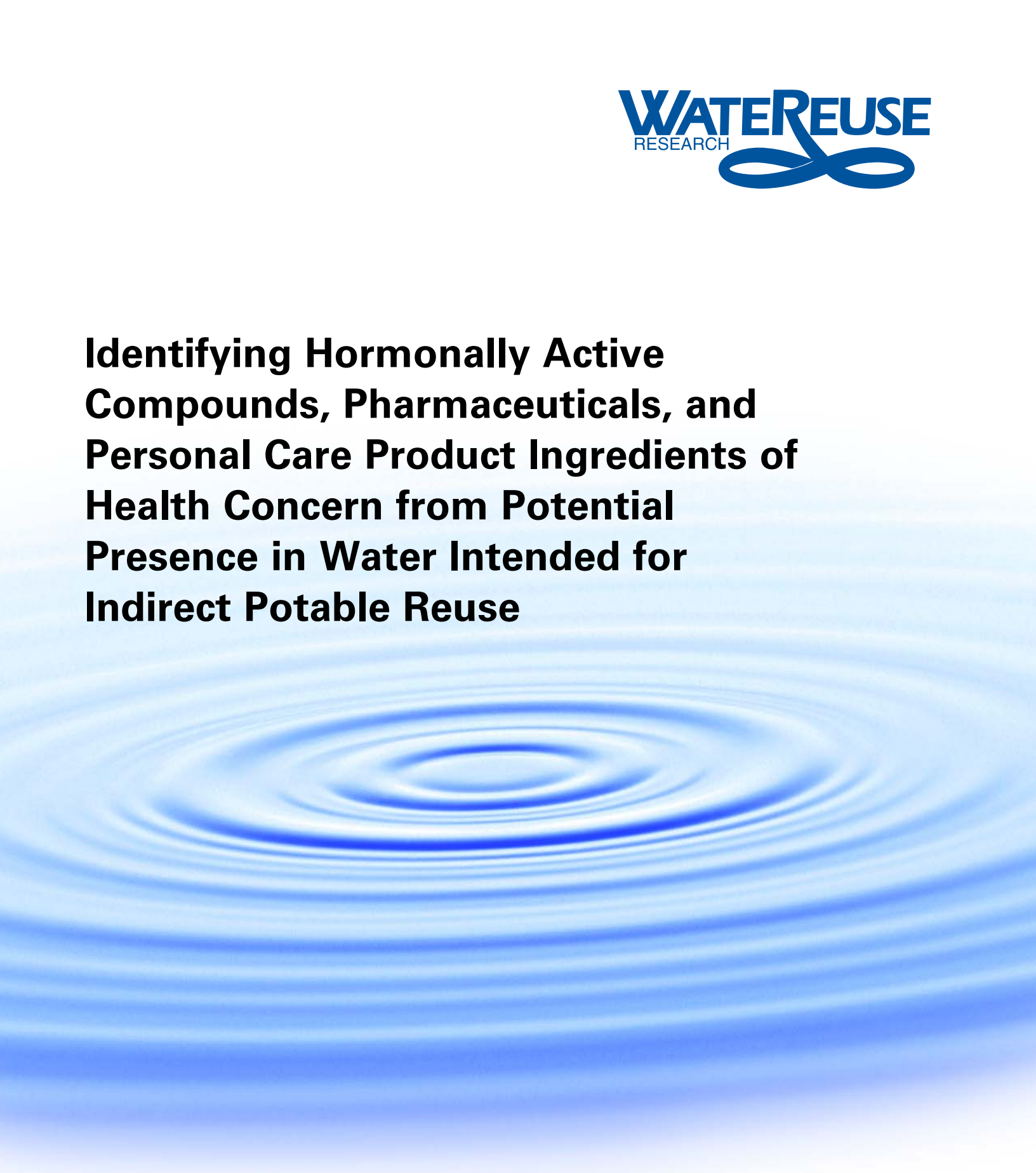
Identifying Hormonally Active Compounds, Pharmaceuticals, and Personal Care Product Ingredients of Health Concern from Potential Presence in Water Intended for Indirect Potable Reuse



WateReuse Research Foundation

Identifying Hormonally Active Compounds, Pharmaceuticals, and Personal Care Product Ingredients of Health Concern from Potential Presence in Water Intended for Indirect Potable Reuse

About the WateReuse Research Foundation

The mission of the WateReuse Research Foundation is to conduct and promote applied research on the reclamation, recycling, reuse, and desalination of water. The Foundation's research advances the science of water reuse and supports communities across the United States and abroad in their efforts to create new sources of high quality water through reclamation, recycling, reuse, and desalination while protecting public health and the environment.

The Foundation sponsors research on all aspects of water reuse, including emerging chemical contaminants, microbiological agents, treatment technologies, salinity management and desalination, public perception and acceptance, economics, and marketing. The Foundation's research informs the public of the safety of reclaimed water and provides water professionals with the tools and knowledge to meet their commitment of increasing reliability and quality.

The Foundation's funding partners include the Bureau of Reclamation, the California State Water Resources Control Board, the California Energy Commission, and the California Department of Water Resources. Funding is also provided by the Foundation's Subscribers, water and wastewater agencies, and other interested organizations.

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Cosponsors
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California State Water Resources Control Board
Nevada Department of Environmental Protection
Clark County Water Reclamation District

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Disclaimer

This report was sponsored by the WateReuse Research Foundation and cosponsored by the Bureau of Reclamation, California State Water Resources Control Board, Nevada Department of Environmental Protection, and Clark County Water Reclamation District. The Foundation, its Board Members, and the project cosponsors assume no responsibility for the content of this publication or for the opinions or statements of facts expressed in the report. The mention of trade names of commercial products does not represent or imply the approval or endorsement of the WateReuse Research Foundation, its Board Members, or the cosponsors. This report is published solely for informational purposes.

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WateReuse Research Foundation Project Number: WRF-05-005
WateReuse Research Foundation Product Number: 05-005-1

ISBN: 978-1-934183-31-1
Library of Congress Control Number: 2010921674

Printed in the United States of America

Printed on Recycled Paper

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ABBREVIATIONS AND ACRONYMS

ACE Inhibitor	Angiotensin-Converting Enzyme Inhibitor
ADI	Acceptable Daily Intake
ADME	Absorption, Dose, Metabolism, Excretion
AERS	Adverse Event Reporting System
ATPase	Adenotriphosphatase
ATSDR	Agency for Toxic Substances and Disease Registry
Australia EPHC	Australia Environment Protection and Heritage Council
AwwaRF	Awwa Research Foundation
BMDL	Benchmark Dose Level
BMDS	Benchmark Dose Software
BMR	Benchmark Response
CA	Chromosomal Aberration Assay
CaDHS	California Department of Health Services
CA OEHHA	California Office of Environmental Health Hazard Assessment
CAS No.	Chemical Abstracts Service Registry Number
CCL	Contaminant Candidate List
CDC	Centers for Disease Control
CDPH	California Department of Public Health
CFR	Code of Federal Regulations
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DEHP	Diethylhexyl Phthalate
DNA	Deoxyribonucleic Acid
DWEL	Drinking Water Equivalent Level
East Bay MUD	East Bay Municipal Utilities District
EDC	Endocrine Disrupting Compound
EDSP	Endocrine Disruptor Screening Program
EE2	Ethynylestradiol
EMEA	European Medicines Agency
EPA	Environmental Protection Agency (U.S. EPA)
ER	Estrogen Receptor
EU	European Union

F	Female
FDA	Food and Drug Administration
FQPA	Food Quality Protection Act
FSH	Follicle-stimulating Hormone
GABAA	Gamma-aminobutyric Acid Receptor A
GD	Gestational Day
GI	Gastrointestinal
GWRC	Global Water Research Coalition
HDL	High Density Lipoprotein
HED	Human Equivalent Dose
HHCB	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran ("Galaxolide")
HMG-CoA	3-hydroxy-3-methyl-glutaryl-Coenzyme A Reductase
HPV	High Production Volume
IARC	International Agency for Research on Cancer
IEH	Institute for Environmental Health
ILSI	International Life Sciences Institute
IRIS	Integrated Risk Information System
K_a	Acid Dissociation Constant
LD_{50}	Dose Required to Kill 50% of Study Animals
LDL	Low Density Lipoprotein
LH	Leutenizing Hormone
LOAEL	Lowest Observed Adverse Effect Level
log D	Octanol Water Distribution Coefficient
log K_{OW}	Octanol Water Partition Coefficient
LTD	Lowest Therapeutic Dose
LTD_{10}	Lowest Dose Required to Induce Tumors in 10% of Study Animals
M	Male
MCL	Maximum Contaminant Level
MCLG	Federal Maximum Contaminant Level Goal
MIC	Minimum Inhibitory Concentration
MLA	Mouse Lymphoma Assay
MN	Micronucleus Assay
MOA	Mechanism of Action

MRL	Method Reporting Limit
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
MW	Molecular Weight
NA	Not Available
NCI	National Cancer Institute
NF	Nanofiltration
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NSAID	Non-steroidal Anti Inflammatory Drug
NTP	National Toxicology Program
OEHHA	California Office of Environmental Health Hazard Assessment
OTC	Over-the-Counter
PABA	p-Aminobenzoic Acid
PAC	Project Advisory Committee
PCBs	Polychlorinated Biphenyls
PCP	Personal Care Product
PD	Pharmacodynamic
PDR	Physicians Desk Reference
PEC	Predicted Environmental Concentration
PHG	Public Health Goal
PK	Pharmacokinetic
pK_a	Negative Logarithm Acid Dissociation Constant
POD	Point of Departure
PND	Postnatal Day
PPCPs	Pharmaceuticals and Personal Care Products
REACH	Registration, Evaluation, and Authorization of Chemicals
RfD	Reference Dose
RNA	Ribonucleic Acid
RSC	Relative Source Contribution
SF	(Cancer) Slope Factor
SOW	Scope of Work
SMILES	Simplified Molecular Input Line Entry Specification
SNWA	Southern Nevada Water Authority
SSRI	Selective Serotonin Reuptake Inhibitor

STORET	EPA STOrage and RETrieval Data System
TCDD	2,3,7,8-Tetrachlorodibenzo-p-dioxin
TD50	Dose Required to Induce Tumors in 50% of Study Animals
TDI	Tolerable Daily Intake
tRNA	Transcriptional Ribonucleic Acid
TSCA	Toxic Substances Control Act
TTC	Threshold of Toxicologic Concern
U.S.	United States
UF	Uncertainty Factor
ULPRO	Ultra-low-pressure Reverse Osmosis
VLDL	Very Low Density Lipoprotein
VSD	Virtually Safe Dose
WA DOH	Washington State Department of Health
WERF	Water Environment Federation
WHO	World Health Organization
WRF	WateReuse Research Foundation
WWTP	Municipal Wastewater Treatment Plant

FOREWORD

The WateReuse Research Foundation, a nonprofit corporation, sponsors research that advances the science of water reclamation, recycling, reuse, and desalination. The Foundation funds projects that meet the water reuse and desalination research needs of water and wastewater agencies and the public. The goal of the Foundation's research is to ensure that water reuse and desalination projects provide high-quality water, protect public health, and improve the environment.

An Operating Plan guides the Foundation's research program. Under the plan, a research agenda of high-priority topics is maintained. The agenda is developed in cooperation with the water reuse and desalination communities including water professionals, academics, and Foundation Subscribers. The Foundation's research focuses on a broad range of water reuse research topics including:

- Defining and addressing emerging contaminants;
- Public perceptions of the benefits and risks of water reuse;
- Management practices related to indirect potable reuse;
- Groundwater recharge and aquifer storage and recovery;
- Evaluation and methods for managing salinity and desalination; and
- Economics and marketing of water reuse.

The Operating Plan outlines the role of the Foundation's Research Advisory Committee (RAC), Project Advisory Committees (PACs), and Foundation staff. The RAC sets priorities, recommends projects for funding, and provides advice and recommendations on the Foundation's research agenda and other related efforts. PACs are convened for each project and provide technical review and oversight. The Foundation's RAC and PACs consist of experts in their fields and provide the Foundation with an independent review, which ensures the credibility of the Foundation's research results. The Foundation's Project Managers facilitate the efforts of the RAC and PACs and provide overall management of projects.

