6-55
- Chirality, 8-28
- Cholinesterase-inhibiting compounds, 4-102–4-103, 5-45
- Chronic dietary exposure assessments, 6-67–6-68
- Chronic exposures, lviii, lxiv, 4-24, 4-92, 6-2, 6-5, 6-46, 6-67, 8-6, 8-8, 8-9, 8-16. *See also* Long-term toxicity study
- ¹⁴C-labelled residues, 3-18, 4-25
- Clarifying agents, 3-7
- Class 1 food allergy, 4-120, 4-124
- Class 2 food allergy, 4-120, 4-124
- Clastogenicity, xlix, 4-56–4-58
- Clearance (CL), 4-27, 4-31–4-32, 4-35–4-37, 5-52, 7-8, 8-4, 8-23
- Clinical chemistry tests, 4-45–4-46
- Clinical food allergy (elicitation), 4-125–4-126
- Codex Alimentarius Commission (CAC), xlv, lxiii, 1-2–1-4, 1-10–1-11, 2-1–2-3, 2-5, 2-7, 2-9, 2-11, 3-3, 4-131, 4-134, 6-2, 6-4, 6-7, 6-50, 6-58, 7-1, 8-2–8-3, 8-17, 8-19
- Codex Committee on Contaminants in Food (CCCF), 2-9
- Codex Committee on Food Additives and Contaminants (CCFAC), 1-8, 1-14
- Codex Committee on Food Additives (CCFA), 2-9
- Codex Committee on Methods of Analysis and Sampling (CCMAS), 3-3
- Codex Committee on Pesticide Residues (CCPR), lxiii, 2-9, 8-3
- documents for single-laboratory validation, 3-3
 - maximum residue levels for pesticide residues, 1-10
 - re-evaluation approaches, 2-13
- Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), lxiii–lxiv, 2-9, 3-3
- Coeliac disease, 4-118, 4-132–4-134
- Cohort studies, lii, 4-114, 4-143, 4-147–4-148
- Collaborative International Pesticides Analytical Council (CIPAC), 3-11

- Collaborative studies, 3-4-3-5, 6-26
- Colonization barrier, lvii, 5-40
- Colouring agent, 3-7, 9-21
- Combined Compendium of Food Additive Specifications, 3-7-3-8
- Combined exposure, lxi-lxii, 6-72, 7-8. *See also* Aggregate exposure; Cumulative exposure
- Common moiety, 3-19
- Composite sample, 6-10, 6-15, 6-92-6-94
- Concentration-effect relationship, 4-149. *See also* Concentration-response relationship; Dose-effect relationship; Dose-response relationship
- Concentration-response relationship, 5-11, 7-15. *See also* Concentration-effect relationship; Dose-effect relationship; Dose-response relationship
- Concentrations, of marker residue, lxxv, 6-11, 6-53-6-54, 8-9, 8-19-8-25, 8-29, 8-38-8-39. *See also* Marker residue (veterinary drugs)
- Concentrations of a chemical, xlv-xlvi, lvii-lviii, lix, lx, lxii, lxiii, lxiv, 1-13, 2-7, 3-2, 3-4, 3-12, 3-17-3-22, 4-27, 4-29-4-31, 4-46, 4-74, 4-134, 4-156, 6-6, 6-92, 6-94, 7-10, 8-6, 8-8-8-9, 8-11, 9-2, 9-18, 9-25. *See also* Deterministic estimate of dietary exposure; Dietary exposure assessments
- Confidence intervals, for model predictions, 5-9, 5-30, 7-6, 8-14
- Conservative estimates, of dietary exposure, lxxvii, 4-156, 6-50-6-52, 9-8
- Consumer days, 6-37-6-38, 6-56
- Consumer loyalty, lx, 6-57
- Consumption cluster diets. *See* GEMS/Food consumption cluster diets
- Contaminants, xliv, xlv-xlvi, li-liii, 3-2, 3-7, 4-23, 4-41, 4-43, 4-50, 4-106, 4-126, 4-137-4-138, 4-140, 7-2, 8-17
 - acute dietary exposure assessments, 6-71
 - analytical methods to measure the concentrations, 3-23
 - bioavailability, use of, 4-23
 - in blood, assessment, 6-75
 - CAC Procedural Manual definition, 8-17
 - characterization of, 3-22
 - and chemical speciation, 4-6
 - databases of information, 6-28
 - decisions on safety regarding food, 2-12-2-14
 - dietary exposure assessments, 6-5, 6-13, 6-20, 6-22, 6-58-6-59, 6-67, 6-71
 - drug, lvii, lxii-lxiii, lxxvii, 6-43. *See also* Veterinary drug residues
 - environmental, 6-76, 9-2
 - enzyme preparations, 9-19, 9-21, 9-23-9-24
 - exposure assessment of, 1-14-1-15

- extraneous maximum residue limits (EMRLs) assessment, 3-22
- food, lv, lxi, 1-2-1-3, 1-6-1-8, 1-14-1-15, 3-22, 4-146, 5-21, 5-31, 5-42-5-43
- risk characterization, 7-9, 7-11, 7-13-7-15
- sources of chemical concentration data, 6-8-6-9
- sources of food consumption data, 6-30, 6-34, 6-39
- stepwise or tiered assessment, 6-43-6-44
- tolerable intake (TI) for, 2-7, 7-9, 7-11
- in whole foods, 9-40-9-41
- Continuous measures, 5-7
- Control groups, 4-42, 4-76-4-77
- Coplanar polychlorinated biphenyls (PCBs), 7-12
- Corn oil, 4-74
- Counts, 5-7
- Critical groups, lviii, 6-4
- Critical issues, of experimental study, lii, 4-138
- Critical period, concept of, 4-80
- Crop metabolism studies, lxiv, 8-4, 8-29-8-30
- Cross-reactive foods, 4-121, 4-124, 4-129-4-130
- CSAF. *See* Chemical-specific adjustment factor (CSAF)
- Cumulative exposure, lxi, 6-71-6-74. *See also* Aggregate exposure;
Combined exposure
- Cytokines, 4-110-4-111

D

- Data-driven uncertainty factors. *See* Chemical-specific adjustment factor (CSAF)
- Decision tree, in risk characterization of micronutrients, 9-31-9-32, 9-41
- Delayed-type hypersensitivity (DTH), 4-111
- Deoxyribonucleic acid (DNA), 4-25-4-26, 4-60, 4-61, 4-63
- Deterministic estimate of dietary exposure, lix, 6-21, 6-45. *See also*
 - Point estimate of dietary exposure
 - models, 6-55-6-58
 - screening method for, 6-45-6-55
- Detoxification process, 4-26-4-27, 4-33-4-34, 5-11, 7-15, 9-27
- Developmental neurotoxicity, 4-98-4-100
- Developmental toxicity, xlix, l, li, 4-13, 4-39, 4-84-4-85, 7-3, 9-5.
 - See also* Reproductive toxicity; Teratogenicity
 - assays used in screening, 4-91
 - gaps in the testing protocols for assessment of, 4-92
 - interpretation of data, 4-88-4-91
 - issues specific to category of chemical, 4-88
 - tiered and combined approaches to, 4-86

- Dietary exposure assessments, lvii–lxi, 1-12–1-15
- acute cases, 6-68–6-71
 - aggregate/cumulative exposures, 6-71–6-74
 - approaches for obtaining food chemical concentration data, 6-10–6-14
 - biomarkers, 6-74–6-77
 - budget method, 6-47–6-50
 - chemical concentration data, 6-8
 - chronic cases, 6-67–6-68
 - Codex Alimentarius Commission’s (CAC) Procedural Manual, 6-2
 - concentration data, estimation of, 6-9–6-10, 6-21–6-22
 - conservative estimates, lxxvii, 4-156, 6-50–6-52, 9-8
 - considerations, lxi, 6-42–6-43
 - consumption levels considered in the TAMDI calculation, 6-50–6-51
 - contaminants, 6-5, 6-13, 6-20, 6-22, 6-58–6-59, 6-67, 6-71
 - data analysis, 6-18–6-21
 - data sources, 6-2–6-3
 - deterministic estimates, lix, 6-21, 6-45–6-61
 - flavouring agents, 9-8–9-15
 - food composition data, 6-26–6-28
 - food consumption data, 6-29–6-41
 - general principles and considerations, 6-3–6-5, 6-42
 - maximum levels (MLs) or maximum residue limits (MRLs), use of, 6-7–6-9
 - methods, 6-5–6-6
 - migration from packaging materials, 6-54–6-55
 - model diets, 6-50–6-55
 - of nutrients, 6-3
 - point estimates. *See* Point estimate of dietary exposure
 - poundage data, lx, 6-44, 6-46–6-47
 - presentation of the results, 6-6
 - probabilistic analysis of exposure variability, lx, 6-62–6-67
 - refinements, 6-61–6-67
 - sampling, 6-14–6-18
 - screening methods, lix–lx, 6-45–6-55
 - sources of information, lviii–lix
 - stepwise approach, 6-43–6-44
 - uncertainty in food chemical concentration data, 6-22–6-26
 - used by JMPR, 6-92–6-95
 - use of standard terminology, 6-3
- Dietary exposure estimates, lx, lxxvii, 1-13–1-16, 2-8, 2-12, 6-4, 6-6, 6-8–6-9, 6-13, 6-18, 6-21–6-22, 6-36, 6-42, 6-46–6-47, 6-52, 6-56–6-58, 6-61, 6-66, 6-69, 6-92–6-95, 7-6, 8-5, 8-9, 9-12–9-15.
- See also* Dietary exposure assessments

- Dietary record. *See* Food record
- Dietary supplement. *See* Food supplements
- Diet history survey, 6-32–6-33
- Diffusion of volatile substances, 4-21, 4-24
- Diglycerides, 3-6
- Dimethylhydrazine, 3-12
- Dioxins, Iv, lxii, 3-12, 4-15, 4-35, 5-27, 5-42–5-43, 6-20, 8-19, 9-8
- Direct animal treatment studies, 3-17, 8-27, 8-36–8-39
- Disease resistance measures. *See* Host resistance assays
- Distribution, of a substance, 4-23–4-26
- Dithiocarbamates, 3-16
- DNA damages, 4-54–4-55, 4-60–4-61, 4-92
- DNA-reactive genotoxic carcinogen, 4-76, 9-7
- DNA-reactive mechanism, 4-63, 4-71–4-72, 4-76, 4-92, 9-3. *See also*
Genotoxicity
- DNA repair, 4-68, 5-11, 7-15
- Dose addition, 7-8–7-9
- Dose conversion table, A-43
- Dose–effect relationship, 4-136. *See also* Dose–response relationship.
- Dose metric, 5-4–5-6, 7-14
- Dose–response assessment, xlv, liii–liv, 2-5, 2-7, 4-31, 4-49, 7-13
- adverse responses, 5-6
 - approaches, 5-3
 - basic concepts, 5-2–5-7
 - basic steps in, 5-8–5-12
 - continuous measures, 5-7
 - counts, 5-7
 - data sources, 5-2
 - duration of dosing, 5-5
 - exposure measurements, 5-5
 - external dose, 5-4
 - internal dose, 5-4
 - modelling, 5-7–5-17
 - ordinal categorical measures, 5-7
 - primary criteria, 5-2
 - quantal responses, 5-6–5-7
 - reference point or point of departure (POD), 5-3
 - setting of health-based guidance values. *See* Health-based
guidance values
 - tissue dose, 5-5
 - use of a physiologically based toxicokinetic (PBTK) model, 5-6
- Dose–response curve, 4-52, 4-80, 4-91, 5-3, 5-22, 5-26, 5-53, 7-3, 7-11, 7-15
- Dose–response modelling (DRM)
- biologically based, 5-17–5-18

