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
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.
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)


ISSN 0250-861X

© 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, xlvii, 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, lxviii, 9-18–9-20
Acceptable daily intake (ADI), lii–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, lxv–lxvi, 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)
biochemical 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, lii
in tissue-associated lymphoid tissues, 4-108
Index

in toxicological studies, xlvi, xlviii, 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, li, 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, lxv, 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, lixi, 4-56, 4-72
Animal food allergens, 4-123
Animal models, xlviii. See also Transgenic mouse models
Animal studies, xlviii, 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, xlvi, 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, 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

I-4
Index

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, lxviii, 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, lxix, 9-42
Carcinogenicity studies, xlviii, 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, l, 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, xlv, 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, xliv, 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), xliv, 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, lli, 4-114, 4-143, 4-147–4-148
Collaborative International Pesticides Analytical Council (CIPAC), 3-11
I-8

EHC 240: Principles for Risk Assessment of Chemicals in Food

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, lii–liii, 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, lxv, 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, li, lx, liii, 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, lixii, 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, xlv–xlvi, li–lii, 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, lii–liii, lxvii, 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, lxix, 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, xlxi, 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–lx, 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, lxvii, 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, lx–lx, 6-45–6-55
  sources of information, lviii–lx
  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, lxvii, 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
Index

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, lv, 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, xli, lii–liii, 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
I-12

EHC 240: Principles for Risk Assessment of Chemicals in Food

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, xlvi, l, 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

I-12
Index

End-points, xlix, xlviil, l–111, 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, lii, 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), lxvi, 1-13, 6-53, 8-7
17β-Estradiol, 4-66
Ethinylestradiol, 4-57
Ethylenediaminetetraacetic acid (EDTA), 3-9
Ethylenthiourea 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
Index

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, lviii, 3-5–3-8
group ADIs/TIs, 5-43
information from humans, 4-137–4-138
information on analytical methodology used, 3-10–311
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, liii, lix, 6-30, 6-39–6-40, 6-59
Food challenge tests, 4-125
Food chemical safety, risk assessment of, xlii–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, liii, 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, lxvii–lxviii, 6-54–6-55, 9-15
Index

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, xlvi, 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, lx, 6-40, 6-58–6-59, 8-7
GEMS/Food database, lxviii–lx, 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, xlxi, 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

I-18
Index

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), lxv, 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, xliv, xlvi, xlviii, l, lii, 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, xliv, 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, lxvii, lii–lxiii, liv–lvi, 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
EHC 240: Principles for Risk Assessment of Chemicals in Food

- 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

I-20
I-21

Index

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)
derend-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, lxi, 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

I-22
Index

In silico methods, xlvii, 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, 4-155, 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, xlviii, 4-9–4-11, 4-34, 4-37, 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, 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, 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

I-23
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, xlxi, xlvi, 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
$K_{oc}$ 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
**Index**

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
$K_w$ 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
Magnetic resonance imaging, 4-97
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), xlv, 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
good 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
Index

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, lx, 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, xlxi, xlvii, 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, lxii, 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, lxviii, 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”, lxv, 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, lxix, 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, lxviii, 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, lxviii, 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
Index

devontal 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
coeeliac 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, lxix, 1-4, 9-40–9-45
5′-Nucleotidase, 4-45
Nucleotide excision repair, 4-68
Nutrients, safety assessment of, lxviii, 2-9
absorption of nutrients, 4-21, 4-24, 4-43, 4-133
ADIs, 9-26–9-27
Codex standards for, 6-9
certainty 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), lxix, 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 ($C_{\text{max}}$), 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), xlvii
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
Index

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, xlvi, 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 ($C_{\text{max}}$), 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, lixiii, 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, livii, 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, lix, 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, lix, 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

I-32
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, xl, 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, li, liii, lvii, lxi–lxxiii, 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
Index

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, xliv, 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, lxvi–lxviii, 6-54, 9-15
of fortified foods, lxvi, 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

I-35
I-36

EHC 240: Principles for Risk Assessment of Chemicals in Food

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, xlvi, 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, xlvi, l, 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), lxvi
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, lxvi, 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, 6-58, 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, xlvi–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, xlvi–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)
Temephos, 7-4
Index

data, 4-31
  guidance on the design of, 4-20
  parameters, 4-31–4-32
  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

\( \alpha \)2u-microglobulin-induced rat nephropathy, 4-73
Uncertainty, lvi, lxi–lxii, lxviii, 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

I-40
**Index**

Upper level of intake (UL), lxviii–lxix, 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, lxv–lxvi, 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, lxv, 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
**EHC 240: Principles for Risk Assessment of Chemicals in Food**

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