The Foundation's primary funding partners include the Bureau of Reclamation, California State Water Resources Control Board, the California Energy Commission, Foundation Subscribers, water and wastewater agencies, and other interested organizations. The Foundation leverages its financial and intellectual capital through these partnerships and funding relationships.

The overall goal of this study was to review methodologies for developing screening level human health risk-based criteria for emerging contaminants potentially present in water intended for indirect potable reuse and develop decision criteria. This approach will help in the selection of an appropriate screening methodology to rapidly develop a screening level if a "new" chemical is detected in water.

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ACKNOWLEDGMENTS

This project was funded by the WateReuse Research Foundation in cooperation with the Bureau of Reclamation, California State Water Resources Control Board, Nevada Department of Environmental Protection, and Clark County Water Reclamation District. The project team is grateful for the support of the individuals and organizations that contributed to this project. In addition to the names listed below, the authors wish to acknowledge the following individuals from the Southern Nevada Water Authority's Applied R&D Center: David Rexing, Linda Parker, Brett Vanderford, Dan Gerrity, and Mark Benotti; and Ammon Gilbert from Intertox, Inc., for their assistance and guidance on this project. The team also expresses our sincere appreciations to Frankie Lewis from Southern Nevada Water Authority who provided technical review, proofreading, and formatting for this report. The project team also wishes to thank the experts who were willing to participate in the workshop held in November 2008 in Las Vegas, NV. Their input and suggestions greatly strengthened this report.

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EXECUTIVE SUMMARY

Over the past decade, a diversity of emerging contaminants has been identified in waters around the globe. Of particular interest are pharmaceuticals and personal care products (PPCPs) and potential endocrine disrupting compounds (EDCs), both of which are generally detected in extremely low (sub-µg/L) concentrations in water. Despite these low levels, public, scientific, and regulatory communities have shown increasing interest and concern about the potential occurrence of these compounds in drinking water and their potential health effects. The vast majority of these compounds are not regulated, and developing toxicity criteria can be time consuming and resource intensive. For example, regulatory determinations often require rigorous review of available pharmacokinetic and toxicity data and the elicitation of additional toxicity studies. As a result, it can be years before toxicity estimates are available. As critical water reuse projects continue to develop, the lack of drinking water guidelines for emerging contaminants can lead to public and political rejection of otherwise sustainable reuse projects. The use of advanced water treatment processes could reduce the concentrations of emerging contaminants, but they require increased energy use and still cannot remove all contaminants below the limits of sensitive analytical methods.

The overall goal of WRF-05-005, *Identifying Hormonally Active Compounds, Pharmaceuticals, and Personal Care Product Ingredients of Health Concern from Potential Presence in Water Intended for Indirect Potable Reuse*, was to review methodologies for developing screening level human health risk-based criteria for PPCPs and EDCs potentially present in water intended for indirect potable reuse and develop decision criteria. This approach will help in the selection of an appropriate screening methodology to rapidly develop a screening level if a "new" chemical is detected in water. If the concentration of the contaminant is at or above this screening level, then more detailed evaluation of the toxicity and occurrence of the compound is recommended; if the concentration is below the screening level, then the risk to public health is predicted to be well below levels of concern and the presence of the compound does not alone warrant further toxicological studies. Screening values could also be used to develop method reporting limits based on human health endpoints.

To support these goals, several methodologies and their information requirements were characterized and applied to representative "case study" chemicals. These case studies were presented at an expert panel workshop held on November 5 and 6, 2008, in Las Vegas, Nevada, comprised of regulators, scientists, and other interested parties to evaluate and optimally reach consensus on the best approaches to efficiently develop screening level health risk-based values for compounds of this type. The panel emphasized that application of the decision tree in the development of screening values should be performed in consultation with appropriate experts in toxicology and risk assessment.

This report shows that several methodologies can be applied to develop screening level guidance for protection of public health. Each of the screening methodologies has advantages and disadvantages, which are discussed in detail in this report. Ultimately, the team, in conjunction with the expert panel, devised a simple, conservative approach for the development of health risk-based guidelines for emerging contaminants that selects the lowest calculated level (i.e., most protective of human health) from several possible risk assessment schemas.

The overall suggested approach is summarized as follows:

1. If the chemical is a pharmaceutical, select the lowest value from among comparison values derived using the following processes:

    a. Divide the therapeutic dose (on a milligram per kilogram body weight basis, based on the range of doses and age groups for which the pharmaceutical is prescribed) by a default uncertainty factor (UF) of 3000; divide by an additional UF of 10 if the compound is either a non-genotoxic carcinogen or an EDC.

    b. Divide the literature-based no observed adverse effect level (NOAEL) by a default UF of 1000 or the lowest observed adverse effect level (LOAEL) by a default UF of 3000; divide by an additional UF of 10 if the compound is either a non-genotoxic carcinogen or an EDC.

    c. If the compound is a genotoxic carcinogen and tumor incidence data are available, develop a cancer slope factor and establish a comparison value assuming a *de minimis* cancer risk of 1 in 1,000,000.

    d. If the compound is a genotoxic carcinogen and no tumor incidence data are available, use the lower of the virtually safe dose (VSD) derived using the method of Gaylor and Gold (1998) or the threshold of toxicologic concern (TTC).

2. If the chemical is not a pharmaceutical and either a literature-based NOAEL or LOAEL can be identified or the chemical is a genotoxic carcinogen, set guidelines based on toxicological data following (b), (c), and (d) from No. 1 above.

3. If the chemical is not a pharmaceutical but does not have either a literature-based NOAEL or LOAEL or there is no evidence it is a genotoxic carcinogen, derive a screening level based on the TTC.

The panel also recommended that if the risk assessor/ toxicologist notes potential for unique toxicity (e.g., evidence from toxicity studies suggests the compound is a frank teratogen at the lowest dose or the compound is a chemotherapeutic), then the compound should be subject to a compound-specific risk analysis rather than using the screening approach presented here.

Using the approach suggested in this report, it is possible to rapidly establish conservative health risk-based screening level values. However, it is critical to note that the screening level values are not the same as regulatory standards, nor should they be interpreted as levels above which adverse human health effects are likely. In order to develop a regulatory value, significantly more information will be required, including more detailed evaluation of the toxicological database and possibly additional toxicological studies, collection of additional occurrence data, and cost–benefit analysis. One beneficial use for screening values is the establishment of sound analytical method reporting limits (MRLs). Currently, most analytical approaches for emerging contaminants are based on maximum method sensitivity without consideration of toxicological relevance. With such a screening protocol in place, it may be appropriate to set MRLs at 1/10 to 1/100 of the screening value. However, this is not to state that low detection limits are not without their place: an appropriate application of extremely low detection limits, for example, could be in specialized studies tracking the changes in PPCPs and EDCs over time. This report describes the methodologies evaluated, summarizes data gathered for the case study chemicals, and presents the conclusions of the workshop.

CHAPTER 1

INTRODUCTION

1.1 PROJECT OBJECTIVES

Increasing numbers of "emerging" unregulated chemical compounds, including pharmaceutical and personal care product (PPCP) ingredients and endocrine disrupting compounds (EDCs), are being detected in surface, drinking, and reuse water. In general, health criteria for long-term low-level environmental exposure to the general population do not exist for these classes of compounds. In our initial research (AwwaRF #3085/WRF-04-003: "Toxicological Relevance of Endocrine Disruptors and Pharmaceuticals in Drinking Water," Snyder et al., 2008), we developed acceptable daily intakes (ADIs) for 16 pharmaceuticals and 13 potential EDCs according to traditional methods prescribed by regulatory agencies for developing toxicity criteria for low-level, chronic exposures (e.g., the U.S. Environmental Protection Agency (U.S. EPA) reference dose method, which relies on a thorough review of the toxicological database to identify the lowest levels at which adverse effects occur in animals or humans). Because the list of compounds potentially present in surface, drinking, and reuse water is extensive, the list of compounds for which ADIs are desired is very large and growing. Until the potential health risks associated with these compounds are understood, regulators, utility managers, and the public will continue to question whether the presence of these chemicals presents a risk to human health.

The Scope of Work (SOW) for WRF-05-005 addressed four fundamental goals:

- Develop scientifically based decision criteria to support selection of an appropriate methodology for identifying human health risk-based screening levels for emerging compounds (specifically, PPCPs and EDCs), if a "new" chemical (i.e., one without an existing human health risk-based toxicity criterion) is found in source or drinking water.
- Review and establish the advantages/disadvantages and resource requirements of several possible methods for rapidly developing health risk-based screening levels relative to accepted methodologies (e.g., the U.S. EPA "reference dose" approach), for a representative set of case study compounds.
- Present the case studies and findings at a meeting of experts, regulators, and stakeholders to support discussion and derive consensus on a recommended approach.
- Develop a report summarizing the evaluations and workshop conclusions.

It is expected that the results presented in this report will be of interest to water industry professionals, regulators, toxicologists, risk assessors, and other professionals involved in assessing the safety of chemicals found in water intended for human consumption or use. However, it is important to emphasize that this report represents a demonstration of a suggested approach for efficiently developing screening levels for newly detected compounds without existing criteria, not a recommendation for maximum contaminant levels (MCLs) or other criteria. These screening levels are intended to be interpreted as conservative "first cut" estimates of daily exposure levels below which adverse health effects are not expected; they are not considered thresholds for adverse health effects. Because of the multiple levels of

conservatism incorporated into these values, the true threshold for adverse health effects is expected to be much higher. If an identified chemical is present at a concentration that would yield a daily dose that exceeds screening levels developed using methods proposed here, it does not mean that adverse health effects are expected or likely, but that further evaluation of the potential for adverse health effects is recommended. Further, because of the technical nature of the required data analysis, workshop participants emphasized that the methods for developing screening levels proposed here are intended for use only by trained toxicologists or risk assessors.

1.2 BACKGROUND

Specific regulatory guidance has not been established prescribing how to assess human health risks associated with exposure to PPCPs or EDCs in drinking water. U.S. EPA and other agencies have identified standard methodologies for determining exposure levels to environmental contaminants that are not likely to be associated with adverse health effects, including noncarcinogenic and carcinogenic effects, assuming daily exposure over an extended period of time (WHO, 1994; U.S. EPA, 2002a; ATSDR, 2007). However, derivation of regulatory criteria can be time and resource intensive, and often years can pass between initiation of efforts and publication of a final value by a regulatory agency.

In light of the many thousands of chemicals potentially present in the environment to which people can be exposed, and the need to establish "acceptable" levels of exposure and support selection of treatment or remediation goals, various entities have proposed methods to more quickly develop screening level concentrations. The utility of these methods varies depending upon the chemical type. For example, thresholds of toxicologic concern (TTCs) have been proposed for a range of chemical classes and exposure media below which exposures are assumed to not pose a concern (e.g., FDA 1995; Cheeseman et al., 1999; Kroes et al., 2004). For pharmaceuticals, in light of the extensive database of toxicological and pharmacological data that exists for these compounds, others have proposed basing target levels on the lowest therapeutic dose (Schwab et al., 2005).

To evaluate the utility of different methods for efficiently developing human health risk-based screening levels for emerging compounds in water, focusing on PPCPs and EDCs, the project team used several methods to derive screening levels for a subset of case study compounds. Case study compounds represented a range of structures, mechanisms of action, toxicity potential, and information availability.

The methods considered include:

- The traditional U.S. EPA reference dose (RfD) and cancer slope factor (SF) approaches.
- Use of a TTC, which assumes that any intake below a published and documented toxicological threshold does not pose a health concern.
- Use of the virtually safe dose approach proposed by Gaylor and Gold (1998) for compounds with evidence of carcinogenicity in animals, to derive screening values based on evidence of cancer.
- Application of the lowest therapeutic dose for pharmaceuticals as a surrogate lowest observed adverse effect level (LOAEL).