- for continuous data, 5-12–5-14
- with covariates, 5-17
- extrapolation issues, 5-18–5-19
- mathematical models, 5-12
- model fitting and estimation of parameters, 5-14–5-17
- overview, 5-7
- for quantal data, 5-14
- steps in, 5-7–5-12
- uncertainty issues, 5-18
- uses, 5-10–5-11
- Dose–response relationships, xlvii, 1, 4-5, 4-136, 5-8, 5-11–5-12, 5-26, 7-8, 7-11, 7-13–7-14, 9-30
- characterization of, 4-92, 4-102
- EHC on, 4-136
- in interpreting tumours, 4-75–4-76
- non-genotoxic carcinogens in, 4-72
- in risk characterization, 4-49
- significance, 5-4
- and tiered screening, 4-86–4-87
- toxicokinetic studies, 4-31
- using epidemiological studies, 4-147–4-148
- Dose selection, for toxicity studies, xlviii, 4-42
- Double-blind placebo-controlled food challenge (DBPCFC) tests, 4-125–4-126
- DRM. *See* Dose–response modelling (DRM)
- Drosophila melanogaster*, 4-52
- “Drug-metabolizing” enzymes, 4-26
- Duplicate portion diets, lix, 6-28, 6-44, 6-60–6-61
- Duplicate portion studies, 6-60–6-61

E

- Ecological studies, lii, 4-147. *See also* Case-series
- EDSTAC screening battery, 4-87
- Effective dose for 10% of the population (ED_{10}), 4-127
- Elimination, 4-19, 4-24–4-30, 4-35–4-37, 4-138, 5-27, 5-48, 6-24, 6-65, 9-29
 - of a chemical, overall rate of, 4-29–4-30
 - half-life ($t_{1/2}$), 4-32
 - of radioactive compound and metabolite, 4-33
 - via the bile, 4-28–4-29
- Embryolethality, 4-86
- Endocrine toxicity, 4-86–4-88
- Endogenous substances, 3-18, 4-7, 8-13, 8-15, 8-22, 9-11–9-12, 9-30

- End-points, xlix, xlvi, l–lii, liv–lvii, 1-7, 4-7, 4-43, 4-56, 4-145, 5-17,
5-22–5-24, 5-37–5-40, 6-4, 8-29, 9-5, 9-29, 9-34, 9-38
animal studies, 4-13, 4-137–4-138
assessing toxicity, 4-11–4-16, 4-38, 4-40, 4-48, 4-50–4-51
of biomarkers, 4-144
in carcinogenicity studies, 4-69–4-71
in the derivation of an ARfD, 5-44–5-51, 5-53–5-55
genetic, 4-56
immunotoxicity, 4-107
in immunotoxicology studies, 4-105–4-107, 4-112–4-116
in vitro approaches, 4-9
in neurotoxicity studies, 4-94, 4-96, 4-99–4-101, 4-104–4-105
in reproductive toxicity studies, 4-79–4-81, 4-83–4-84, 4-89, 4-92
toxic, 7-11, 7-17
toxicological, 6-73, 7-4, 8-10
- Enterohepatic circulation, 4-29
- Environmental Health Criteria (EHC) 57, 4-20
- Environmental Health Criteria (EHC) 60, 4-93
- Environmental Health Criteria (EHC) 70, xliii, 1-2, 1-5, 1-8, 1-10–1-16,
4-20, 4-136, 5-28, 7-18, A-43
- Environmental Health Criteria (EHC) 104, xliii, 1-2, 1-5, 1-10–1-16, 3-11,
4-20, 4-136, 5-29
- Environmental Health Criteria (EHC) 180, 4-114
- Environmental Health Criteria (EHC) 212, 4-114
- Environmental Health Criteria (EHC) 223, 4-93
- Environmental Health Criteria (EHC) 236, 4-114
- Environmental Health Criteria (EHC) 239, liii, 5-4, 5-12
- Enzyme deficiencies, 4-117–4-118
- Enzyme induction, 4-61, 4-142
- Enzyme inhibition, 4-61, 4-142
- Enzyme-linked immunosorbent assay (ELISA), 4-110, 4-134
- Enzyme-linked immunosorbent spot (ELISPOT), 4-110
- Enzyme preparations
glutaraldehyde in, 3-7
JECFA specification, 3-8, 3-10
safety assessment of, lxviii, 4-102–4-103, 9-18–9-20
- Enzymes, lii, lxvi, lxviii, 1-6, 4-26–4-27, 4-31–4-34, 4-37, 4-45–4-46,
4-133, 4-144, 4-149–4-150, 9-18–9-20, 9-25, 9-42
- Epidemiological studies, lii, 4-106, 4-114, 4-116, 4-137–4-138,
4-146–4-148, 4-147–4-148, 5-4–5-5, 5-17, 5-43, 5-55, 7-15.
See also Case-control studies; Case-series; Cohort studies;
- Ecological studies
- Epigenetic event, 4-54, 4-60
- Epimerization, 3-15

- Epitopes, 4-123
- Equivalence, 3-12
- Errors, in analytical measurements, 6-23–6-24, 6-26
- Estimated daily intake (EDI), lxx, 1-13, 6-53, 8-7
- 17 β -Estradiol, 4-66
- Ethinylestradiol, 4-57
- Ethylenediaminetetraacetic acid (EDTA), 3-9
- Ethylenethiourea residues, analysis of, 3-18
- EU model diet, 6-54
- European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 4-58
- European Food Consumption Survey Method (EFCOSUM) project, 6-33
- Excretion, 4-28–4-29. *See also* Absorption, distribution, metabolism and excretion (ADME) study; Elimination
- Expert judgement, 5-32, 7-12
- Exposure assessment, for a compound. *See* Dietary exposure assessments; Intake assessment
- Exposure estimates, based on poundage data, 6-46–6-47
- Exposure route, 4-21, 4-36–4-37, 4-74, 4-110, 6-73, 8-37
- Exposure scenarios, xlviii, 2-8, 4-13, 4-39, 4-74, 4-79, 5-10, 6-22, 6-71, 7-10
- External dose, 4-23, 4-31, 4-37, 5-4–5-5, 5-12, 5-27, 7-14
- Extraction solvents, 9-16–9-18
- Extraneous maximum residue limit (EMRL), 3-22–3-23, 8-15
- Extrapolation, l, liv, 4-5, 4-11, 4-28, 4-42, 4-62, 4-136, 4-149, 5-8–5-11, 5-33, 5-44, 6-65, 7-14–7-15. *See also* Interspecies extrapolation; Linear extrapolation; Route-to-route extrapolation
- Extrapolation issues, liv, 4-37, 5-18–5-19
 - geographic, 8-48–8-49
 - honey, 8-48
 - pesticide residues, 8-44–8-45, 8-48–8-49
 - possible extension of MRLs to other animal species, 8-47–8-48
 - residues of veterinary drugs, 8-45–8-47, 8-49
- Eye examinations, 4-44–4-45

F

- FAO/WHO Conference on Food Standards, Chemicals in Food and Food Trade, 1-10
- FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals, 1-12, 1-15
- FAO/WHO Technical Workshop on Nutrient Risk Assessment, 9-37
- Fate of additives, in food, 3-9–3-10, 4-11
- Fate of a substance, in body, 4-20, 4-31, 4-144, 5-27
- Fate of pesticide residues, in soil, 8-4, 8-17, 8-19, 8-27, 8-29

- Fate of residues, during commercial food processing, 8-35–8-36, 8-42
- Favism, 4-135
- Fetotoxicity, 4-86
- FFQ. *See* Food frequency questionnaire (FFQ)
- First-pass metabolism, 4-23
- Flat-slope syndrome, 6-31
- Flavouring agents, safety evaluation of, lviii, lxvi, 1-5, 1-10
 - decision tree approach, lxvi, 9-10
 - dietary exposures, 1-16, 6-5, 6-36, 6-42, 6-44, 6-49, 6-52, 6-58, 6-71, 9-12–9-15
 - JECFA procedure and specification, lxvi–lxvii, 1-16, 3-8, 7-10–7-11, 9-8–9-15
 - SPET estimate, lxvii, 9-14
 - TAMDI model diet, 6-50–6-52
 - toxicological evaluation, 4-8, 9-8–9-15
 - TTC concept, lxvi–lxvii, 4-8, 9-2–9-8
- “Flip-flop” kinetics, 8-28
- Foliar absorption, 8-26
- Food additives, safety evaluations for, xliii, xlv, lx, lxviii, 1-2, 4-139–4-140, 7-2, 9-21, 9-30
 - absorption, metabolism and excretion in humans, 4-141, 4-144
 - acute dietary exposure assessments, 6-71
 - ADI values, liii–lv, 2-7, 2-11, 5-20, 5-33–5-35, 7-9, 7-11, 9-12
 - allergic reactions, 4-123, 4-135
 - bioavailability, 4-23
 - dietary exposure assessments, lviii, lxviii, 6-5, 6-22, 6-30, 6-46–6-49, 6-59, 6-71
 - effects of the gut microflora, 4-150
 - formulation of specifications and information requirements, 3-8–3-9
 - general considerations, li, lv, lvii, 3-5–3-8
 - group ADIs/TIs, 5-43
 - information from humans, 4-137–4-138
 - information on analytical methodology used, 3-10–3-11
 - JECFA procedure, lxii–lxiii, xlv, 1-6–1-8, 1-14–1-15, 2-13, 3-2, 3-5–3-8, 4-5
 - metabolized by enzymes, 4-26, 4-33
 - of mixtures, lxii, 7-10
 - NOELs, 9-5
 - packaging and storage conditions, 3-9–3-10, 6-54–6-55
 - reviews, 2-12–2-14
 - route of administration of the test substance, 4-43
 - screening method, lx, 6-6, 6-45–6-55
 - stability and quality of, 3-9–3-10
 - TTC approach, 9-5, 9-8