Information on the methodologies and case study compounds were compiled by the project team into an interim report and provided to expert panelists prior to the expert panel

workshop, held on November 5 and 6, 2008, in Las Vegas, Nevada. The expert panel was comprised of water industry and risk assessment experts, as well as stakeholders and regulatory agency representatives involved in the task of addressing risks of emerging compounds in surface and reuse waters. The project team then presented the case studies in detail at the workshop and facilitated discussion among the panelists, who were charged with discussing and reaching a consensus on the most appropriate methods for efficiently developing screening level values for PPCPs and EDCs found in various water sources. Specifically, a "road-map" approach was developed which used a decision tree to suggest specific approaches based on compound classification and information availability. At the completion of the workshop, the project team edited the report to reflect the workshop discussions and conclusions.

The workshop participants and expert panelists included:

Workshop Participant	Agency/Role
Katharine Cupps	WA Dept of Ecology
David Cunliffe	Department of Health, South Australia
Joyce Donohue	Environmental Protection Agency (U.S. EPA)
Andrew Humpage	Australian Water Quality Centre
Roger Meyerhoff	Lilly Research Labs
Michael Narotsky	Environmental Protection Agency (U.S. EPA)
Tony Priestly	Australian Water Quality Centre
Craig Riley	WA Dept of Health
Richard Sakaji	East Bay MUD
James Stevens	Wake Forest University
Joe Cotruvo	Cotruvo & Associates/Technical Advisor
James Crook	Consulting Engineer/Technical Advisor
Brian Bernados	California Dept. of Health Services/PAC
Richard Bull	MoBull Consulting/PAC
Gary Ginsberg	Connecticut Dept. of Public Health/PAC
Djanette Khiari	Water Research Foundation/PAC
Dan Gerrity	Southern Nevada Water Authority (SNWA)
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Gretchen Bruce	Intertox
Rick Pleus	Intertox/Co-PI
Jorg Drewes	Colorado School of Mines/Co-PI
Anna Durden	WRF/Project Manager

The remainder of this report is organized as follows:

- *Chapter 2: Selection of Case Study Compounds*. This section describes the considerations taken in selecting case study compounds and lists the selected compounds.
- *Chapter 3: Methodologies for Developing Human Health Risk-Based Screening Values*. This section describes the methods for developing screening values that were evaluated in this investigation.
- *Chapter 4: Presentation of Case Studies and Summary of Expert Panel Discussion*. This section summarizes and compares "comparison values" using each of the applicable methods for the case study compounds, and discusses issues in the application of these methods.
- *Chapter 5: Expert Panel Discussion and Final Recommendations*. This section discusses the consensus from the workshop and presents the decision tree.

CHAPTER 2

SELECTION OF CASE STUDY COMPOUNDS

2.1 INTRODUCTION

Thousands of PPCPs are marketed in the United States today, and several hundred chemicals have been identified as potential endocrine disruptors. To compare different methods for developing screening values, the project team identified a small subset of all possible PPCPs and EDCs that could be found in water intended for indirect potable reuse to be evaluated as case study compounds.

Currently, the FDA has approved more than 3,000 drugs for prescription in the United States, and several thousand more are sold for over-the-counter (OTC) or veterinary use. Thousands more personal care products (PCPs) are sold for use as cosmetics, fragrances, skin care products, and other uses. With regard to potential EDCs, the Institute for Environmental Health (IEH, 2005) compiled and summarized various reports and listings produced by national or international governments and non-governmental organizations as well as supplementary data taken from original studies or review articles to produce a consolidated listing of 966 chemicals or elements that have been suggested in the published literature to be potential endocrine disrupters. Tens of thousands of other chemicals used in commerce have not been screened for endocrine disrupting potential. In the following, the criteria used to select compounds for evaluation as case studies in this project, to represent a range of mechanisms of action, toxicity potential, information availability, and so forth, are described.

2.2 COMPOUND SELECTION CRITERIA

The following criteria were considered in selecting representative PPCPs and EDCs to serve as case studies:

- *Mechanism of action*. Compounds were selected with a range of mechanisms of action, including compounds that act on different biological receptors (e.g., selective serotonin reuptake inhibitors, beta-blockers), compounds with mechanisms of action that could present a direct threat to the fetus (e.g., statins), cytotoxic compounds (e.g., chemotherapy agents), psychoactive compounds (e.g., anti-psychotic agents, anti-depressants, anxiety agents), compounds that contribute to pathogen resistance (e.g., antibiotics), and endocrine-active compounds.

  For EDCs, we considered compounds for which there is relatively stronger evidence of potential for in vivo human health effects mediated through the endocrine system and that, specifically, are known to act through the estrogenic/antiestrogenic, androgenic/antiandrogenic, or neuroendocrine modes of action, or that have the potential to interfere with the function of the thyroid. Numerous definitions of EDCs have been proposed; these were summarized in the AwwaRF/WRF 3085/04-003 report, “Toxicological Relevance of Endocrine Disruptors and Pharmaceuticals in Drinking Water” (Snyder et al., 2008). Consistent with that report, for the purposes of the current study, EDCs were defined as chemicals that have produced an adverse effect mediated through the endocrine system in at least one in vivo test system using a laboratory animal serving as a surrogate for humans (e.g., rats, mice, guinea pigs,

rabbits, nonhuman primates) or that have been reported to produce an endocrine effect in humans, regardless whether the effect is considered negative or therapeutic (e.g., ethynylestradiol, diethylstilbesterol, phytoestrogens).

- *Toxicity potential/effects on sensitive population groups.* Particular consideration was given to compounds that show some evidence of toxicity potential at lower doses, and the potential to cause effects on the fetus, children, or the elderly. Some pharmaceuticals have been shown to be carcinogenic in animal bioassays conducted as part of the drug development process. Thus, carcinogenicity could be a concern for these chemicals.
- *Exposure potential*. Exposure potential was assumed to be correlated with such factors as volume of use (e.g., number of prescriptions per year), environmental persistence, and resistance to water treatment. However, lack of detection in water systems did not exclude a chemical from consideration.
- *Availability of data*. For some drugs, data on toxicity and mechanism of action may not be easily available (e.g., proprietary or grandfathered drugs). For example, minimal toxicity data were located for Meprobamate, an anti-anxiety drug introduced in 1955. For compounds such as this, evaluation of other types of data may be appropriate (e.g., data are available for carisoprodol, a muscle relaxant that is metabolized to meprobamate and has undergone toxicity testing).

The project team considered the PPCPs and EDCs evaluated in AwwaRF/WRF 3085/04-003 because they represent a range of compound types and because of the team's familiarity with these compounds and their toxicological databases. Table A-1 (Appendix A) lists the PPCPs evaluated in AwwaRF/WRF 3085/04-003. Table A-2 lists the EDCs evaluated in AwwaRF/WRF 3085/04-003.

Numerous other compounds were also considered as potential candidates for case studies; these are listed in Tables A-3, A-4, and A-5. Table A-3 lists top-selling pharmaceuticals that were not evaluated in AwwaRF/WRF 3085/04-003 but were identified in that study as having possible toxicologic interest. Table A-4 lists other types of compounds (veterinary drugs, cancer agents, personal care products, and X-ray contrast agents) that have been detected in water samples in the United States. Table A-5 lists the top 300 most prescribed pharmaceuticals in 2005, by drug group. Additional compounds were selected from these compounds to represent the following compound groups:

- Antacid/ proton pump inhibitor. These show some evidence of carcinogenicity and developmental toxicity and are frequently prescribed. Lansoprazole (Prevacid) was selected.
- Antifungal. Representative compounds show some evidence of carcinogenicity and developmental toxicity and are frequently prescribed. Fluconazole (Diflucan) was selected.
- Antihistamine. Representative compounds show some evidence of carcinogenicity and developmental toxicity and are frequently prescribed. Desloratadine (Clarinex) was selected.
- Bisphonate inhibitor of bone resorption. Representative compounds show some evidence of carcinogenicity and developmental toxicity and are frequently prescribed. Alendronate (Fosamax) was selected.
- Chemotherapy agent. Representative compounds show evidence of carcinogenicity and developmental toxicity and some have been detected in water supplies and/or are

frequently prescribed. Ifosfamide, Tamoxifen, and Methotrexate were selected.

- Loop diuretic. Representative compounds show some evidence of carcinogenicity and developmental toxicity and are frequently prescribed. Furosemide (Lasix) was selected.
- Tetracyclic antidepressant. Representative compounds show some evidence of carcinogenicity and developmental toxicity. Mirtazapine (Remeron) was selected.
- Tetracycline antibiotic. Representative compounds show some evidence of developmental toxicity and are frequently prescribed. Doxycycline was selected.
- Musk. These have been detected in wastewater and surface water in Europe and the United States. Galaxolide was selected.
- X-ray contrast media. These have been detected in wastewater and surface water in Europe and the United States. Iopamidol/iopromide (Isovue) was selected.

Table 2.1 lists the compounds evaluated in the case studies used for this project. Table A-6 shows the chemical structure of these compounds.

Table 2.1. Compounds Evaluated as Case Studies

Compound	Category	Primary Pharmacological or Endocrine Mode of Action
PPCPs		
Alendronate (Fosamex®)	Bisphonate inhibitor of bone resorption	Reduces elevated rate of bone turnover
Atenolol (Tenormin®)	Beta-blocker	Competes with sympathomimetic neurotransmitters for binding at beta(1)-adrenergic receptors in the heart and vascular smooth muscle
Atorvastatin (Lipitor®)	Antilipidemic	Inhibits HMG-CoA reductase, reducing conversion of HMG-CoA to mevalonate, a precursor of cholesterol
Carbamazepine (Tegretol®)	Anticonvulsant and mood stabilizer	Inhibits sustained repetitive firing by blocking use-dependent sodium channels
Desloratadine (Clarinex®)	Antihistamine	Competes with free histamine for binding at H1-receptors, blocking the action of endogenous histamine
Diazepam (Valium®)	Benzodiazapine antianxiety	Binds to benzodiazepine receptors that mediate sleep, affect muscle relaxation, anticonvulsant activity, motor coordination, and memory
Diclofenac (Cataflam®, Voltaren®)	NSAID	Inhibits leukocyte migration and COX-1 and COX-2, leading to the peripheral inhibition of prostaglandin synthesis
Doxycycline (generics)	Tetracycline antibiotic	Reversibly binds to ribosomal subunits, blocking the binding of aminoacyl tRNA to mRNA and inhibiting bacterial protein synthesis
Enalapril (Enalaprit®)	ACE inhibitor	Competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II, leading to decreases in blood pressure and stimulation of baroreceptor reflex mechanisms
Fluconazole (Diflucan®)	Antifungal	Interacts with 14-α demethylase, an enzyme necessary to convert lanosterol to ergosterol, an essential component of the fungal cell membrane
Fluoxetine (Prozac®)	SSRI anti-depressant	Blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT1A autoreceptors
Furosemide (Lasix®)	Loop diuretic	Inhibits the reabsorption of sodium and chloride in the ascending limb of the loop of Henle
Gemfibrozil (Lopid®)	Antilipidemic	Increases the activity of extrahepatic lipoprotein lipase, increasing lipoprotein triglyceride lipolysis
HHCB (Galaxolide®)	Musk	NA
Ifosfamide (NA)	Chemotherapy agent	Metabolites alkylate or bind with intracellular molecular structures, including nucleic acids
Iopamidol/ iopromide (Isovue®)	X-ray contrast media	Blocks x-rays as they pass through the body, allowing body structures containing iodine to be delineated
Lansoprazole (Prevacid®)	Antacid/ proton pump inhibitor	Suppresses gastric acid secretion by specific inhibition of the (H+,K+)-ATPase enzyme system

Compound	Category	Primary Pharmacological or Endocrine Mode of Action
Meprobamate (Equanil®, Miltown®)	Antianxiety agent	Mechanism of action not known; affects multiple sites in the central nervous system, including the thalamus and limbic system; binds to $GABA_A$ receptors which interrupt neuronal communication in the reticular formation and spinal cord
Methotrexate (NA)	Chemotherapy agent	Inhibits folic acid reductase, leading to inhibition of DNA synthesis and inhibition of cellular replication
Mirtazapine (Remeron®)	Tetracyclic antidepressant	Antagonist at central pre-synaptic alpha(2)-receptors, inhibiting negative feedback to the presynaptic nerve
Naproxen (Aleve®)	NSAID	Inhibits cyclooxygenase activity; inhibition of COX-2 provides anti-inflammatory activity
Phenytoin (Dilantin®)	Anticonvulsant	Acts on sodium channels on the neuronal cell membrane, limiting seizure activity and reducing seizure propagation
Risperidone (Risperidal®)	Antipsychotic	Blocks dopaminergic D2 receptors in the limbic system and serotonergic 5-HT2 receptors in the mesocortical tract, causing an increase in dopamine transmission
Simvastatin (Zocor®)	Antilipidemic	Inhibits the hepatic enzyme HMG-CoA reductase, reducing conversion of HMG-CoA to a precursor of cholesterol
Sulfamethoxazole (Cotrim®)	Antibacterial	Inhibits bacterial dihydrofolate synthetase, causing interference in the conversion of p-aminobenzoic acid into folic acid, an essential component of bacterial development
Tamoxifen (NA)	Chemotherapy agent	Binds to estrogen receptors, inducing a conformational change in the receptor
Triclosan	Antibacterial	Antibacterial
Trimethoprim (Cotrim®)	Antiinfective	Binds to bacterial dihydrofolate reductase, subsequently interfering with the uptake of p-aminobenzoic acid into folic acid
EDCs		
Atrazine	Herbicide	Neuroendocrine
Bisphenol A	Industrial chemical	Estrogenic / Anti-estrogenic
Butylbenzyl phthalate	Industrial chemical; PPCP ingredient	Estrogenic / Anti-estrogenic
DEHP	Industrial chemical; ; PPCP ingredient	Estrogenic / Anti-estrogenic, Androgenic / Anti-androgenic
Dibutyl phthalate	Industrial chemical; PPCP ingredient	Estrogenic / Anti-estrogenic, Androgenic / Anti-androgenic
17ß-Estradiol	Endogenous hormone	Estrogenic / Anti-estrogenic
Estrone	Endogenous hormone	Estrogenic / Anti-estrogenic
Ethynylestradiol	Pharmaceutical	Estrogenic / Anti-estrogenic
Lindane (BHC-gamma)	Pesticide	Estrogenic / Anti-estrogenic, Androgenic / Anti-androgenic

Compound	Category	Primary Pharmacological or Endocrine Mode of Action
Linuron	Herbicide	Androgenic / Anti-androgenic
Methoxychlor	Pesticide	Estrogenic / Anti-estrogenic, Androgenic / Anti-androgenic
4-Nonylphenol	Industrial chemical; PPCP ingredient	Estrogenic / Anti-estrogenic
4-tert-Octylphenol	Industrial chemical; PPCP ingredient	Estrogenic / Anti-estrogenic
Vinclozolin	Fungicide	Androgenic / Anti-androgenic

CHAPTER 3

METHODOLOGIES FOR DEVELOPING HUMAN HEALTH RISK-BASED COMPARISON SCREENING VALUES

3.1 INTRODUCTION

The goal of this project was to review methodologies for developing human health risk-based screening values for PPCPs and EDCs potentially present in water intended for indirect potable reuse, and to recommend approaches that can be applied relatively quickly and efficiently for deriving health protective values in the event that new compounds are detected in a particular water supply. The derived values are meant to be "screening level" in that if the concentration of a new or emerging contaminant found in water is at or above the screening value, then more detailed evaluation of the toxicity and occurrence of the compound is recommended. Exceedence of a screening value does not mean that adverse health effects are likely or expected, but rather, comparison to screening values provides a "first cut" to identify those compounds more likely to be of health concern and therefore to warrant further study. Several methodologies for developing screening values are available and were considered. Upon evaluation of these methodologies, it became evident that not all are equally appropriate for developing human health risk-based screening values for PPCPs and EDCs that may be present in water. In this evaluation, the selected methodologies were applied to each of the case study compounds—the values derived using these approaches were called "comparison values." In Chapter 4, the comparison values developed for each compound are summarized. In Chapter 5, the expert panel's recommendations are presented.

The following methodologies were considered for developing comparison values for the case study compounds:

- Use of a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) from animal studies or studies in humans (e.g., clinical trials) divided by uncertainty factors applied to derive comparison values based on noncancer endpoints.
- Use of tumor incidence data from animal studies and linear extrapolation models to derive cancer SFs and comparison values based on evidence of cancer.
- Use of a lowest therapeutic dose in humans as an assumed minimally toxic dose, with uncertainty factors applied to extrapolate to sensitive population groups, to derive comparison values based on therapeutic endpoints.
- Use of the TTC approach to assign comparison values for noncancer and cancer endpoints based on assumptions about the relationships between chemical structure, genotoxicity, general toxicity, and carcinogenicity.
- Use of the virtually safe dose approach proposed by Gaylor and Gold (1998) for compounds with evidence of carcinogenicity in animals, to derive comparison values based on evidence of cancer.

Each of these methods is described in the following.

3.2 DERIVATION OF COMPARISON VALUES USING NOAELS OR LOAELS FROM TOXICITY STUDIES

Comparison values for noncancer endpoints were derived using data on NOAELs or LOAELs for noncancer effects from animal toxicity studies or studies in humans (e.g., clinical trials).

When establishing guidelines or standards for noncarcinogenic effects, including RfDs (U.S. EPA, 2002a), minimal risk levels (ATSDR, 2007), and tolerable daily intakes (TDIs) (WHO, 1994), agencies charged with developing guidance values typically assume that there is some threshold level of exposure below which adverse health effects do not occur and, based on review of toxicity data, identify a point of departure on which to base the guidance level. This is typically the highest dose at which an effect is not seen (the NOAEL) or the lowest dose at which an effect is seen (the LOAEL). Below this dose, there is no evidence in animals or humans of a statistically or biologically significant increase in adverse effects, although some changes may occur that are not considered adverse (e.g., changes in certain enzyme levels). The point of departure is then divided by uncertainty factors (UFs) to derive a screening value considered protective to broader population groups, including sensitive populations, such as children or people with immune-compromised systems.

Generally, several multiplicative UFs are applied, individually ranging in value from 3 to 10 with each factor representing a specific area of uncertainty in the available data (e.g., intraspecies uncertainty/variability, interspecies uncertainty/variability, extrapolation from a LOAEL to a NOAEL, extrapolation from less-than-lifetime exposure to lifetime exposure, and database uncertainties). Table 3.1 shows the range of uncertainty factors recommended by U.S. EPA (2002a) based on the type and quality of data that are available. When high-quality toxicity data are available, combined UFs typically range from 30 to 1000. Per U.S. EPA risk assessment guidance (U.S. EPA, 2008a), a factor of 3 represents a "partial" uncertainty factor, equal to the half-log (square root) of 10 (i.e., $10^{1/2}$), usually rounded to 3 for use in risk assessment. As such, by convention, when two UFs with a value of 3 are multiplied together, the resulting combined UF is 10 (not $3 \times 3 = 9$).

For the purposes of this evaluation, published toxicity data were identified and reviewed for each of the case study chemicals, and comparison values were derived by dividing NOAELs or LOAELs by UFs:

$$\text{Comparison value}_{\text{Noncancer}}\ (\text{mg/kg-d}) = \frac{\text{NOAEL or LOAEL (mg/kg-d)}}{\text{UFs}}$$

Toxicity data were gathered from well-conducted studies in animals (preferably with multiple dose groups) or studies of humans (e.g., clinical trials for pharmaceutical compounds) that identify NOAELs and LOAELs for reproductive, developmental, systemic, and other toxicity endpoints. Sources of information included the National Library of Medicine (NLM) PubMed database of toxicological literature citations, as well as reports of toxicological investigations by the National Toxicology Program (NTP), information submitted to the U.S. Food and Drug Administration (FDA) as part of the drug approval process (e.g., Drugs@FDA), or drug labels or monographs (e.g., the *Physician's Desk Reference* [PDR]). For compounds that are not PPCPs, other sources of toxicity information were considered, including monographs prepared by the U.S. EPA, the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), and other agencies as appropriate.

In a manner analgous to U.S. EPA RfDs, screening levels derived using this approach are assumed to correspond to the amount of a chemical to which a person, including members of sensitive subpopulations, can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect (U.S. EPA, 1993). Study types of most relevance for evaluating long-term low level exposures to compounds in water are assumed to be subchronic, chronic, reproduction, and teratology studies with exposure primarily via the oral route. Short-term and acute studies are not recommended as they are less relevant to establishing chronic NOAELs. Animal species of interest primarily include mice and rats, but can also include rabbits, dogs, primates, and other animals.

In considering the NOAEL/LOAEL approach among other approaches for deriving guideline values for PPCPs and EDCs, the project team identified several advantages in its application:

- It has been recommended by the National Research Council since 1983 (the Red Book), and is the foundation of risk assessment for many federal and state agencies. Therefore, it is a generally well accepted and frequently used approach.
- It is based on toxicological information specific to the compounds of interest and, therefore, allows determination of sensitive target organs and subpopulations and increased confidence of the protectiveness of the derived screening value.
- For pharmaceuticals and many EDCs, data are relatively abundant and available because these compounds have undergone study for toxicity potential according to standardized testing protocols in order to gain FDA or U.S. EPA approval.
- It focuses on identifying thresholds for toxicologic effects, either the lowest dose at which an adverse effect has been observed or the highest dose at which there is no observation of an adverse effect and, therefore, provides a level of confidence about the relative safety of any screening levels that are based on these values.
- The computational methods are straightforward. In the future, if new scientific data become available, the information can be substituted rather easily into the calculations.

Disadvantages of the NOAEL/LOAEL approach include:

- Full toxicity study descriptions are often not available (e.g., for some pharmaceuticals, studies were conducted by pharmaceutical company laboratories, and the results are not published in the peer reviewed literature but are summarized in drug application documents that are not readily available to the general public).
- Establishing the relative quality of different studies and determining the relevance to humans can be difficult and requires specific expertise.

Table 3.1. Uncertainty Factors Recommended by U.S. EPA (2002a) for Derivation of Reference Doses (RfDs) From NOAELs or LOAELs

Category	Use	Value Applied
Interspecies differences	To extrapolate from an animal study to humans	1 or 10 (a factor of 10 is recommended if the critical study is in animals)
Intra-individual susceptibility	To account for variations in sensitivity among humans	1, 3, or 10* (if the critical study is based on a known sensitive population group, e.g., developmental data, a factor of 3 is recommended; otherwise, a factor of 10 is recommended)
LOAEL to NOAEL	To extrapolate from a LOAEL to a NOAEL	1 or 10 (a factor of 10 is recommended if the point of departure is a LOAEL)
Study duration	To extrapolate from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure)	1, 3, or 10 (a factor of 10 is recommended to extrapolate from a subchronic to chronic study, or 3 if the critical study is a reproductive/ developmental study, and fetus/children is the most sensitive population group)
Database	To account for limitations in the available quantity or quality of data	1, 3, 10 (a factor of 3 is recommended if either a prenatal study or a 2-generation reproduction study is missing from the database, or 10 if both are missing)

*The Food Quality Protection Act (FQPA) requires the EPA to apply an additional safety factor of 10 during its risk assessment of pesticides to account for the potential for pre- and postnatal toxicity, as well as for the completeness of the toxicology and exposure database, unless the Agency determines that another factor is adequately protective (U.S. EPA, 2002b).

3.3 DERIVATION OF COMPARISON VALUES FOR CARCINOGENICITY BASED ON TUMOR INCIDENCE DATA

Comparison values based on evidence of cancer were derived using data on tumor incidence from animal toxicity studies and a linear extrapolation model.