- USFDA regulation, 9-4
- Food allergens, 4-122-4-124
- Food allergy and other food hypersensitivities, study, li, 4-121
 - clinical, 4-125-4-126
 - food intolerance, 4-117
 - of genetically modified food, 4-129-4-132
 - IgE-mediated food allergy. *See* IgE-mediated food allergy
 - non-IgE-mediated immunological reactions, 4-117-4-118, 4-132-4-134
 - non-immune-mediated food hypersensitivity, 4-134-4-135
 - pathological mechanisms underlying, 4-118
 - prevalence, 4-119
 - risk assessment, 4-126-4-129
 - self-reported studies, 4-119
- Food balance sheet, lviii, lix, 6-30, 6-39-6-40, 6-59
- Food challenge tests, 4-125
- Food chemical safety, risk assessment of, xliii-xliv, 2-6-2-9. *See also*
 - Risk assessment
 - exposure assessment. *See* Dietary exposure assessments
 - hazard characterization. *See* Hazard characterization
 - hazard identification. *See* Hazard identification
 - need for guidance, 1-1-1-2
 - probability calculation of harm, 2-5
 - risk characterization. *See* Risk characterization
- Food composition data, 6-8
 - GEMS/Food databases, 6-28
 - for nutrients, 6-27-6-28
- Food consumption data
 - approaches for data collection, 6-30-6-34
 - databases, 6-39-6-41
 - data collection methods for, 6-30-6-34
 - data format/modelling, 6-35-6-36
 - data reporting and uses, 6-34-6-38
 - food portion sizes, 6-36-6-38
 - mapping of data, 6-34-6-35
 - patterns, 6-38-6-39
 - requirements, 6-29-6-30
- Food diary. *See* Food record
- Food frequency questionnaires (FFQs), 6-29, 6-32-6-33, 6-36
- Food group composite approach, 6-16, 6-17
- Food groups, lviii, 4-123, 6-14, 6-16-6-17, 6-30, 6-32, 6-38, 6-56-6-57, 6-60
- Food habit questionnaire, 6-33
- Food intolerance, 4-117-4-118
- Food packaging materials, safety assessment of, lxxvii-lxxviii, 6-54-6-55, 9-15

Food processing studies, lxiv, 3-17, 8-5-8-6, 8-35-8-36
Food Quality Protection Act of 1996, 4-87
Food record, 6-31
Foods for special dietary use, lxix, 1-4, 9-40
Food supplements, lxviii, 6-3, 6-29, 9-26, 9-30
Foreign chemicals, transfer of, 4-21
“Foreign” organic molecules, 4-26
Fortified foods, safety assessment of, lxviii, 6-58, 9-26, 9-30
Functional foods, lxviii, 9-26, 9-30
Functional immune tests, 4-113

G

Gamma-glutamyl transpeptidase (GGT), 4-45
Gamma multi-hit model, 5-14-5-15
Gastrointestinal absorption, 5-52. *See also* Absorption, of a substance
Gastrointestinal tract, study of the role of gut microflora in, lii-liii, 4-11, 4-28, 4-41, 4-121, 4-124, 4-131, 4-133, 4-135, 4-142, 5-50, 5-52, 9-24, 9-44
 chemical effects on gut microflora, 4-153-4-154
 decision tree approach, 4-154-4-156
 general considerations, 4-150-4-151
 gut microflora on the chemical, effects of, 4-151-4-153
Gavage doses, xlviii, 4-23, 4-35-4-37, 4-39, 4-43, 4-74-4-75, 5-47, 5-49, 5-51
GCP. *See* Good Clinical Practice (GCP)
GEMS/Food consumption cluster diets, lix, 6-40, 6-58-6-59, 8-7
GEMS/Food database, lviii-lix, 6-8, 6-28, 6-38
GEMS/Food diets, lix, 1-14, 3-22, 6-5, 6-34, 6-36, 6-71, 6-76, 8-6.
 See also GEMS/Food consumption cluster diets; GEMS/Food regional diets
GEMS/Food Europe, 6-21
GEMS/Food regional diets, lix, 6-40, 8-6-8-7
Gene mutation test, xlix, 4-56, 4-59
General systemic toxicity study
 body weight and feed intake data, 4-44
 caloric restriction, 4-43
 clinical chemistry tests, 4-45-4-46
 conclusions, 4-49
 dose selection, 4-39, 4-42
 goal, 4-39
 histological examination, 4-47-4-48
 immunotoxicity, 4-48
 longevity of species, 4-41

- mortality measurement, 4-44
- necropsy, 4-47
- neurotoxicity, 4-48
- observations of test animals, 4-44
- OECD guidelines, 4-38
- organ weight, 4-47
- pair-feeding, 4-43
- reversibility of toxic effect, 4-48
- route of administration of the test substance, 4-42–4-43
- species, 4-41–4-42
- study design and data interpretation, 4-40–4-43
- testing strategies, 4-39–4-41
- United States Environmental Protection Agency (USEPA) test guidelines, 4-38
- urinalyses, 4-46–4-47
- Genetically modified foods, li, 4-129–4-132
- Genotoxic carcinogen, 4-14, 4-60, 4-66–4-68, 5-11, 5-39, 9-5
- Genotoxicity, xlviii, 4-7, 4-9, 4-14, 7-13, 9-5–9-7, 9-11. *See also* Mutagenicity
 - commonly used tests, 4-54
 - data assessment, 4-56–4-58
 - early experiments, 4-52
 - germline and somatic cells, 4-58
 - germ cell effects, importance of, 4-53
 - mode of action, 4-60–4-61
 - regulatory decisions, 4-53
 - in relation to carcinogenicity, 4-58–4-61
 - relevant to humans, 4-71–4-72
 - test categories, 4-53–4-54
 - testing strategy, 4-54–4-56
 - validation, 4-58–4-60
 - in vivo and in vitro, 1, 4-14, 4-57–4-58
- Germ-free animals, liii, 4-152
- Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme (GEMS/Food) diets.
See GEMS/Food diets
- Glossary of terms, A-1–A-41
- GLP. *See* Good Laboratory Practice (GLP)
- Glutamate dehydrogenase, 4-45
- “Gluten-free” food, 4-133–4-134
- Gluten intolerance, 4-132
- GMP. *See* Good Manufacturing Practice (GMP)
- Gnotobiotic animals, liii, 4-152
- Good Agricultural Practice (GAP), lxiv, 1-8, 1-12, 3-19, 5-45, 6-7, 6-10, 6-14, 8-2, 8-4–8-5, 8-7–8-8, 8-14, 8-16, 8-41–8-42, 8-46, 8-48–8-49

- Good Clinical Practice (GCP), 4-139
- Good Laboratory Practice (GLP), xlvii, 3-4, 4-9, 4-40, 8-31
- Good Manufacturing Practice (GMP), 3-6, 4-6, 5-34, 9-20
- Good Practice in the Use of Veterinary Drugs (GPVD), lxx, 1-12, 6-7, 8-3, 8-8, 8-10-8-11, 8-13-8-16, 8-41-8-43
- GPVD. *See* Good Practice in the Use of Veterinary Drugs (GPVD)
- Gross errors, 6-23
- Group acceptable daily intake (ADI), 5-43-5-44, 7-9, 7-11
- Group maximum residue level, 8-44, 8-45
- Group tolerable daily intake (TDI), 5-43-5-44, 7-11
- Guidance values. *See* Health-based guidance values
- Gut microflora, effects of, lii-liii, 4-11. *See also* Gastrointestinal tract, study of the role of gut microflora in
- impact of veterinary drug, lvii, 4-151-4-154
 - in vivo methods for studying, 4-152

H

- Haematology, 4-45
- Half-lives, 4-29, 4-35
- Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, 2-4
- Hazard, definition of, 2-4
- Hazard assessment, 2-6-2-7, 3-13, 4-91
- Hazard characterization, xlv, xlvi, xlviii, 1, liii, lxi, 2-2-2-3, 2-5, 2-7-2-8, 4-36, 5-2, 5-8, 7-1, 7-10, 7-13-7-14, 9-45. *See also* Risk assessment; Toxicological and human studies
- Hazard identification, xlv, xlvi, xlviii, 2-6, 7-10, 7-13, 9-35, 9-38. *See also* Risk assessment; Toxicological and human studies
- 24 h dietary recall, 6-29, 6-31
- Health-based guidance values, lxxviii, liii-lxiii, liv-lvii, 2-7-2-8, 4-13, 4-15, 4-33, 4-36, 4-40, 4-61, 4-72, 4-143, 4-144, 6-2, 9-2, 9-8, 9-27-9-28, 9-37. *See also* Acceptable daily intake (ADI); Acute reference dose (ARfD); Tolerable daily intake (TDI)
- benchmark dose approach, 5-30-5-33
 - calculation of, 5-21, 5-30, 5-32
 - CSAFs, concept of. *See* Chemical-specific adjustment factor (CSAF)
 - data for, 5-22-5-24
 - for default uncertainty subfactors, 5-28
 - from developmental (embryo/fetal) effects, 7-16-7-17
 - in dietary exposure assessments, 6-4-6-5, 6-9, 6-44, 6-47, 6-49, 6-54, 6-68, 6-71
 - dose selection, 5-30
 - experimental variation, 5-30

- group ADIs and TIs, 5-43–5-44
- group size, 5-29–5-30
- JECFA/JMPR procedure for determining, 5-19–5-22, 7-13–7-16
- NOAEL approach to deriving, 5-20–5-21, 5-28–5-30
- in risk characterization of substances, 7-1–7-4, 7-10–7-11
- safety and uncertainty factors, 5-24–5-28
- “tolerable” and “acceptable,” 5-21, 5-42–5-43
- Hepatobiliary function, assessment of, 4-45
- Hershberger assay, 4-87
- Hexachlorobenzene, 3-12
- Hierarchical patterns, of results, 4-57
- High-consumption substances, assessment of, xlvi, 1-5, 3-2, 4-6–4-8
 - chemical analysis for, 3-23–3-25, 9-22–9-23
 - food additives, 9-21–9-22
 - identification of impurities, 9-22–9-23
 - intake of foods from unconventional or novel sources, 9-39–9-45
 - intake of nutrient substances, 9-26–9-39
 - materials included, 9-21
 - metabolic studies, 9-24
 - nutritional studies, 9-23
 - toxicity studies, 9-24–9-25, 9-24–9-26
- Highest residue – processing (HR-P), 6-93–6-94
- Highest residues (HRs), lxiv, 3-20, 6-8, 6-10, 6-22, 6-69, 6-93–6-95, 8-5
- Histological examination, 4-47–4-48, 4-95–4-96, 4-108–4-109
- Histone code, 4-61
- Histopathology, 4-11, 4-30, 4-43, 4-70, 4-80, 4-94, 4-108–4-109
- Historical control data, 4-76–4-78, 4-89–4-90
- Honey, 8-48
- Hormonal disruption, 4-72
- Host resistance assays, 4-112–4-113
- Host resistance studies, 4-107–4-109, 4-113
- Human data, use of, 5-54–5-55, 9-43
- Human exposure
 - in carcinogenicity testing, 4-62–4-63, 4-65, 4-74
 - in cytotoxicity testing, 4-74
 - in dose–response assessment, liii–liv, 5-2–5-3, 5-5, 5-11, 5-19
 - and dose selection, 4-42
 - health-based guidance values for, 5-25, 6-71, 7-2–7-3, 7-13
 - in interpreting bioassay results, 4-65
 - in *in vitro* tests, 4-56
 - in pesticide risk assessment, 4-136–4-137
 - and PMTDIs, lv, 5-21, 5-43
 - and relevance of reversibility, 4-48
 - in reproductive and developmental toxicity testing, 4-86

- in risk characterization, lxi, lxiii, 4-13, 5-22, 7-15
- and route administration of doses, 4-42
- in setting ArfDs, 5-48, 5-50
- and testing, xlviii, 1
- in toxicity testing, 4-11, 4-13, 4-36, 4-39–4-40, 4-42
- and TTC values for, lxvi, 4-8, 9-3–9-5
- Human leukocyte antigen (HLA) genes, 4-133
- Human milk, 6-76
- Human-specific metabolites, 4-13
- Human studies, general principles, xlvi–liii, 1-7, 1-9, 2-6, 2-8, 2-11, 4-14, 4-76, 4-114–4-116, 8-25, 8-30
 - ARfDs, 4-136–4-137, 5-54–5-55. *See also* Acute reference dose (ARfD)
 - assessment of immunotoxicity, 4-114–4-116
 - design of studies, 4-18
 - dose–response modelling, 4-136. *See also* Dose–response modelling (DRM)
 - end-points, 4-138
 - epidemiological studies, 4-146–4-148. *See also* Epidemiological studies
 - ethical, legal and regulatory issues, 4-149–4-150
 - human tissues and other preparations in vitro, 4-149
 - information from humans, 4-17, 4-137–4-138
 - long-term clinical laboratory studies, 4-144–4-145
 - mechanisms relevant to humans, 4-71–4-72
 - on novel foods, lxix, 9-43
 - poisoning cases, 4-148–4-149
 - post-marketing surveillance, 4-145–4-146
 - potential effects of veterinary drug residues, 4-154–4-156
 - principles of VICH GCP, 4-139
 - short-term clinical laboratory studies, 4-141–4-144
 - study of pharmaceutical compounds, 4-139–4-141
- Human tissues and other preparations in vitro, 4-149
- Human variability, lvi, 4-19, 4-26–4-27, 4-34, 4-37, 5-3, 5-27, 5-51, 7-4, 9-33.
 - See also* Chemical-specific adjustment factor (CSAF); Variability
- Humoral immunity, 4-110
- Hyperplasia, 4-7, 4-61, 4-65, 4-73–4-74
- Hypersensitivity, 4-105, 4-111, 4-118–4-119, 4-134–4-135, 6-70, 9-43

I

- IgE epitopes, 4-124, 4-130
- IgE-mediated food allergy, 4-117
 - common characteristics of food allergens, 4-122–4-124

- evaluation of the safety of genetically modified (GM) foods,
 - 4-129–4-132
- risk assessment, 4-126–4-129
- sensitization, 4-119–4-121
- symptoms and diagnosis, 4-121–4-122
- thresholds, 4-125–4-126
- ILSI-HESI Collaborative Program on Alternative Models for
Carcinogenicity Assessment, 4-66
- Immobilizing agents, 9-20–9-21
- Immobilizing enzymes, 9-20–9-21
- Immunostimulation, 4-105
- Immunosuppression, 4-105–4-107, 4-110, 4-113, 4-115–4-116
- Immunotoxicity, xlviii, xlix, 4-48, 5-50, 9-5
 - allergic contact dermatitis, evaluation of, 4-113–4-114
 - cellular immunity, 4-111–4-112
 - commonly employed disease resistance models, 4-114
 - configurations of testing panels, 4-107
 - disease resistance measures or host resistance assays, 4-112–4-113
 - end-points, 4-107
 - evaluation of allergic contact dermatitis, 4-113–4-114
 - examinations of lymphoid tissues, 4-108
 - focus of, 4-105
 - functional measures of immune responses, 4-110–4-112
 - haematological data, 4-107
 - histological standpoint, 4-108–4-109
 - human studies, 4-114–4-116
 - humoral immunity, 4-110
 - ICH S8 guideline, 4-106
 - immunology studies, 4-107–4-113
 - innate immunity, 4-112
 - interpretation of data, 4-116
 - laboratory animal studies, 4-106–4-107
 - lymphocyte phenotyping, 4-109–4-110
 - OECD Test Guideline No. 407, 4-106
 - surface marker analysis, 4-115
 - toxicokinetic data, use of, 4-106
- Incurred residues, xlv, 3-2–3-3, 8-35
- Index compound, 6-73
- Individual-based methods, 6-40–6-41, 631–6-33
- Individual food approach, lviii, lix, 6-14, 6-16–6-18, 6-22, 6-32, 6-34–6-35,
6-44, 6-50, 6-60
- Injectable sustained-release formulations, 8-29
- Innate immunity, 4-112
- Innocuous metabolic products, 4-10, 9-8, 9-10–9-12

- In silico methods, xlvi, 4-9-4-11
- Intake assessment, lxiii, 7-14, 8-8, 8-14, 8-16, 8-21, 8-36, 9-28, 9-38-9-39.
See also Dietary exposure assessments
- Intake-response assessment, 9-35
- Internal dose, 4-31, 4-37, 5-4-5-5, 7-9
- International Agency for Research on Cancer (IARC), 4-61
- International Code of Conduct on the Distribution and Use of
Pesticides, 3-12
- International Cooperation on Harmonisation of Technical Requirements
for Registration of Veterinary Medicinal Products (VICH) for
Good Clinical Practice (GCP), lvii, 4-86, 4-139, 4-155, 8-11
- International estimated daily intake (IEDI), 1-13, 6-58, 8-16
- International estimated short-term intake (IESTI), 1-15, 6-36, 6-92, 8-16
- International Organization for Standardization (ISO), 3-11
- International Programme on Chemical Safety (IPCS), xliii, 4-16, 4-76
definitions of hazard and risk, 2-4
Harmonization Project, 5-3-5-4
- International Union of Pure and Applied Chemistry (IUPAC), 3-11, 3-13,
3-19
- Interpolation, 5-44
- Interspecies extrapolation, 4-18, 4-31, 4-33, 4-142, 5-6, 5-52
- Interspecies uncertainty factor, 4-37
- Intolerance, 4-117-4-118, 4-135, 4-142-4-143, 6-71, 7-17, 9-39
- In vitro assays, xlix, 4-55-4-56. *See also* In vitro studies
- In vitro minimum inhibitory concentration (MIC) data, 5-40
- In vitro studies, xx, xlvi, xlviii, 4-9-4-11, 4-34, 4-57, 4-87, 4-91, 4-93,
4-103-4-104, 4-131, 4-136, 4-138, 4-149, 4-152-4-153, 4-155,
5-2, 5-40-5-41, 7-11-7-12
- In vivo assays, 4-55. *See also* In vivo studies
- In vivo studies, liii, xlvi, xlviii, 4-5, 4-7, 4-12-4-13, 4-14, 4-18, 4-32,
4-34-4-35, 4-53-4-54, 4-57-4-60, 4-72, 4-139, 4-151-4-152,
5-2, 5-40-5-41, 8-28, 9-2, 9-42
- ISO/IEC 17025, norm for competence of testing and calibration
laboratories, 3-3-3-4

J

- JECFA. *See* Joint FAO/WHO Expert Committee on Food Additives
(JECFA)
- Joint FAO/WHO Expert Committee on Food Additives (JECFA), xliii,
xlix, xlvi, liv, lvi, lxi, lxii, 1-1, 2-1
acute toxicity study, 4-50
ADIs for nutrients, 9-26-9-27
assessment processes for residues of veterinary drugs, 8-7-8-13

- comparison with JMPR, 8-14–8-16
- conditions of use of commercial products, 8-43
- criteria for laboratory testing and analytical methods, 3-2–3-4
- establishment of the MRLs for a veterinary drug (MRLVDs), 3-20–3-22
- for flavouring agents, lxvi–lxvii, 1-16, 3-8, 7-10–7-11, 9-8–9-15
- health-based guidance values, 5-19–5-22, 7-13–7-16
- historical overview, 1-6–1-8
- maximum residue limits (MRLs), for pesticides and veterinary drugs. *See* Maximum residue limit (MRL)
- model diet, 6-52–6-53
- multilaboratory and collaborative studies of methods, 3-5–3-6
- priority setting for, 2-11–2-12
- processing aids, 3-7, 3-10
- re-evaluation approaches, 2-13
- requirements for validation of analytical methods, 3-21
- reviews of past decisions on safety, 2-12–2-14
- risk assessment committees under, 2-11–2-12
- risk assessment principles and procedures, 1-2–1-6
- safety evaluation of flavouring agents, 1-16
- safety evaluations for food additives, 3-5
- specifications on the analytical techniques, 3-10–3-11
- specifications to cover the normal shelf-life of the additive, 3-9
- use of maximum survey-derived intake (MSDI), lxvii, 9-12
- Joint FAO/WHO Expert Consultation, 1-12
- Joint FAO/WHO Meeting on Pesticide Residues (JMPR), xliii, xlix, xlvii, liv, lvi, lxi, lxii, lxiv, 2-1
 - active ingredients of pesticide formulations, 3-14
 - acute reference doses (ARfDs), 6-69
 - ADIs based on specific purity, 3-12
 - 2002 and 2004 reports, 1-15
 - criteria for laboratory testing and analytical methods, 3-2–3-4
 - dietary exposure assessments of chemicals, 6-92–6-95
 - extraneous maximum residue limits (EMRLs) for contaminants, 3-22–3-23, 8-15
 - health-based guidance values, 5-19–5-22, 7-13–7-16
 - historical overview, 1-8–1-10
 - K_{ow} of a pesticide, 3-15
 - maximum residue limits (MRLs), for pesticides and veterinary drugs. *See* Maximum residue limit (MRL)
 - meetings, 1-9–1-10
 - methods used for generating preregistration residue data, 3-16–3-17
 - multilaboratory and collaborative studies of methods, 3-5–3-6
 - priority setting for, 2-11–2-12

- procedures for estimating an ARfD, 1-15
 - reviews of past decisions on safety, 2-12–2-14
 - risk assessment committees under, 2-11–2-12
- Joint FAO/WHO Meeting on Pesticide Specifications (JMPS), xlv, 3-12