For chemicals that show positive evidence of carcinogenicity in high dose animal studies, linear extrapolation models can be used to predict the tumorigenic response at low doses—these types of models are recommended as a default for tumor sites where the mode of action is unknown—and assume a linear relationship between risk and dose at low doses (U.S. EPA, 2005). The slope of the risk/dose line, known as the slope factor (SF), is an upper-bound estimate of risk per increment of dose (e.g., per 1 mg/kg-day of exposure) that can be used to estimate risk probabilities for different exposure levels.

In this assessment, if sufficient data on tumor incidence per dose level were available for a given compound with evidence of carcinogenicity in animal bioassays, and data indicate that the compound is genotoxic and assumed to have a linear relationship between carcinogenicity and dose, a standard one-hit model was used to estimate a SF. For these compounds, U.S. EPA's Benchmark Dose Software v. 2.0 (BMDS 2.0; U.S. EPA, 2008c) was used to model the data in the observed range and estimate a benchmark dose level (BMDL) corresponding to a benchmark response of 10% extra risk, which is generally at the low end of the observable range for standard cancer bioassay data. This BMDL serves as the "point of departure" for linear extrapolation or a nonlinear quantitative approach, depending on the mode of action of the carcinogen (U.S. EPA, 2000a).

Comparison values were calculated assuming an acceptable lifetime excess cancer risk of 1 in 1 million and that a person is exposed to the chemical at this dose daily over a lifetime (U.S. EPA, 2005):

$$\text{Comparison value}_{CSF}\ (\text{mg/kg-d}) = \frac{10^{-6}}{\text{SF}\ (\text{mg/kg-d})^{-1}}$$

In considering the cancer slope factor approach among other approaches for deriving screening values for PPCPs and EDCs, the project team identified several advantages in its application:

- It extrapolates directly from available tumor incidence data.
- It uses accepted methodologies (U.S. EPA, 2000a; U.S. EPA, 2000c).
- If high quality tumor data are available, a high level of precision in carcinogenic potency estimates can be expected.

Disadvantages include:

- The linear extrapolation method requires the use of a program to fit the tumor data (U.S. EPA, 2000a); although the U.S. EPA provides this program free of charge, it requires familiarity with low dose extrapolation techniques that are utilized in human health risk assessment to determine which models are most appropriate, as well as the ability to make some judgment about the carcinogenic mode of action.

- Tumor incidence data (i.e., data on the number of tumors seen per known number of animals, for specific dose groups) are not readily available for many compounds, even when drug or other chemical monographs report that the compound has tested positive for carcinogenicity in animal studies.
- SFs should be developed from high quality cancer bioassays; however, assessing the quality of some cancer studies can be difficult because of limitations in the descriptions of published studies, particularly older studies conducted by independent laboratories (e.g., not conducted by the National Institutes of Health's [NIH] Toxicology Program or a similar program).

3.4 DERIVATION OF COMPARISON VALUES BASED ON THE LOWEST THERAPEUTIC DOSE OF PHARMACEUTICALS

The lower end of a drug's therapeutic range can be considered an estimate of the threshold for appreciable biological activity in target populations and, therefore, may be considered a threshold for potential adverse effects. Following an approach analgous to the NOAEL/ LOAEL approach (Section 3.1), comparison values for pharmaeceuticals were also derived by dividing the lowest therapeutic dose by UFs to account for extrapolation from the LOAEL (i.e., the thereapeutic dose) to a NOAEL, variations in susceptibility between different members of the population, or gaps in the dataset:

$$\text{Comparison value}_{\text{LTD}}\ (\text{mg/kg-d}) = \frac{\text{Lowest Therapeutic Dose}\ \ (\text{mg/kg-d})}{\text{UFs}}$$

Other authors have used the lowest therapeutic dose as a starting point to characterize acceptable levels of pharmaceuticals in drinking water. Webb (2001) identified lowest therapeutic doses for 67 pharmaceuticals and compared assumed lifetime consumption rates (assuming consumption of 2 L water/day) to predicted environmental concentrations (PECs) in surface water in the European Union; PECs were estimated based on usage rates. Webb et al. (2003) and Schwab et al. (2005) also used therapeutic doses to develop screening levels for pharmaceuticals assuming exposure to them in drinking water (Appendix B). Webb et al. (2003) developed a screening level for a single compound, clenbuterol, by applying an uncertainty factor of 10, for interindividual differences, to the therapeutic dose. Schwab et al. (2005) developed screening levels for 16 compounds by dividing the lowest therapeutic dose by uncertainty factors ranging from 10.2 to 150. Schwab et al. (2005) also developed screening levels for six antibiotic compounds based on the minimum inhibitory concentration against human intestinal flora following European Medicines Agency (EMEA) methodology. For two compounds, Schwab et al. (2005) developed a screening level based on its no observed effect level (NOEL), not its no observed adverse effect level, from animal studies, divided by an uncertainty factor of 100.

In developing screening levels from therapeutic doses, Schwab et al. (2005) assumed that pharmacological effects are undesirable in the general population and that the therapeutic effect usually occurs at a dose considerably below those expected to result in toxicity. The authors then applied uncertainty factors to reduce the point of departure dose to one for which a reasonable certainty of no adverse effect was assumed; combined uncertainty factors ranged from 9 to 150 based on five general categories of uncertainty (Appendix B).

The assumption that the therapeutic effect usually occurs at a dose considerably below doses expected to result in toxicity requires additional consideration. Many drugs are recognized to pose significant toxicological risks to some segments of the population at the therapeutic dose. For example, drugs in FDA Pregnancy Categories D and X may pose significant risks to the fetus and are not recommended for use during pregnancy; many (e.g., atenolol, carbamazepine, enalapril) have been associated with congenital effects in either case reports or more definitive epidemiological studies. Other drugs are intended for use in life-threatening illnesses (e.g., chemotherapy drugs, heart medications) such that a certain amount of risk of other health effects is expected and accepted, and effects other than the "therapeutic effect" may routinely occur at the lowest therapeutic dose. Other drugs have not undergone clinical testing in children such that the lowest therapeutic dose can only be confidently applied to adults. Consequently, assuming categorically that a therapeutic dose is below a toxic effect level is erroneous. At a minimum, application of uncertainty factors to account for the toxicity that could occur at the therapeutic dose is warranted.

In considering use of the lowest therapeutic dose among other approaches for deriving screening levels for PPCPs and EDCs, the project team identified several advantages in its application:

- Therapeutic doses are readily available in drug monographs and various online sources (e.g., Drugs.com; RxList.com). Information that can be used to assign UFs are also generally available from these sources.
- The approach is easily understood and explained to the general population, because the public is familiar with therapeutic dosing.
- The calculation of screening levels is simple and transparent.

Disadvantages of the therapeutic dose approach include:

- The therapeutic dose is not a true threshold for adverse effects, and because different types of drugs produce different levels of adverse effects at therapeutic doses, it is difficult to determine what magnitude of UF is appropriate to extrapolate from a given therapeutic dose to a true NOAEL.
- Information on incidence and severity of adverse effects at the therapeutic dose may not be readily available, particularly for newer drugs.

3.5 DERIVATION OF COMPARISON VALUES BASED ON THRESHOLDS OF TOXICOLOGIC CONCERN

The TTC approach assigns an exposure level (or concentration) to a given compound that is thought very unlikely to produce an adverse effect from exposure, based on an assessment of toxicological data for structurally and chemically similar compounds. The concept was originally developed for food additives (Federal Register, 1995; Rulis, 1986; Rulis, 1989; Kroes et al, 2000, 2004; Munro, 1990; Munro et al., 1996; Munro et al., 1999; Cheeseman et al., 1999; Renwick, 2004; Renwick, 2005) and has been expanded to consider ingredients of pharmaceuticals (Dolan et al., 2005) and personal and household care products (Blackburn et al., 2005). In general, the stated goal of application of TTCs is to help focus research efforts on those chemicals likely to pose the greatest toxicologic risk. Kroes et al. (2000, p. 258), for example, stated,

> One does not have to argue that it is impossible to subject all the chemical substances to which humans are exposed to extensive toxicological testing. Furthermore, if sufficient facilities to perform such testing within a reasonable time were available, it still can be questioned whether testing of all these substances would be a rational and practical approach. Therefore, the establishment of a scientifically based generic threshold will be a useful tool to discern which substances of concern should be subjected to elaborate testing, when human intake is higher than the generic threshold.

In general, TTCs are best applied to compounds for which no or very limited toxicity data are available to conduct a traditional toxicity assessment (e.g., developing a screening level using compound-specific NOAELs and LOAELs; Kroes et al., 2004; Dolan et al., 2005; Australia EPHC, 2008). For example, Kroes et al. (2004, p.74-75), stated,

> Prior to application of the TTC approach, all available toxicity data on the compound should be collected and evaluated…The TTC approach should only be used in cases where the available chemical-specific data are inadequate for normal risk characterization….The TTC is not designed to replace conventional approaches to risk characterization for established and well-studied chemicals, such as food additives and pesticides. In addition, because of the nature of the databases used to derive the different TTC values, the approach would not normally be applied to…heavy metals…and compounds with extremely long half-lives that show very large species differences in bioaccumulation, such as TCDD and structural analogues; or proteins.

3.5.1 Summary of TTCs

The TTC approach has evolved over time. Several key publications are summarized in Table 3.2. These are described in the following.

3.5.1.1 U.S. FDA (Federal Register, 1995): TTC for untested compounds in food with no evidence of carcinogenicity in animals or humans or based on structural alerts (0.5 ppb)

The FDA (Federal Register, 1995; Rulis, 1986, 1989) proposed 0.5 ppb as a threshold of regulatory concern for untested compounds in food (which is assumed to correspond to a daily dose of 1.5 µg/person-day; FDA, 2002). This value was calculated based on a probabilistic distribution describing the range of cancer potencies for 477 carcinogenic compounds in the Gold et al. (2005, 2006) Carcinogenic Potency Database, and on assumptions about the level of dietary exposure that would correspond to an assumed acceptable lifetime excess cancer risk of 1 in 1 million for each compound. Per FDA (Federal Register, 1995), this threshold is intended to be applied to compounds that have not been shown to be carcinogens in humans or animals and for which there is no reason, based on the chemical structure of the substance, to suspect it is a carcinogen (FDA is prohibited by law [Section 409(c)(3)(A) of the Federal Food Drug and Cosmetic Act, i.e., the "Delaney Clause"] from regulating substances as food additives if they have been shown to be carcinogens by appropriate studies). Substances meeting the threshold of regulatory concern are granted an exemption by FDA from the food additive listing regulation. However, components of food-contact articles that enter the diet at concentrations greater than 0.5 ppb and that meet the food additive definition in the Federal Food Drug and Cosmetic Act must under an extensive safety review via the food additive petition process (Cheeseman et al., 1999). The 1.5 µg/day dose is equal to 0.021 µg/kg-day assuming exposure to a 70 kg adult.

3.5.1.2 Munro, I. C., R. A. Ford, E. Kennepohl, and J. G. Sprenger (1996). TTCs for chemicals in three structural classes with no presumption of genotoxic carcinogenicity (90 to 1800 µg/day)

Munro et al. (1996) expanded on the work conducted by FDA by compiling a reference database of NOELs for 613 organic compounds representing a range of industrial chemicals, pharmaceuticals, food substances, and environmental, agricultural, and consumer chemicals likely to be encountered in commerce. In this work, compounds were placed in three classes based on chemical structure as defined by Cramer et al. (1978; see Section 4.4.2), and NOELs were identified from studies of oral exposure, including subchronic, chronic, reproduction, and teratology studies. For each class, the fifth percentile NOEL was calculated; this represented a value that would provide 95% confidence that the NOEL of any other substance in the same structural class, but of unknown toxicity, would not have a NOEL less than that at the fifth percentile. A safety factor of 100 was then applied to calculate a TTC. Resulting TTCs for Cramer classes I, II, and III were 1800, 540, and 90 µg/day, respectively. The authors acknowledge that these thresholds are much higher than the FDA's 1.5 µg/day threshold, but indicate that these values apply to "chemically-defined substances for which there is no presumption of genotoxic carcinogenicity. Otherwise, the 1.5 µg/day threshold may be a more appropriate value" (Munro et al., 1996, p. 835).