K

- K6/ODC mouse model, 4-68
- Kidney tumours, 4-73
- K_{ow} of a pesticide, 3-15

L

- L5178Y cell $tk^{+/-}$ locus test for gene mutations, 4-59
- Laboratory animal studies, 5-20, 9-2, 9-26, 9-36, 9-42. *See also*
 - Absorption, distribution, metabolism and excretion (ADME) study; Animal studies; Toxicological and human studies
- Laboratory studies
 - GLP. *See* Good Laboratory Practice (GLP)
 - multiple, benefits, 4-57
- Lactose intolerance, 4-135
- Large portion (LP) sizes, 6-37, 6-92, 8-7
- Latin hypercube, 6-66
- Laxative effect, 5-44
- Lethality of a substance, 4-14
- Leukocytes and leukocyte differentials, 4-45, 4-107, 4-133
- Levamisole, 5-42
- Limit of detection (LOD), 3-3, 4-134, 5-31–5-32, 6-10, 7-13
- Limit of quantification (LOQ), 3-3, 3-16–3-17, 3-22, 3-23, 6-10, 8-14–8-15
- Linear extrapolation, lxiii, 5-10–5-11, 5-33, 7-16, 9-3
- List-based diet history. *See* Food frequency questionnaires (FFQs)
- Livestock feeding studies, 3-17, 8-6, 8-15, 8-26, 8-36–8-39
- Livestock metabolism studies, 8-4, 8-27–8-29
- LOAEL. *See* Lowest-observed-adverse-effect level (LOAEL)
- Local lymph node assay (LLNA) test, 4-113
- Logistic distribution, 5-15
- Log-logistic distribution, 5-13, 5-15
- Lognormal distribution, 5-14, 6-57, 6-65
- Longevity, 4-41
- Long-term animal study, 5-35, 5-39. *See also* Chronic exposures;
 - Long-term toxicity study
- Long-term exposure. *See* Chronic exposures; Long-term toxicity study
- Long-term food consumption, lx, lxiv, lxvii, 6-38–6-39, 6-67, 8-6, 9-14
- Long-term tests, xlvii–xlviii

Long-term toxicity study, xlvii , xlviii, 1-9, 3-13, 4-14, 4-39, 4-41–4-42, 4-46, 4-49, 4-143
Lower-percentile food consumption data, 6-37
Lowest-observed-adverse-effect level (LOAEL), liv, 4-52, 4-126–4-128, 5-10, 5-22, 5-25–5-26, 5-53–5-54, 7-3, 9-35–9-37
Lymphocyte phenotyping, 4-109–4-110

M

Macronutrients, lxxix, 6-30–6-32, 9-24, 9-29–9-30, 9-32, 9-42, 9-45
Magnetic resonance imaging, 4-97
Malformation, 4-89
Malignant neoplasms, 4-70
Mancozeb residues, 3-18
Margin of exposure (MOE), liv, 4-127, 5-3, 7-2, 9-45. *See also*
 Margin of safety
Margin of safety, lv, lxvi, 4-51, 5-20, 5-24, 5-33, 5-37, 8-13, 8-15, 9-10–9-11, 9-20. *See also* Margin of exposure (MOE)
Marker residue (veterinary drugs), xlvi, lxiv, lxv, 3-20, 6-11, 6-53–6-54, 8-9, 8-19–8-23, 8-29, 8-32, 8-34, 8-36, 8-39, 8-43, 8-47–8-48
Maternal toxicity, li, 4-80–4-82, 4-86, 4-90, 4-96
Maximum level (ML), lviii, 1-8, 3-2, 6-7–6-9, 6-43, 6-47–6-48, 9-25, 9-27
Maximum residue level, 8-2–8-7, 8-16, 8-23, 8-42, 8-44
Maximum residue limit (MRL), xlv, lvi, lviii, lxiii–lxvi, 1-9–1-10, 1-12–1-14, 2-12–2-13, 3-2, 3-16–3-17, 5-38, 6-13
 analytical methods and residue stability in stored analytical samples, 8-31–8-36
 animal treatment, 8-43–8-44
 based on the application of GLP, GAP and GPVD, 8-42
 bound residues, 8-22
 comparison of JMPR and JECFA approaches, 8-14–8-16
 data evaluation, 8-41–8-43
 data selection, 8-39–8-41
 definition of a residue (for estimation of dietary intake), 8-21–8-22
 in dietary exposure assessments, 6-7–6-9, 6-18, 6-22, 6-34, 6-36, 6-53
 extension to other animal species, 8-47
 extrapolation issues, 8-44–8-48
 GEMS/Foods, pesticide residues, 8-6–8-7
 geographic extrapolation issues, 8-48–8-49
 Good Agricultural Practice (GAP), 5-45–5-46, 6-10, 8-42
 guidelines for injection site residues, 6-71
 honey, 8-48
 identification and description of residues and methods, 8-16–8-23

- JECFA guidelines for veterinary drugs, 6-53–6-54, 6-70, 8-3, 8-7–8-13
- JMPR guidelines for pesticide residues, 8-2–8-3, 8-2–8-7
- livestock feeding studies, 8-6, 8-36–8-39
- livestock metabolism studies for veterinary drug and pesticide evaluation, 8-27–8-29
- marker residue, 8-19–8-21
- for pesticides and veterinary drugs, lxiii–lxvi
- pharmacokinetics, toxicokinetics and metabolic data for, 8-23–8-27
- plant metabolism studies, 8-29–8-31
- re-evaluation approaches, 2-13
- for veterinary drugs. *See* MRL for a veterinary drug (MRLVD)
- Maximum survey-derived intake (MSDI), lxvi, 9-12
- Meal-based diet history survey, 6-32
- Mean, lviii, 5-6, 5-14, 6-10, 6-14, 6-20–6-23, 6-35, 6-39, 6-55–6-57, 6-59–6-60, 6-62, 6-65, 6-68, 6-92. *See also* Central tendency, of a probability distribution
- Mean body weight, 4-42, 6-93
- Mean dietary exposure, 6-36, 6-46, 6-60, 6-68
- Mean food consumption, lxvii, 6-35, 6-59, 9-14
- Mechanism of action, lxi, 1-9, 4-60, 4-99, 5-9, 5-35, 6-73, 7-8–7-9.
See also Mode of action
- Mechanism of toxicity. *See* Mechanism of action; Mode of action
- Membrane transporters, 4-24
- Metabolic disorders, 4-134–4-135
- Metabolic fate, of the test substance, 4-7–4-9, 4-151, 4-153, 9-9, 9-24
- Metabolism studies, lxiv, 3-18–3-20, 4-26–4-28, 5-45, 8-4, 8-23–8-30, 8-33, 8-37, 8-42–8-43
- factors affecting, 4-27
- at low substrate concentrations, 4-27
- phase I and phase II metabolic reactions, 4-26–4-27
- saturation of, 4-27, 4-30
- Metabonomics, 4-16
- Metals, in food, xlix, xlvi, lv, lxix, 1-6, 3-9, 3-22, 3-24, 4-50, 4-74, 5-42, 6-12, 9-6–9-8, 9-40
- Microbiological ADI, lvii, 4-155, 5-39–5-40
- Micronutrients, lxix, 4-106, 4-143, 9-24, 9-29, 9-30–9-31, 9-41–9-42, 9-45
- Minimum inhibitory concentration (MIC), 4-155, 5-40
- Model diets, 6-50–6-55
- Modelling dietary exposures
- for high consumers, 6-56–6-57
- for regular consumers, 6-57–6-58
- Mode of action, xlix, 2-12, 4-49, 4-138, 5-51, 6-72–6-73. *See also* Mechanism of action

- carcinogenicity, 1, 4-62–4-64, 4-71, 4-75–4-76
- chemical hazard identification, 2-6
- dose–response data, 5-2, 5-4, 5-26–5-27, 5-43, 5-47
- genetic toxicity, 4-53, 4-60–4-61
- health-based guidance value. *See* Health-based guidance values
- neurotoxicity, 4-102
- of pesticides, 7-9, 7-11
- related to GLP, 4-40
- role of biomarkers, 4-16
- of toxic action, 5-51
- in toxicity studies, 4-5, 4-15–4-16, 4-26
- Modified starches, safety assessment of, lxxviii, 3-7, 4-11, 9-21
- Monitoring data, 3-22, 6-10, 6-12, 8-15–8-16
- Monoglycerides, 3-6
- Monte Carlo simulation. *See* Random sampling
- Mortality, 4-44
- Mouse ear swelling test (MEST), 4-113
- Mouse liver neoplasms, 4-72
- MRL. *See* Maximum residue limit (MRL)
- MRL for a veterinary drug (MRLVD), 1-8, 1-12, 1-14, 3-20–3-22, 5-37–5-38, 5-41–5-42, 6-11, 6-18, 6-52–6-54, 6-71, 8-3, 8-7–8-13, 8-15
- MRL “not specified”, lxx, 8-13, 8-15
- Mugwort-celery syndrome, 4-124
- Multidrug resistance associated protein (MRP), 4-24
- Multiresidue methods, xlv, 3-16, 8-32
- Mutagenicity, 4-53–4-54, 4-56. *See also* Genotoxicity
- Mycotoxin screening programme, xlix, lxxix, 3-22, 3-24, 4-50, 5-42, 6-20, 6-60, 9-23, 9-40

N

- National estimated short-term intake (NESTI), 6-92
- Necropsy, 4-47
- Neonatal development, 4-36, 4-79, 4-97, 4-100
- Neonatal mouse model, xlvi, 4-66
- Nervous system, 4-78, 4-85, 4-92–4-95, 4-98–4-101, 4-103–4-104, 4-132
- Neurobehavioural evaluation, 4-98
- Neuropathy target esterase (NTE), 4-103
- Neurotoxicity, xlvi, 4-15, 4-39–4-40, 4-44, 4-48, 4-79, 4-85, 5-50, 9-5
 - alternative test methods, 4-103–4-104
 - chemical-specific neurotoxicity, 4-96
 - cholinesterase-inhibiting compounds, 4-102–4-103
 - cognitive functioning, assessment of, 4-101
 - definition, 4-92, 4-93