3.5.1.3 Cheeseman, M .A., E. J. Machuga, and A. B. Bailey (1999). TTCs for food additives (0.5 to 15 ppb, equivalent to 1.5 to 45 µg/day)

Cheeseman et al. (1999) presented an approach for applying the principals of the FDA's 0.5 ppb threshold and raising the threshold to a range of 0.5 to 15 ppb (dietary concentration) to be applied to food additives depending on whether structural data (i.e., "structural alerts") or genotoxicity testing suggest the substance may be carcinogenic. Cheeseman et al. (1999) evaluated an expanded cohort of 709 carcinogens from the Carcinogenic Potency Database. They determined that carcinogens that test negative in the Ames assay are more than 8-fold less potent than carcinogens testing positive in the Ames assay, and that substances negative in the Ames assay with LD_{50}s greater than 1000 mg/kg are 15 to 30 times less potent than substances positive in the Ames assay. Based on this, they suggest the following TTCs:

- 0.5 ppb (1.5 µg/day) for compounds with positive genotoxicity test results but the genotoxicity results are judged "not biologically relevant" to the potency of these compounds (Cheeseman et al. were not specific as to the specific conditions that would lead to the conclusion that the genotoxicity results are not biologically relevant, but suggest no clear correlation between potency and positive Ames test results for heavy metals and alpha nitro-furyl compounds), or positive genotoxicity tests but no structural alerts suggesting the potential for greater carcinogenic potency (nitroso compounds; endocrine disruptors; strained heteronuclear rings; polycyclic amines including polycyclic aromatic amines, polyheterocyclic amines, biphenyl amines, aromatic acetamides and benzidines, and hydrazine/ triazene/ azide/ azo/ azoxy compounds)
- 5 ppb (15 µg/day) for compounds that test negative on the Ames test or have no structural alerts
- ~10-15 ppb (30-45 µg/day) for compounds that test negative on the Ames test or have no structural alerts and have a minimum LD_{50} (lethal dose to 50% of a test population) of 1,000 mg/kg or greater

Compounds with positive results on the Ames test or other tests of genotoxicity that are judged to be biologically relevant or that possess certain structural alerts (nitroso compounds, endocrine disruptors, strained heteronuclear rings, benzidine compounds, or hydrazine/ triazene/azide azo/azoxy compounds) were judged to require a compound-specific toxicological evaluation.

3.5.1.4 Kroes, R., C. Galli, I. Munro, B. Schilter, L. Tran, R. Walker, and G. Wurtzen (2000): TTC for trace chemicals in the diet (1.5 µg/ day)

Kroes et al. (2000, p. 260) evaluated toxicologic data for more than 600 compounds to "assess human exposure threshold values for the specific endpoints neurotoxicity and developmental neurotoxicity, immunotoxicity and developmental toxicity, and to examine these endpoints in order to determine whether changes in the different parameters of these specific systems would occur at particularly low levels of exposure, and what these levels would be." They proposed a TTC of 1.5 µg/person-day for trace chemicals in the diet based on toxicologic data for more than 600 compounds, concluding that this level poses "no appreciable risk" of carcinogenic (i.e., a 10^{-6} risk level) as well as developmental, endocrine, immunological, and neurotoxicity endpoints (Kroes et al., 2000, p. 280). The authors showed that cumulative distributions of NOAELs for developmental toxicity did not differ greatly from the cumulative distribution of NOAELs for chronic toxicity for the class III chemicals described by Munro et al. (1996), and the NOAELs for immunotoxicity did not differ from the NOAELs for other endpoints. In the case of neurotoxicants, the distribution was almost one order of magnitude lower than the distribution of NOAELs for chronic toxicity for class III compounds. The distribution of the NOAELs for class III chemicals differed considerably (about three orders of magnitude higher) from the distribution of 10^{-6} risk levels derived by linearized low-dose extrapolation for the carcinogens contained in the Gold et al. (2006) Carcinogenic Potency Database.

3.5.1.5 Kroes, R., A. G. Renwick, M. Cheeseman, J. Kleiner, I. Mangelsdorf, A. Piersma, B. Schilter, J. Schlatter, F. van Schothorst, J. G. Vos, and G. Würtzen, European Branch of the International Life Sciences Institute (2004): TTCs for trace chemicals in the diet (0.15 to 1800 µg/day)

Kroes et al. (2004; also discussed in Barlow [2005]) proposed a decision tree for selection of TTCs based on structure activity assumptions for trace chemicals in the diet. The approach is based on deliberations of the International Life Sciences Institute (ILSI) Europe Expert Group and a workshop held in March 2003, and expands on the work by Cheeseman et al. (1999). Kroes et al. (2004) evaluated the same 709 compounds considered by Cheeseman et al. (1999), plus additional compounds from the Gold et al. (2006) Carcinogenic Potency Database to give a total of 730 compounds. Kroes et al. (2004) identified structural alerts of most concern at low dietary concentrations based on those proposed by Ashby and Tennant (1991) and Cheeseman et al. (1999) with some refinements. Kroes et al. (2004) then computed how many compounds in each structural group would give an upper bound risk for cancer of greater than 1 in 1 million, calculated by linear extrapolation from the TD_{50} values (i.e., chronic dose-rates in mg/kg body weight/day that would induce tumors in half the test animals at the end of a standard lifespan) as presented in the Gold et al. (2006) Carcinogenic Potency Database.

Kroes et al. (2004) identified several groups of compounds determined to have a significant fraction of their members that may still be of concern at an intake of 0.15 µg/person-day and, therefore, require a compound-specific toxicity assessment. These were aflatoxin-like compounds, N-nitroso-compounds, azoxy-compounds, non-essential metal or metal-

containing compounds, steroids, and polyhalogenateddibenzo-p-dioxins and dibenzofurans. They proposed a TTC for other compounds with structural alerts that raise concern for potential genotoxicity as proposed by Cramer et al. (1978), Ashby and Tennant (1991), and Cheeseman et al. (1999), including steroids, of 0.15µg/person-day. This threshold is based on linear extrapolation of animal dose-response data to a theoretical risk of 1 in 1 million. This threshold gives a probability of 86–97% that any risk would be less than 1×10^{-6} if the intake were at or below the TTC and the compound was a genotoxic carcinogen (Kroes et al., 2004).

For compounds in Cramer classes I, II, and III, thresholds in the decision tree of Kroes et al. (2004) are based on the 5th percentile of the distributions of NOAELs, with the NOAELs from the chronic animal studies divided by a factor of 100 and the NOELs from subchronic studies divided by a factor of 300. Resulting TTCs for Cramer classes I, II, and III were 1800 µg/day, 540 µg/day, and 90 µg/day respectively.

3.5.1.6 Dolan, D.G., B. D. Naumann, E. V. Sargent, A. Maier, and M. Dourson (2005): TTCs for pharmaceutical ingredients (1 to 100 µg/day)

Dolan et al. (2005) proposed TTCs of 1, 10, and 100 µg/day for pharmaceutical ingredients other than the active pharmaceutical ingredient, including impurities or degradants, depending on whether they are likely to be carcinogenic or highly toxic. They suggest the following TTCs for compounds that do not fall within the five structural groups of highly potent carcinogenic chemicals identified by Kroes et al. (2004; i.e., steroids, polyhalogenated dibenzo-p-dioxins and -dibenzofurans, aflatoxin-like, azoxy-, and N-nitroso compounds):

- 1 µg/day for compounds that are likely to be carcinogenic, based on positive results in mutagenicity tests and/or structural alerts suggesting genotoxic potential, confirmed with positive results in an appropriate in vivo test such as an in vivo micronucleus test. The authors state, "Based on cancer potency estimates for hundreds of regulated carcinogens, the level of incremental cancer risk associated with lifetime exposure at this threshold value for a majority of compounds in this group is not likely to exceed one-in-a-million (1×10^{-6}), which is widely viewed as a de minimis level of risk" (Dolan et al., 2005, p. 2). This dose is equal to a screening level of 0.014 µg/kg-d assuming exposure to a 70 kg adult. The authors cite this value as being the same as the 1st percentile of screening levels developed by Merck for active pharmaceutical ingredients since 1981, which included genotoxic compounds, and slightly below the TTC value of 1.5 µg/day presented by Kroes et al. (2004) and proposed by the European Medicines Agency Committee for Medicinal Products for Human Use, for genotoxic impurities in pharmaceuticals that have insufficient evidence of a threshold-related mechanism.
- 10 µg/day for "relatively unstudied compounds" with evidence of pharmacological activity at relatively low doses but without confirming evidence of mutagenicity or evidence that it is an extremely potent drug. This dose is equal to a comparison screening level of 0.14 µg/kg-d assuming exposure to a 70 kg adult. The authors cite this value as being the same as the 10th percentile of oral RfDs and minimal risk levels established by the U.S. EPA and ATSDR, respectively, and at the 6th percentile of screening levels developed by Merck for active pharmaceutical ingredients.
- 100 µg/day for relatively unstudied compounds that have no a priori evidence of unusual toxicity or potency and that are not considered to be mutagenic (e.g., have no structural alerts and are negative in the Ames test). This dose is equal to a comparison value of 1.4 µg/kg-d assuming exposure to a 70 kg adult. The authors cite this value as being at the 25th percentile of oral RfDs and minimal risk levels established by the U.S. EPA and ATSDR, respectively, and at the 21st percentile of screening levels developed by Merck for active pharmaceutical ingredients.

Table 3.2. Summary of the Evolution of TTCs

Author	Chemical Group	Human Exposure Threshold (µg/day)	Equivalent Dose (µg/kg BW-d)[a]
U.S. FDA (Rulis 1986, 1989; Federal Register, 1995)	Untested compounds in food for which there is no evidence of carcinogenicity in humans or animals and no reason, based on chemical structure, to suspect the substance is a carcinogen.	1.5	0.021
Munro et al. (1996)	1) Cramer structural class III* 2) Cramer structural class II* 3) Cramer structural class I* *All compounds "for which there is no presumption of genotoxic carcinogenicity. Otherwise, the 1.5 µg/day threshold may be a more appropriate value."	1) 90 2) 540 3) 1800	1) 1.3 2) 7.7 3) 26
Cheeseman et al. (1999)	1) Compounds with positive results in the Ames test or other tests of genotoxicity that are judged to be biologically relevant, or that possess certain structural alerts (nitroso compounds, endocrine disruptors, strained heteronuclear rings, polycyclic amines, or hydrazine/ triazene/ azide/ azo/ azoxy compounds) 2) Compounds with no genotoxicity testing data, or positive genotoxicity tests but the genotoxicity results are judged "not biologically relevant" to their potency (e.g., positive Ames tests for heavy metals or alpha nitro-furyl compounds), or positive genotoxicity tests but no structural alerts suggesting potential for greater carcinogenic potency (e.g., nitroso compounds, endocrine disruptors, strained heteronuclear rings, benzidine compounds, hydrazine/ triazene/ azide/ azo/ azoxy compounds) 3) Compounds with negative Ames test or no structural alerts and a minimum LD_{50} (lethal dose to 50% of a test population) of less than 1000 mg/kg 4) Compounds with negative Ames test or no structural alerts and a minimum LD_{50} of 1,000 mg/kg or greater	1) NA; require compound-specific toxicity assessment 2) 1.5 (0.5 ppb in diet) 3) 15 (5 ppb in diet) 4) 30–45 (10–15 ppb in diet)	1) NA; require compound-specific toxicity assessment 2) 0.021 3) 0.21 4) 0.43–0.64