- developmental neurotoxicity, 4-98–4-100
 - evaluation, 4-93–4-100
 - guidelines, 4-94
 - histological evaluation, 4-95–4-96
 - interpretation of data, 4-104–4-105
 - morphological evaluations, 4-94–4-98
 - and nervous system features, 4-93
 - neural network, factors affecting formation of, 4-99–4-100
 - neurobehavioural testing, 4-98
 - neurotoxic effects, 4-93
 - observational methods, 4-101
 - ontological profiles, 4-96
 - quantitative neuropathological approaches, 4-97–4-98
 - screening of the adult, 4-101
 - tiered testing strategy, 4-100–4-102
- NOAEL. *See* No-observed-adverse-effect level (NOAEL)
- Non-fortified foods, 6-58
- Non-genotoxic mechanisms of carcinogenesis, 4-63–4-64
- Non-IgE-mediated immunological reactions, 4-117–4-118
- coeliac disease, 4-118, 4-132–4-134
 - risk assessment, 4-134
- Non-immune-mediated food hypersensitivity, 4-134–4-135
- Non-parametric probability distribution, 6-21, 6-39, 6-65–6-66
- Non-toxic metabolite, 4-29
- Non-traditional foods, lxix, 9-40
- No-observed-adverse-effect level (NOAEL), xlviii, lv, 9-2, 9-11. *See also*
- Benchmark dose (BMD); Benchmark dose lower limit (BMDL);
 - Lowest-observed-adverse-effect level (LOAEL); No-observed-effect level (NOEL)
- and ADI, 5-37, 5-43–5-44, 8-11
 - allergenic foods, 4-126–4-128
 - and cut-off value for ARfDs, 5-46–5-49, 5-51, 5-53–5-54
 - dose–response assessment, 5-3, 5-10
 - enzyme preparation, 9-19
 - for general systemic toxicity, 4-39
 - hazard characterization, 4-16
 - intake–response assessment, 9-35–9-37
 - neurotoxicity testing, 4-102
 - pesticide characterization, 3-14
 - role in derivation of health-based guidance values, liv–lvi, 4-36–4-37, 5-20–5-30, 7-13, 7-17
 - safety factor, application to, 5-39
 - single-dose study, 4-52
 - toxicokinetic data for, 4-31, 4-33

- No-observed-effect level (NOEL), 5-28, 5-38, 9-4-9-5, 9-10-9-11
- Novel foods, safety assessments of, lxi, 1-4, 9-40-9-45
- 5'-Nucleotidase, 4-45
- Nucleotide excision repair, 4-68
- Nutrients, safety assessment of, lxxviii, 2-9
 - absorption of nutrients, 4-21, 4-24, 4-43, 4-133
 - ADIs, 9-26-9-27
 - Codex standards for, 6-9
 - concepts concerning adverse health effects, 9-30-9-34. *See also*
 - Adverse effects
 - decision tree, in risk characterization of micronutrients, 9-31-9-32
 - derived from 24 h recalls, 6-31
 - dietary exposure assessments of, 6-2-6-5, 6-8
 - effects on blood levels, 4-143
 - food composition data for, 6-27-6-28
 - JECFA guidelines, 1-8, 1-14
 - lower-bound or upper-bound values, 6-20
 - microbial metabolism of nutrients, 4-154
 - total diet studies (TDSs), 6-13, 6-59
 - upper level of intake (UL), lxi, 6-44, 9-27-9-28, 9-34-9-39
 - using FFQs, 6-32-6-33
 - using food consumption data, 6-37, 6-39, 6-58

O

- Observational epidemiological studies, 5-4
- Observed peak concentration (C_{\max}), 4-31-4-32
- OECD. *See* Organisation for Economic Co-operation and Development (OECD)
- Ophthalmology, 4-44-4-45
- Oral food challenge trials, 4-125
- Oral itching, 4-121
- Ordinal categorical measures, 5-7
- Organ-directed toxicity assessment, 4-47
- Organic anion transporters (OAT), 4-28
- Organic cation transporters (OCT), 4-28
- Organisation for Economic Co-operation and Development (OECD), xlix,
 - xlvi, lxiv, 4-8-4-9, 4-13, 4-99, 8-6, 8-48
 - data assessment guidelines in genetic toxicological studies, 4-56-4-58
 - endocrine toxicity, 4-87-4-88
 - general systemic toxicity guidelines, 4-38
 - immunotoxicity guideline, 4-106
 - pathological evaluation of veterinary drugs, 4-70
 - reproductive and developmental toxicity guidelines, 4-79, 4-82-484, 4-86

- in silico and in vitro methods of, 4-9
- Organogenesis, 4-85
- Organophosphate-induced delayed neuropathy (OPIDN), 4-103
- Oxfendazole sulfone, 5-38

P

- Paired-feeding techniques, 4-43, 9-24
- Paired or two-sample comparisons, 4-16, 5-3, 5-8, 5-10, 5-23
- Palatability, xlviii, 4-15, 4-43–4-44, 4-144, 5-53, 9-24
- Paraffin waxes, 4-21
- Parametric statistical analysis, 4-102, 6-21, 6-39, 6-65–6-66
- Paternally mediated effects, 4-91–4-92
- PBTK models. *See* Physiologically based toxicokinetic (PBTK) models
- Peak plasma concentrations (C_{\max}), 4-31–4-32, 5-28, 5-48, 5-52
- Peroxisome proliferation, 4-73
- Persistent organic pollutants (POPs), 6-60, 6-76
- Pesticides
 - acute dietary exposure assessments, 6-69–6-70
 - ADI values, 5-35–5-37
 - analytical methods for residue analysis, 3-16–3-19
 - bioavailability, use of, 4-23
 - estimated daily intake (EDI), 1-13
 - estimated maximum daily intake (EMDI), 1-13
 - exposure assessments of residues, 1-13–1-14
 - general considerations in evaluation, 3-11–3-14
 - maximum residue limits (MRLs) for. *See* Maximum residue limit (MRL)
 - nominal lowest feeding level for, 8-37
 - physical and chemical properties of active ingredient, 3-15
 - purity considerations, 3-14
 - residue. *See* Residues of pesticides
 - reviews of past decisions on safety issues, 2-12–2-13
 - revised guidelines of 1995, 1-13–1-14
 - specifications for, 3-14
 - stability, 3-14–3-15
 - supervised trials median residue (STMR) level. *See* Supervised trials median residue (STMR)
- P-glycoprotein, 4-22, 4-24, 4-28
- P-glycoprotein-dependent limits, 4-12
- Pharmacodynamics, 8-28
- Pharmacokinetics, xlv, 3-2, 3-20–3-21, 4-8, 4-20–4-21, 4-23, 4-34, 4-86, 4-92, 4-99–4-100, 5-33, 8-12, 8-23, 8-25–8-28, 8-31, 8-43.
See also Toxicokinetics

- Phase I and phase II metabolic reactions, 4-26–4-27, 4-37
- pH-dependent passive reabsorption, 4-28
- Physiologically based toxicokinetic (PBTK) models, 4-10–4-11, 4-26, 4-34
- Plant metabolism studies, 8-24, 8-26–8-27, 8-29–8-31
- Plasma concentration, 4-19, 4-22, 4-29, 4-32, 4-35, 5-4, 5-28, 5-48, 8-28
- Plasma concentration–time curve, 4-19, 4-25
- P53^{+/-} mouse model, 4-67
- PMTDI. *See* Provisional maximum tolerable daily intake (PMTDI)
- POD. *See* Point of departure (POD)
- Point estimate of dietary exposure, lix, 6-45. *See also* Deterministic estimate of dietary exposure
 - GEMS/Food consumption cluster diets, 6-58–6-59
 - modelling, 6-55–6-58
 - screening method for, 6-45–6-55
 - total diet studies (TDSs), 6-59–6-60
- Point of departure (POD), xlviii, lvi, lxiii, 5-3, 5-33, 7-14. *See also*
 - Benchmark dose (BMD); Benchmark dose lower limit (BMDL);
 - No-observed-adverse-effect level (NOAEL)
- Polybrominated diphenyl ethers, 7-4
- Polychlorinated dibenzodioxins (PCDDs), 7-12
- Polychlorinated dibenzofurans (PCDFs), 7-12
- Polycyclic aromatic hydrocarbons (PAHs), 7-12
- Polyhalogenated dibenzodioxins, 4-21, 4-25, 7-10, 9-6–9-7
- Polyols, 4-7
- Population-based methods, lix, 1-16, 6-30, 6-35, 6-39–6-40
- Population subgroups, lvii, 4-5, 4-140, 4-142, 5-24, 5-54, 6-4, 6-13, 6-30, 6-35, 6-59–6-60, 7-16–7-17
- Post-marketing surveillance studies, 4-18, 4-137, 4-145–4-146, 9-23, 9-43
- Post-regulation dietary exposure assessments, 6-8
- Poundage data, lx, 6-44, 6-46–6-47
- Precision, 3-3, 3-17, 3-20–3-21, 4-70, 6-26, 6-30, 8-31–8-32
- Precursor effects, 4-16
- Preneoplasia, 4-69
- Preneoplastic lesions, 4-70–4-71
- Presystemic metabolism, 4-22–4-23, 4-32, 4-46, 4-74
- Principles for the Safety Assessment of Food Additives and Contaminants in Food (EHC 70). *See* Environmental Health Criteria (EHC) 70
- Principles for the Toxicological Assessment of Pesticide Residues in Food (EHC 104). *See* Environmental Health Criteria (EHC) 104
- Probabilistic analysis, of exposure variability, lx, 6-21. *See also*
 - Probabilistic distribution
- Probabilistic distribution, 6-61–6-67. *See also* Probabilistic analysis, of exposure variability
- Probabilistic exposure estimates, 6-44, 6-67

- Probabilistic model
 applicability, 6-66–6-67
 development from data sets, 6-64–6-65
 Latin hypercube, 6-65–6-66
 Monte Carlo simulation, 6-65–6-66
 simple empirical distribution estimate, 6-64
 stratified sampling method, 6-65–6-66
- Probability distributions, lxii, 5-18, 6-62–6-63, 7-5. *See also* Central tendency, of a probability distribution
- Problem formulation, xliv, 1-4, 2-9–2-11, 5-3, 5-9
- Processing aids, lviii, lxvi–lxviii, 3-7, 3-10, 4-144, 6-2, 6-5, 6-50, 6-58, 9-8, 9-16–9-21
- Processing factors, 6-12–6-13, 6-67, 6-93, 8-5, 8-36
- Processing studies, lxiv, 3-17, 6-12, 8-4–8-6, 8-31, 8-35
- Provisional maximum tolerable daily intake (PMTDI), lv, 5-21, 6-44, 7-16
- Provisional tolerable monthly intake (PTMI), lv, 5-21
- Provisional tolerable weekly intake (PTWI), lv, 5-21, 6-58, 7-13
- PTMI. *See* Provisional tolerable monthly intake (PTMI)
- PTWI. *See* Provisional tolerable weekly intake (PTWI)

Q

- Quality assurance, 4-40, 4-108, 6-10, 6-18–6-19, 6-23, 8-43
- Quality control, xlvi, 3-22, 6-19
- Quantal responses, 5-6–5-7
- Quantitative neuropathological approaches, 4-97
- Quantitative structure–activity relationship (QSAR), 4-9

R

- Random errors, 6-23–6-24, 6-26
- Random sampling, lx, 6-44, 6-57, 6-66
- Range-finding study, 4-39, 4-41
- Rate of absorption, 4-22
- Rat stomach neuroendocrine neoplasm, 4-73
- Receptor sites, 4-102
- Recoveries. *See* Analytical recoveries
- Re-evaluation, of safety assessments, 2-12–2-14
- Reference dose. *See* Acute reference dose (ARfD)
- Refined exposure assessment, lviii, 6-5, 6-42, 6-45–6-46
- Regenerative hyperplasia, 4-73–4-74
- Regional diets. *See* GEMS/Food regional diets
- Release agents, 3-7
- Relevant impurity, 3-12
- Renal excretion of a compound, 4-28

- Repeated-dose animal studies, xlviii, 4-39. *See also* Long-term animal study; Long-term toxicity study
- Reproductive testing, 4-87
- Reproductive toxicity, xlix, 4-15, 4-36, 4-79, 4-82–4-84. *See also*
- Developmental toxicity
 - chemical exposure of mother and neonatal development, 4-79
 - data interpretation, li, 4-88–4-91
 - endocrine toxicity, 4-86–4-88
 - end-points, 4-79–4-81
 - exposure during fetal period and developmental period, 4-78
 - information gaps, 4-92
 - in vitro tests, 4-91
 - issues specific to category of chemical, 4-88
 - OECD guidelines, 4-79
 - paternally mediated effects, 4-91–4-92
 - study design, 4-81–4-87
 - tiered and combined approaches to, 4-85
- Residue depletion studies, xlv, lviii, lxiv, 3-2, 3-20–3-21, 6-7–6-8, 6-10–6-11, 8-9, 8-11–8-12, 8-15, 8-31, 8-34, 8-36–8-38, 8-43, 8-47
- Residue exposure estimates, 8-11
- Residue methods, validation of, 3-17–3-18, 8-32
- Residues of pesticides, xliii, xxxiii, liii, liv, 1-2, 2-11–2-12, 4-6, 4-20, 4-43, 5-2, 5-20, 6-2, 6-58, 6-71, 8-42, 9-2, 9-8
- Residues of veterinary drugs. *See* Veterinary drug residues
- Resistant bacteria, lvii, 4-154, 5-40
- Response, definition of, 5-6–5-7
- Response addition, 7-9
- Retrospective epidemiological studies, 4-114–4-115, 4-146–4-148, 5-49
- Reversibility, of a toxic effect, 4-48
- Reviews, of safety assessments, 2-12–2-14
- Ribonucleic acid (RNA), 4-25–4-26, 4-96
- Risk, definition of, 2-4
- Risk analysis paradigm, liii, 1-4, 2-1–2-3, 2-14, 4-92, 5-2, 5-4, 9-30
- Risk assessment. *See also* Safety assessment
 - definition, 2-2
 - in food allergy, 4-126–4-129
 - interactive relationship with risk management, 2-9–2-14
 - need for, 1-1–1-2
 - principles and procedures of JECFA and JMPR, 1-2–1-6
 - role in risk analysis for food chemicals, 2-4–2-5
 - steps of hazard identification in food chemicals, 2-5–2-9
- Risk characterization, xlv, 1, liii, lviii, lxi–lxiii, 1-15–1-16, 2-2–2-3, 2-5, 2-8–2-9, 2-11, 4-19, 4-33, 4-36, 4-49, 4-61, 5-2–5-3, 5-8, 5-33, 6-2, 8-16, 9-7, 9-29

- approaches, 7-1–7-2
- decision tree, 9-31–9-32, 9-41
- definition, 2-8
- at estimated levels of exposure, 7-3–7-8
- from exposure to multiple substances, 7-8–7-11
- for genotoxic and carcinogenic compounds, 7-13–7-16
- of novel foods, 9-45
- sensitive subpopulation, 7-16–7-18
- sensitivity analysis, 7-7–7-8
- for substances that are genotoxic and carcinogenic, 7-2
- surrogate approach to mixture evaluation, 7-12
- toxic equivalency factor (TEF) approach, 7-11–7-12
- types, 7-4
- uncertainty and variability analysis, 7-5–7-7
- Risk communication, xlv, 1-3, 1-5, 2-1–2-3, 2-5
- Risk management, xxi, xlv, 1-4–1-5, 1-8, 2-1–2-3, 2-5–2-6, 2-8–2-10, 4-74, 5-54, 7-2–7-4, 7-13, 7-15–7-16, 8-45, 9-39
- Risk profiling, 2-9–2-10
- Root absorption, 8-26
- Route of elimination, 4-28–4-29
- Route of exposure. *See* Exposure route
- Route-to-route extrapolation, 4-21, 4-36–4-38

S

- Safety assessment. *See also* Risk assessment
 - of bulk sweeteners, lxviii, 5-44, 9-21
 - of enzyme preparations, lxviii, 9-18–9-20
 - establishing ADIs for enzymes, 9-20
 - of food packaging materials, lxvii–lxviii, 6-54, 9-15
 - of fortified foods, lxviii, 6-58, 9-26, 9-30
 - of modified starches, lxviii, 3-7, 4-11, 9-21
 - of novel foods, lxix, 1-4, 9-40–9-45
 - of nutrients. *See* Nutrients, safety assessment of
 - re-evaluation of, 2-12–2-14
 - reviews of, 2-12–2-14
 - substances consumed in large amounts, safety assessment.
 - See* High-consumption substances, assessment of
 - substances consumed in small amounts, safety assessment.
 - See* Substances consumed in small amounts, safety assessment
- Safety factor, lvi, 1-7, 1-9, 4-17, 4-52, 4-137, 5-21, 5-23–5-28, 5-34, 5-36–5-37, 5-39, 5-41, 5-48–5-49, 5-51–5-53, 9-26. *See also*
 - Chemical-specific adjustment factor (CSAF); Uncertainty factor
- Salmonella*/microsome assay, xlix, 4-56, 4-59, 4-60

- Sample preparation, 6-10, 6-15–6-16, 6-25–6-26
- Sample processing, 6-15, 6-25, 8-33
- Sampling procedure, 6-10, 6-14, 8-13
- Saturation of metabolism, 4-27, 4-30
- Screening methods, xlix, xlvii, lix–lx, lviii, 1-13, 3-3, 4-82–4-84, 4-87, 4-91, 4-95, 4-100–4-101, 4-104, 4-108, 4-113, 6-5–6-6, 6-42–6-46, 6-49, 6-51–6-52, 6-55, 6-62, 9-23
- Selective studies, of individual foods, 6-60
- Sensitivity analysis, lxii, 5-10, 7-7–7-8
- Sensitization threshold, 4-125
- Serum enzyme levels, changes, 4-46
- Serum glutamate–oxaloacetate transaminase (SGOT), 4-45
- Serum glutamate–pyruvate transaminase (SGPT), 4-45
- Shelf-life stability, 3-13–3-14
- Short-term exposure, lxiv, 1-15, 4-14, 5-55, 8-3, 8-7, 8-16, 9-44. *See also*
 - Acute exposure; Subchronic exposure
- Short-term guidance values, 4-22. *See also* Acute reference dose (ARfD)
- Short-term studies, lx, 4-14–4-15, 4-46, 4-48–4-49, 4-144, 5-39. *See also*
 - Short-term toxicity study
- Short-term tests, xix, xlvii, 1, 4-60
- Short-term toxicity study, 4-51, 9-20
- Single-blind placebo-controlled food challenge (SBPCFC) tests, 4-125.
 - See also* Double-blind placebo-controlled food challenge (DBPCFC) tests
- Single-dose studies, 4-19
- Single-dose toxicokinetic studies, 4-31, 4-35–4-36
 - guidance for, 4-51–4-52
- Single-laboratory validation, 3-2–3-4
- Single portion exposure technique (SPET), lxvii, 6-52, 9-14–9-15
- Small-consumption substances, assessment of. *See* Substances consumed in small amounts, safety assessment
- Soil metabolites, 8-23, 8-27
- Sorbitol, 7-17, 9-18, 9-21
- Sorbitol dehydrogenase, 4-45
- Soybean oil, 4-126
- Special dietary foods, 9-40
- Specialized studies, on consumer dietary exposure, 6-60–6-61
- Specific migration limit (SML), 6-54
- Specific serum screen, 4-130
- Spontaneous neoplasms, 4-69–4-70
- Standard portion sizes, lxvii, 6-36–6-37, 9-14
- Statistical uncertainty. *See* Uncertainty
- Steady-state body burden, 4-35–4-36
- Steady-state condition, 4-35–4-36

- Stepwise approaches, 6-5
for deriving an ARfD, 5-53–5-54
to exposure assessment, 6-43–6-44
toxicological studies, lviii, 4-10, 4-50
- STMR. *See* Supervised trials median residue (STMR)
- Stratified sampling, lx, 6-65–6-66
- Structured risk analysis process, 2-2
- Subchronic exposure, 4-83. *See also* Short-term exposure
- Subpopulation-specific end-points, lvii, 7-17
- Substances, for re-evaluation, 2-14
- Substances consumed in large amounts, safety assessment. *See*
High-consumption substances, assessment of
- Substances consumed in small amounts, safety assessment, 4-6
dietary exposures for consumers of flavouring agents, 9-12–9-15
of food packaging materials, 6-54–6-55, 9-15–9-16
JECFA procedure for flavouring agents, 9-8–9-12
of processing aids, 9-16–9-21
threshold of toxicological concern (TTC) approach, 9-2–9-8
- Substrate concentrations, rate of metabolism, 4-27
- Supervised residue trials, lxiv, 3-17, 8-5, 8-48
- Supervised trials, lviii, lxiv, 4-17, 6-10–6-12, 6-21–6-22, 8-4, 8-6–8-7,
8-21, 8-34, 8-42
- Supervised trials median residue (STMR), lxiv, 1-14, 6-8, 6-22, 6-58,
6-93, 6-95, 8-5–8-6, 8-8, 8-21
- Supervised trials median residue – processed (STMR-P), 6-93–6-94
- Surface and luminal tissue chronic irritation, 4-72
- Surrogate approach to mixture evaluation, 7-6, 7-12, 9-33–9-34
- Surveillance-type studies, lii, lviii, 3-16, 4-17–4-18, 4-137, 4-145–4-146,
4-148, 6-8–6-9, 6-11–6-14, 6-18, 6-22, 6-59–6-60, 9-32, 9-41
- Susceptibility factors, 3-20, 4-72, 4-93, 4-133, 5-6, 5-20, 9-30
- Symptoms of food allergies, 4-121–4-122
- Synergism, 7-9–7-10
- Systematic errors, 6-24, 6-26
- Systemic toxicity, xlvii–xlviii, 4-11. *See also* General systemic toxicity
study

T

- TAMDI. *See* Theoretical added maximum daily intake (TAMDI)
- TAMDI model diet, 6-50–6-52
- Target organs, for toxicity testing, xlvii–xlviii, 2-6, 3-20–3-21, 4-37, 4-56,
4-80–4-81, 4-99, 5-17, 8-9, 8-34
- TDI. *See* Tolerable daily intake (TDI)
- Temphos, 7-4