Author	Chemical Group	Human Exposure Threshold (µg/day)	Equivalent Dose (µg/kg BW-d)[a]
Kroes et al. (2000)	Trace chemicals in the diet—the authors concluded that levels in the diet below this threshold pose "no appreciable risk" of carcinogenicity or developmental, endocrine, immunological, and neurotoxic effects	1.5	0.021
Kroes et al. (2004)	1) Nonessential metal or metal-containing compounds; polyhalogenated–dibenzodioxins, –dibenzofurans, or biphenyls; steroids; or aflatoxin-like, azoxy-, or N-nitroso- compounds 2) Compounds with structural alerts that raise concern for potential genotoxicity as proposed by Cramer et al. (1978), Ashby and Tennant (1991), and Cheeseman et al. (1999), other than aflatoxin-like, azoxy-, or N-nitroso-compounds, or metal-containing compounds, or polyhalogenated-dibenzodioxin, -dibenzofuran, or –biphenyl compounds 3) Organophosphates 4) Cramer structural class III 5) Cramer structural class II 6) Cramer structural class I	1) NA; require compound-specific toxicity assessment 2) 0.15 3) 18 4) 90 5) 540 6) 1800	1) NA; require compound-specific toxicity assessment 2) 0.0021 3) 0.26 4) 1.3 5) 7.7 6) 26
Dolan et al. (2005)	1) Compounds that are likely to be carcinogenic (based on in vitro mutagenicity data and/or structural alerts for genotoxic potential; e.g., Cramer et al., 1978), and confirmed by an appropriate in vivo test. Compounds that fall within the five structural groups of highly potent carcinogenic chemicals identified by Kroes et al. (2004; i.e., steroids, polyhalogenated dibenzo-p-dioxins and -dibenzofurans, aflatoxin-like, azoxy-, and N-nitroso compounds) are excluded. 2) Relatively unstudied compounds with limited data indicating they may produce pharmacologic or toxic effects at very low doses, or with evidence of mutagenicity in in vitro studies not confirmed by appropriate in vivo studies 3) Relatively unstudied compounds with no a priori evidence of unusual toxicity or potency and that are not considered mutagenic (e.g., no structural alerts and negative in the Ames test)	1) 1 2) 10 3) 100	1) 0.014 2) 0.14 3) 1.4

[a]Assuming an adult average body weight of 70 kg (U.S. EPA, 1997)

3.5.2 Chemical Classification Schemes and Structural Alerts

As described previously, several of the proposed TTCs (e.g., Kroes et al., 2004) relied on assumptions about a chemical's activity based on chemical structure. Cramer et al. (1978) defined a series of three chemical classes to which compounds can be assigned according to the presence of structural groups and other features based on a decision tree approach. The three classes are:

- Cramer Class I—These compounds are those with structures and related data suggesting a low order of oral toxicity, indicating "an extremely low priority for investigation" (Cramer et al., 1978). Compounds in this group include butyl acetate, citric acid, methyl salicylate, and propylene glycol.
- Cramer Class II—These compounds are intermediate in toxicity between Class I and Class III substances—they are "less clearly innocuous than those of Class I, but do not offer the basis either of the positive indication of toxicity or of the lack of knowledge characteristic of those in Class III" (Cramer et al., 1978).
- Cramer Class III—These compounds "permit no strong initial presumptions of safety, or… may even suggest significant toxicity" and "deserve the highest priority for investigation" (Cramer et al., 1978). These may include halogen-substituted compounds and many persistent compounds with aromatic rings.

The former European Chemicals Bureau provided open source software (ToxTree) that allows the user to assign a chemical to a Cramer class based on the compound's SMILES (simplified molecular input line entry specification) code. The software is currently available at the European Commission Joint Research Centre Institute for Health and Protection (Website: http://ecb.jrc.ec.europa.eu/qsar/qsar-tools/index.php?c=TOXTREE). This software was used to determine the appropriate Cramer class for the case study compounds.

Cheeseman et al. (1999) and Kroes et al. (2004) recommended TTCs based in part on structural alerts identified by Ashby et al. (Ashby and Tennant, 1988; Ashby et al., 1989; Ashby and Tennant, 1991). Ashby et al. drew correlations between structural alerts and evidence of carcinogenicity for substances tested for carcinogenicity by the NTP. Cheeseman et al. (1999) extracted data on 709 carcinogens from the Gold Carcinogenic Potency Database to examine the utility of using short-term toxicity data, the results of genotoxicity testing, and structural alerts to identify more and less potent subsets of compounds in the dataset. Kroes et al. (2004) further refined the structural groups identified by Ashby and Tennant (1991) and Cheeseman et al. (1999). Appendix D summarizes the structural alerts applied in the Cheeseman et al. (1999) and Kroes et al. (2004) schemes.

3.5.3 Application of TTCs

TTCs are generally expressed as an intake (e.g., in micrograms per person/day). These levels can be converted to comparison values (in units of μg/kg-d) based on an assumed adult body weight (e.g., 70 kg; U.S. EPA, 1997) as follows:

$$\text{Comparison value}_{\text{TTC}}\ (\mu g / kg - d) = \frac{\text{TTC}\ (\mu g / day)}{70\ kg\ BW}$$

Several authors have reviewed the application of TTCs to specific compound types:

- Because metals were not in the database used by Munro et al. (1996) to define the TTCs used in the current decision tree, the authors indicate that metals in elemental, ionic, and organic forms would not normally be evaluated using the decision tree.
- Kroes et al. (2000, p. 277) concluded that "The exposure threshold value of 1.5 µg/person/day would be sufficiently low to provide an adequate margin of safety against any adverse endocrine effect associated with dietary environmental substances." However, Kroes et al. (2004) concluded that it is premature to consider low-dose effects for EDCs in the application of TTCs because data on effects at very low doses are inconsistent and not replicated by subsequent studies.
- For allergens, Kroes et al. (2004) concluded there are insufficient dose–response data regarding allergenicity of proteins and low molecular weight compounds on which a TTC for this endpoint can be based.
- Kroes et al. (2004) concluded that specific considerations of metabolism and accumulation are not necessary in the application of a TTC, providing that the decision tree is not applied to substances that are likely to show very large species differences in accumulation such as polyhalogenated dibenzo-p-dioxins and related compounds or metals that have extremely long half-lives and were not included in the Munro et al. (1996) database.
- Blackburn et al. (2005) evaluated the appropriateness of TTCs determined by Munro et al. (1996) for evaluating ingredients of personal and household care products, by assigning 43 chemicals used in household and personal care products to the three Cramer classes and comparing the range of NOELs for those compounds to the range of NOELs used by Munro et al. (1996) to develop the TTCs. The results showed that the distribution of NOELs for household and personal care product ingredients fell well within the range of the NOELs for the larger database analyzed by Munro et al. (1996) and that the published TTC values for the three Cramer classes are adequately protective benchmarks.

In considering use of the TTC approach among other approaches for deriving screening values for PPCPs and EDCs, the project team identified several advantages in its application:

- It is relatively simple to apply, with minimal data requirements—one need only determine a few easily available pieces of information (e.g., structural class, results of genotoxicity tests, LD_{50}s) in order to determine which TTC to apply. For most compounds, these data should be readily available. However, appropriate selection and application of TTCs requires some a priori knowledge of toxicity, for example, to establish whether a compound shows evidence of genotoxicity.

Disadvantages of the TTC approach include:

- None of the TTCs included extensive evaluation of intentionally biologically active compounds such as pharmaceuticals in their derivation and, thus, their applicability to these types of compounds is uncertain.
- The approach does not consider specific toxicological data for a given chemical compound and, therefore, may not be adequately protective of some compounds with unique toxicities (e.g., a number of the TTCs are based on the lower 5th percentile NOAEL for a group of compounds, or similar statistical measure; as such, some compounds may lie outside of the 95% of compounds for which this NOAEL is protective). However, because the databases were analyzed with significant statistical

vigor, there is statistical confidence about the protectiveness of the derived TTCs for specific chemical classes.

3.6 DERIVATION OF A VIRTUALLY SAFE DOSE FOR CARCINOGENS

For compounds with evidence of carcinogenicity in animals, Gaylor and Gold (1998) proposed a method for calculating a virtually safe dose (VSD) without the need to conduct multiyear laboratory studies for carcinogenicity. Gold et al. (2006) created the Carcinogenic Potency Database as part of the Carcinogenic Potency Project at the Lawrence Berkeley Laboratory. The database summarizes results from 6153 chronic, long-term animal cancer tests on 1485 chemicals, as published in the general literature through 1997 and by the National Cancer Institute (NCI) or the National Toxicology Program (NTP) through 1998 (Gold et al. 2005, 2006). Gaylor and Gold (1998) reviewed the results of two-year cancer bioassays for 139 chemicals tested by the NTP and determined that a "virtually safe dose" corresponding to a cancer risk of 1 in 1 million can be estimated by dividing a chemical's maximum tolerated dose from 90-day studies in rodents by 740,000. The maximum tolerated dose is the highest dose predicted to produce minimal systemic toxicity over the course of a carcinogenicity study, estimated from 90-day dose range finding studies, and in practice is usually the high dose selected for a carcinogenicity study (FDA, 1995).

For compounds for which the mechanism of carcinogenicity can be demonstrated to be nonlinear (e.g., not proceeding through genotoxicity), Gaylor and Gold (1998) recommend deriving a reference dose by dividing the lower confidence limit on the dose to produce tumors in 10% of rodents (LTD_{10}) by a composite UF of 1000 (10 for animal to human extrapolation, 10 for sensitive humans, and 10 because the LTD_{10} represents a LOAEL). They suggest applying an additional UF of 10 "to account for possible extra sensitivity of children per the Food Quality Protection Act of 1996" or because of the severity of cancer even from low doses (Gaylor and Gold, 1998, p. 224). The LTD_{10} is estimated by dividing the maximum tolerated dose from 90-day dose range finding studies by a factor of 7 (Gaylor and Gold, 1998).

In considering use of the VSD approach among other approaches for deriving screening values for PPCPs or EDCs, the project team identified several advantages in its application:

- It is simple to apply, with minimal data requirements—one need only identify the maximum tolerated dose from animal studies, which is usually the highest dose used in cancer studies. This information should be readily available for nearly all chemicals that have been tested for carcinogenicity.

Disadvantages of the VSD approach include:

- It is simplistic and because it is a linear approach, it may overestimate carcinogenicity for nongenotoxic carcinogens that have, for example, modes of action indicative of a dose–response threshold for tumor development (e.g., nongenotoxic compounds that cause thyroid-pituitary disruption; U.S. EPA, 1998). However, in the absence of data suggesting a nonlinear mechanism of action, Gaylor and Gold (1998) recommend assuming linearity.

CHAPTER 4

PRESENTATION OF CASE STUDIES AND SUMMARY OF EXPERT PANEL DISCUSSION

4.1 INTRODUCTION

The project team applied the methods described in Chapter 3 to derive preliminary comparison values for the case study compounds. These case studies were compiled into an interim report and provided to expert panelists prior to the expert panel workshop, held on November 5 and 6, 2008, at the Southern Nevada Water Authority's River Mountain Water Treatment Facility in Las Vegas, Nevada. The workshop was attended by 23 experts including toxicologists, chemists, biologists, policy analysts, and pharmaceutical company and drinking water utility representatives (see Section 1.2). The project team then presented the case studies in detail at the workshop and facilitated discussion among the panelists, who were charged with discussing and reaching a consensus regarding the procedural details of a process for rapidly deriving health-protective screening levels, in the event that "new" chemicals are found in source or reuse water.

Though there were minor disagreements on details of the report, the group reached consensus at each stage of the process; the panel's comments and recommendations are presented herein. Based on panel discussions, the project team modified the proposed decision tree as presented in Chapter 5.

The following sections present the derivation of comparison values for each of the case study compounds, using the methods described in Chapter 3. In examining these values, the panel emphasized that this document presents an evaluation of a process for developing screening levels for newly detected contaminants without existing criteria, NOT a list of recommended screening levels for water or other media.

For each compound, the project team identified the following information used to deriving comparison values:

- NOAELs and LOAELs for noncarcinogenic endpoints, particularly endpoints assumed to be of most concern for long-term, low-dose exposure of sensitive population groups (e.g., reproductive and developmental effects) (summarized in Table 4.1 and expanded in Appendix D)
- Results of chronic carcinogenicity studies in animals (summarized in Table 4.2 and expanded in Appendix D)
- Data from in vitro genotoxicity testing (summarized in Tables 4.2 and 4.4 and expanded in Appendix E)
- Lowest therapeutic doses (for pharmaceuticals) and serious adverse effects in humans (e.g., reproductive/ developmental effects, such as congenital abnormalities, carcinogenicity) reported at the therapeutic doses (summarized in Table 4.3)
- The presence or absence of structural alerts (summarized in Table 4.4)

- The maximum tolerated dose (MTD) from 90-day dose range finding studies in animals, or the high dose selected for a carcinogenicity study (summarized in Table 4.5).