- Temporary ADI, lvi, 1-9, 2-12–2-14, 3-6, 5-34–5-37, 5-41–5-42, 8-13, 8-15. *See also* Acceptable daily intake (ADI)
- Temporary MRLs, lxxv, 1-9, 5-41–5-42, 8-13, 8-15. *See also* Maximum residue limit (MRL)
- “Tentative” specifications, lv, 3-6, 3-10, 5-21, 5-43
- Teratogenic defects, 4-80
- Teratogenicity studies, 4-78, 4-86, 5-39. *See also* Developmental toxicity; Reproductive toxicity
- Test portions, 6-15–6-16. *See also* Large portion (LP) sizes; Standard portion sizes
- Test substance, 4-40–4-41
- 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), 7-10
- TG.AC mouse model, 4-67–4-68
- Tg-rasH2 mouse model, 4-68–4-69
- Theoretical added maximum daily intake (TAMDI), lix, 6-44, 6-50–6-52, 9-13
- Theoretical maximum daily intake (TMDI), lxxv, 1-13–1-14, 6-53, 8-8
- Threshold, 4-125–4-126
- Threshold dose, li, lxxii, 4-120, 4-125, 7-2, 9-33
- “Threshold of regulation” for food packaging migrants, 9-16
- Threshold of toxicological concern (TTC), lxxvi–lxxvii, 4-8, 9-2–9-8
- Tiered screening battery, 4-86–4-87
- Tiered testing approaches, xlvi, lx, lxxviii, 4-14, 4-86–4-87, 4-100–4-102, 4-107, 4-112, 6-43, 6-55, 9-16
- Time of the peak concentration (T_{max}), 4-31–4-32
- Tissue efflux transporters, 4-24
- Tissue trophic activity, 4-73
- Tolerable daily intake (TDI), liii, lv, 4-50, 5-2, 5-21. *See also* Acceptable daily intake (ADI); Health-based guidance values; Provisional maximum tolerable daily intake (PMTDI)
- Tolerable intake, lv, 1-14, 2-7, 5-42–5-43, 6-9, 7-9
- Total diet study (TDS), lxxviii, 6-8, 3-16, 3-17, 6-13–6-14, 6-43, 6-59–6-61
- Total organic solids (TOS), 9-19
- Toxic equivalency factor (TEF) approach, lxxii, 6-73, 7-9, 7-11–7-12, 9-7
- Toxicity, xlvi. *See* Developmental neurotoxicity; Developmental toxicity; General systemic toxicity study; Genotoxicity; Immunotoxicity; Neurotoxicity; Reproductive toxicity
- Toxic metabolite, lvii, lxxii, 4-154, 5-17, 5-52, 7-11
- Toxicodynamics, liv, lvi, 4-19–4-20, 4-37, 4-56, 4-149, 5-11, 5-19, 5-27–5-28, 5-51, 7-9–7-10, 8-12, 9-2. *See also* Chemical-specific adjustment factor (CSAF); Pharmacodynamics
- Toxicokinetics, liv, lvi, 4-19–4-20, 4-37, 4-56, 5-27–5-28, 5-51, 7-9–7-10, 8-12. *See also* Chemical-specific adjustment factor (CSAF); Pharmacokinetics

- data, 4-31
- guidance on the design of, 4-20
- parameters, 4-31–4-32
- Toxicological and human studies, xlvii–xlviii, 9-17, 9-19–9-20, 9-24.
 - See also* In vitro studies; In vivo studies
 - absorption, distribution, metabolism and excretion (ADME), 4-11–4-12, 4-18–4-37
 - accumulation of the chemical, 4-15
 - acute toxicity, 4-49–4-52
 - animal studies, 4-13–4-17
 - biomarkers, 4-16
 - cancer bioassay, 4-14
 - carcinogenicity, 4-62–4-78
 - chemical-specific adjustment factor (CSAF). *See* Chemical-specific adjustment factor (CSAF)
 - considerations in study design, 4-15–4-17
 - design of studies in humans, 4-18
 - dietary exposure assessment, 4-8
 - examination of metabolic fate of the test substance, 4-7–4-8
 - examination of structural alerts for toxicity, 4-7–4-8
 - examination of structure–activity relationships, 4-7–4-8
 - findings and interpretation of the results, l–li, 4-6
 - food allergies and food hypersensitivities, li, 4-117–4-135
 - gastrointestinal tract considerations, 4-150–4-156
 - general principles, 4-8–4-18
 - genetic, 4-52–4-61
 - genotoxicity of the substance, 4-14
 - gut microflora, effects of, 4-11
 - human studies, general principles, 4-17–4-18, 4-135–4-150.
 - See also* Human studies, general principles
 - immunotoxicity, 4-105–4-117
 - in vitro approach, 4-9–4-11
 - methods for statistical analysis, 4-16
 - nature of substance and its uses, 4-5–4-6
 - neurotoxicity, 4-92–4-105
 - overall rate of elimination of a chemical from the body, 4-29–4-30
 - physiologically based toxicokinetic (PBTK) models, 4-10
 - preparation of human data, 4-18
 - purpose of, 4-5
 - reference points, 4-16–4-17
 - reproductive and developmental toxicity, 4-78–4-92
 - of reproductive performance, 4-15
 - role in the design of animal toxicity tests, 4-30–4-31
 - role in the interpretation of data from animal toxicity tests, 4-31–4-37

- route-to-route extrapolation, 4-37–4-38
- selection of method and model, 4-12–4-13
- short- and long-term studies, 4-14
- in silico method, 4-9–4-11
- stepwise approach to, lviii, 4-10, 4-50
- studies of precursor effects, 4-14, 4-16
- surveillance-type studies, 4-17–4-18
- tests of general systemic toxicity, 4-38–4-49
- thresholds of toxicological concern (TTCs), 4-8
- toxicokinetic parameters, 4-31–4-32
- tumorigenic response, assessment of, 4-14
- Toxicological end-points. *See* End-points
- Toxicological reference value, 6-4, 6-50. *See also* Acceptable daily intake (ADI); Acute reference dose (ARfD); Health-based guidance values; Provisional maximum tolerable daily intake (PMTDI); Tolerable daily intake (TDI)
- Traditional food allergy, 4-120, 4-131
- Transgenic mouse models, xlviii, 4-57, 4-66–4-69
- Transgenic plant material, 3-18, 8-27, 8-30
- Transplacental carcinogenesis, 4-91
- TTC. *See* Threshold of toxicological concern (TTC)
- Two-stage simulation techniques, 6-63

U

- α 2u-microglobulin-induced rat nephropathy, 4-73
- Uncertainty, lvi, lxi–lxii, lxxviii, 2-4, 4-23, 4-34, 4-150, 5-16, 5-18, 5-31, 6-22–6-26, 6-37, 6-46, 6-63, 6-65, 9-27, 9-36
- Uncertainty analysis, 5-10, 5-12, 7-5–7-7
- Uncertainty factor, liv–lvi, lxi, 5-51–5-54, 7-16, 9-5, 9-33, 9-37. *See also* Assessment factor; Safety factor
 - in calculating ADI, 5-33, 5-39–5-41
 - data-driven. *See* Chemical-specific adjustment factor
 - default, 4-12, 4-34, 5-25, 5-27–5-28, 5-46, 5-49
 - for deriving an ARfD, 5-51–5-54
 - in dose–response modelling, 5-18
 - in food allergy risk assessment, 4-127
 - in food chemical concentration data, 6-22–6-26
 - health-based guidance values, 5-21, 5-24–5-28, 5-30, 5-32
 - interspecies, 4-37
 - risk characterization, 7-5–7-7
- Undernutrition, 4-97
- United States model diet, 6-54–6-55
- Unit weights, 6-36, 6-93, 8-7

Upper level of intake (UL), lxxviii–lxxix, 9-27–9-28
Upper-percentile food consumption data, 6-37
Urinalyses, 4-14, 4-23, 4-46–4-47, 4-70, 5-4, 6-75
USEPA Gene-Tox workshop, 4-58
Use pattern, 8-42–8-43

V

Validation, xlv, 3-3–3-4, 3-16, 3-18, 3-20–3-21, 4-9, 4-54, 4-58–4-60, 4-69, 4-87, 4-97–4-98, 4-142, 5-8, 6-19, 8-28, 8-31–8-34
Variability, liv, lvi, lx–lxii, 1-9, 3-6, 3-10, 3-19, 3-24, 4-19, 4-26–4-27, 4-33–4-34, 4-37, 4-45–4-46, 4-97, 4-115, 4-126, 4-152–4-153, 5-3, 5-8, 5-14, 5-15, 5-17, 5-25–5-27, 5-46, 5-52, 6-32, 6-35, 6-39, 6-46, 6-61–6-65, 7-5–7-7, 7-12, 7-15, 8-26, 9-22, 9-33, 9-36
Variability analysis, 7-5–7-7
Variability factor, 6-15, 6-26, 6-65, 6-92, 6-94–6-95, 7-4–7-7, 7-8, 7-12, 7-15, 8-7, 8-26, 9-22, 9-33, 9-36
Variability in dietary exposure, lxii, 6-61–6-62, 7-5–7-7
Variation, lvi, 1-15, 4-12, 4-17, 4-35, 4-56, 4-59, 4-85, 4-89–4-90, 4-137, 4-145, 4-152–4-153, 5-6, 5-25–5-28, 5-30–5-31, 5-33, 5-43, 5-51–5-52, 6-25–6-26, 7-16, 8-47, 9-39
Veterinary drug residues, li, lxiii, xlv, 1-10–1-11, 2-13, 3-2, 3-20–3-21, 4-6, 4-137, 4-139–4-140, 4-150, 5-37, 5-41, 8-7–8-13, 8-17, 8-35, 8-45–8-47
 acceptable stability criteria, for veterinary drugs, 8-34
 acute dietary exposure assessments, 6-70–6-71
 ADI values, lxxv–lxxvi, 5-37–5-42
 analytical methods for residues, 3-21–3-22
 bioavailability, use of, 4-23
 evaluation of residues, 1-11–1-12
 exposure assessments of residues, 1-14
 general considerations in evaluation, 3-19–3-21
 JECFA guidelines, lxxv, 6-53–6-54, 6-70, 8-3, 8-7–8-13
 maximum residue limits (MRLs) for. *See* Maximum residue limit (MRL)
VICH GCP guidelines. *See* International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) for Good Clinical Practice (GCP)

W

Weight of evidence, 1, 2-6, 4-10, 4-56, 4-60, 4-69–4-70, 4-76–4-77, 4-103–4-104, 4-107, 4-109, 4-131, 5-25, 5-28, 5-47

WHO Scientific Group on Procedures for Investigating Intentional and
Unintentional Food Additives, 4-138
Withdrawal period, 8-3, 8-11

X

Xenobiotics, 4-79, 4-149, 4-151
Xpa^{-/-} homozygous knockout mouse model, 4-68
Xylitol, 9-21

Z

Zinc deficiency, 4-91