Table 4.6 provides a meta summary of comparison values derived using the different methods for each compound. The findings from application of each method, and the panelists' comments and recommendations on each method, are summarized in the following.

4.2 DERIVATION OF COMPARISON VALUES FOR NONCARCINOGENIC EFFECTS USING NOAELS/LOAELS

Appendix D summarizes the NOAELs and LOAELs identified for each case study compound from review of published toxicity data. Prior to the panel meeting, the project team applied UFs to the NOAELs or LOAELs for each study according to the nature of the data and the perceived quality of the study, following the guidelines given by U.S. EPA (2002a) for applying UFs to derive RfDs (originally described in Table 3.1).

Table 4.1 summarizes the NOAELs/LOAELs and study-specific UFs that resulted in the lowest calculated comparison value for each compound. In general, this was the lowest LOAEL identified for each compound or, in the event that the study with the lowest LOAEL also had a NOAEL, the NOAEL from that study. For some compounds (diclofenac, naproxen, triclosan), no LOAELs were identified and the value given is the lowest NOAEL.[1] The majority of selected NOAELs/LOAELs were based on developmental or reproductive effects, or for EDCs, on endocrine-mediated effects.

The panel discussed the manner in which the project team applied UFs to case study compounds and whether different values might be more appropriate for certain compounds or data sets. For example, whereas the project team applied an inter-individual UF of 3 to case study compounds if the critical study evaluated a known sensitive population group (e.g., developmental data) several panel members recommended a default inter-individual UF of 10 as a general rule. The panel suggested that if individually chosen UFs are used for each compound, a written rationale for the selection of specific values should be provided.

Overall, the panel observed that making chemical-specific UF decisions for a large number of compounds is a major endeavor, requiring careful resource-intensive weighing of the database and its various uncertainties, and can engender disagreement. To address this concern and to simplify the process of developing screening values, the panel recommended a more generic screening protocol—applying a statistically derived default cumulative UF of 1000 when the point of departure is a NOAEL and a UF of 3000 when the point of departure is a LOAEL, rather than deriving UFs on a study-specific basis.

Application of default UFs of 1000 and 3000 is supported by a statistical analysis of a set of 216 "learning compounds" with U.S. RfDs, NOAELs, and LOAELs conducted by U.S. EPA as part of the Contaminant Candidate List (CCL) Classification Process (U.S. EPA, 2008b). Based on this evaluation, the U.S. EPA determined that an RfD could be approximated by

[1]If only NOAELs are available and multiple studies examined the same species and toxicological endpoint, the highest NOAEL from among these studies would be selected as the point of departure. However, for diclofenac, naproxen, and triclosan, each of the available studies examined a different species and/or toxicological endpoint. Consequently, for this evaluation, we selected the lowest NOAEL as the point of departure for these compounds.

dividing the NOAEL by 1000 or the LOAEL by 3000. The U.S. EPA used this process to classify potential drinking water contaminants for inclusion on its draft third Drinking Water Contaminant Candidate List (CCL3).

The panel also recommended that an additional UF of 10 be applied to the compound if it is either a nongenotoxic carcinogen or an EDC (see Sections 5.4 and 5.5 for additional discussions of the genotoxicity data).

Table 4.1 compares the default UFs (1000 or 3000 with an additional 10 in some circumstances) to the study-specific derived UFs. This comparison illustrates that the default values are generally conservative—the default UF produced an equivalent or lower comparison value in 36 of 39 cases. The comparison values derived using the default UFs for each of the three remaining compounds (HHCB, meprobamate, triclosan) were within a factor of three of the original estimate, and all three of these compounds are of relatively low toxicity.

For one compound, doxycycline, applying the default 1000 or 3000 UF to the toxicity data as opposed to the study-specific derived UFs resulted in selection of a different study as a point of departure. For this compound, the resulting comparison value was lower using the refined approach than using the initial approach.

Based on examination of all of the values, the panel concluded that the default UFs could be applied without the need for resource-intensive investigation of the mechanism of action and toxicity of each compound and still result in screening values that are health protective.

Table 4.1. Toxicological Data Used to Develop Comparison Values for Noncancer Endpoints for Case Study Compounds and Application of Study-Specific and Default UFs to Those Data

Compound	Species/ Gender/Study Duration	Effect Dose (mg/kg-d)	Effect	Study Reference	Study-Specific Composite UF and Comparison Value (µg/kg-d)	Default UF and Comparison Value (µg/kg-d)
PPCPs						
Alendronate	Rat/(F)/before mating thru gestation	0.5 (LOAEL)	Reproductive (protracted parturition due to maternal hypocalcemia)	Merck, 2006	3,000 0.17 µg/kg-d	3,000 × 10[a] 0.017 µg/kg-d
Atenolol	Human/F/ gestation	0.8 (LOAEL)	Developmental (decreased infant birth weights)	Bayliss et al., 2002; Lip et al., 1997; Lydakis et al., 1999	300 2.7 µg/kg-d	3,000 × 10 [a] 0.027 µg/kg-d
Atorvastatin	Rat/M/ GD 7–PND 21	20 (LOAEL)	Developmental (behavioral effects—reduced acoustic startle; reduced pup weight at 100 mg/kg-d and higher)	Henck et al., 1998	3,000 6.7 µg/kg-d	3,000 × 10 [a] 0.67 µg/kg-d
Carbamazepine	Human/F/ gestation	3 (LOAEL)	Developmental (increased neural tube defects, cardiovascular defects, oral clefts, and urinary tract defects)	Hernandez-Diaz et al., 2000; Samren et al., 1997, 1999	300 10 µg/kg-d	3,000 1.0 µg/kg-d
Desloratadine	Rat/F/ GD 6–PND 21	3 (NOAEL)	Developmental (reduced pup body weights and slow righting reflex)	FDA, 2001	300 10 µg/kg-d	1,000 × 10 [a] 0.30 µg/kg-d
Diazepam	Rat/ gestation	1 (LOAEL)	Developmental (decreased pup viability, neurobehavioral alterations)	Kellogg and Retell, 1986; Ryan and Pappas, 1986; Miranda et al., 1989; Miranda et al., 1990; Kellogg et al., 1991; Silva and Palermo-Neto, 1999	1,000 1.0 µg/kg-d	3,000 0.33 µg/kg-d
Diclofenac	Rat/F/NA	4 (NOAEL)	Reproductive (no effect)	Novartis, 2002	300 13 µg/kg-d	1,000 4.0 µg/kg-d

Compound	Species/ Gender/Study Duration	Effect Dose (mg/kg-d)	Effect	Study Reference	Study-Specific Composite UF and Comparison Value (µg/kg-d)	Default UF and Comparison Value (µg/kg-d)
Doxycycline	Rat/GD 15–19; PND 1 (pups)	8 (LOAEL) [b]	Developmental (skeletal differentiation in long bones was delayed)	Siddiqui and Janjua, 2002	3,000 2.7 µg/kg-d	3,000 2.7 µg/kg-d
	Human/ pregnancy	3.0 (LOAEL) [c]	Developmental (weak association with total malformations)	RxList, 2008f	300 10 µg/kg-d	3,000 1.0 µg/kg-d
Enalapril	Human/F/ gestation	0.070 (LOAEL)	Developmental (congenital malformations)	Tabacova and Kimmel, 2001, Tabacova et al., 2003	300 0.23 µg/kg-d	3,000 0.023 µg/kg-d
Fluconazole	Rabbit/F/ gestation	5 (LOAEL)	Systemic/reproductive (reduced maternal weight gain)	RxList, 2008a	3,000 1.7 µg/kg-d	3,000 × 10 [a] 0.17 µg/kg-d
Fluoxetine	Human/F/ gestation	0.29 (LOAEL)	Developmental (shortened gestation, reduced birth weight, poor neonatal adaptation)	NTP, 2004	300 0.97 µg/kg-d	3,000 0.097 µg/kg-d
Furosemide	Rabbit F/ gestation	25 (LOAEL)	Reproductive/developmental (unexplained maternal deaths and abortions)	RxList, 2008b	3,000 8.3 µg/kg-d	3,000 8.3 µg/kg-d
Gemfibrozil	Rat/F/GD 15–PND 21	92 (LOAEL) [b]	Developmental (reduced offspring body weights)	Fitzgerald et al., 1987	3,000 31 µg/kg-d	3,000 × 10 [a] 3.1 µg/kg-d
HHCB	Rat/F/GD 7–17	50 (NOAEL)	Systemic (maternal; clinical signs, reduced weight gain)	Christian et al., 1999	3,000 17 µg/kg-d	1,000 50 µg/kg-d
Ifosfamide	Rat/F/GD 6–15	3 (LOAEL)	Developmental (embryotoxic effects)	RxList, 2008c	3,000 1.0 µg/kg-d	3,000 1.0 µg/kg-d

Compound	Species/ Gender/Study Duration	Effect Dose (mg/kg-d)	Effect	Study Reference	Study-Specific Composite UF and Comparison Value (µg/kg-d)	Default UF and Comparison Value (µg/kg-d)
Iopamidol/ iopromide	Human/M&F/ PND 3–7	150 (LOAEL)	Endocrine (higher mean thyrotropin and lower free triiodothyronine and thyroxine levels in infants)	Parravicini et al., 1996	300 500 µg/kg-d	3,000 50 µg/kg-d
Lansoprazole	Dog/13 weeks	3.3 (LOAEL)	Systemic (inflammation and fibrosis of vein wall, hyperplasia of fundic glands, atrophy of parietal cells of stomach)	TAP, 2004	10,000 0.33 µg/kg-d	3,000 × 10 [a] 0.11 µg/kg-d
Meprobamate	Mouse/13 weeks	75 (NOAEL)	Systemic (increased liver weights)	NTP, 2000	3,000 25 µg/kg-d	1,000 75 µg/kg-d
Methotrexate	Human/ pregnancy	0.010 (LOAEL)	Systemic (increased myeloid and erythroid bone marrow hypoplasia)	Janssen and Genta, 2000	300 0.033 µg/kg-d	3,000 0.0033 µg/kg-d
Mirtazapine	Human/F/ gestation	0.21 (LOAEL)	Reproductive/developmental (increased number of spontaneous abortions)	Djulus et al., 2006	300 0.70 µg/kg-d	3,000 × 10 [a] 0.0070 µg/kg-d
Naproxen	Rat & rabbit/ gestation	20 (NOAEL)	Reproductive/ Developmental (no evidence of impaired fertility or harm to fetus)	Roche, 2006	300 67 µg/kg-d	1,000 20 µg/kg-d
Phenytoin	Human/ gestation	4.3 (LOAEL)	Developmental (congenital effects)	Hernandez-Diaz et al., 2000; Ornoy, 2006	300 14 µg/kg-d	3,000 1.4 µg/kg-d
Risperidone	Rat/gestation/ lactation	0.16 (LOAEL)	Reproductive (impaired mating); Developmental (increased pup death 4 days postnatal)	Drugs.com, 2007a	3,000 0.053 µg/kg-d	3,000 × 10 [a] 0.0053 µg/kg-d

Compound	Species/ Gender/Study Duration	Effect Dose (mg/kg-d)	Effect	Study Reference	Study-Specific Composite UF and Comparison Value (µg/kg-d)	Default UF and Comparison Value (µg/kg-d)
Simvastatin	Human, children/ M&F/48 weeks	0.2 (LOAEL)	Developmental/Systemic (decrease in adrenal hormones)	de Jongh et al., 2002	30 6.7 µg/kg-d	3,000 × 10 [a] 0.0067 µg/kg-d
Sulfamethoxazole	Rat/gestation	512 (NOAEL)	Developmental (primarily cleft palate)	Monarch Pharmaceuticals, 2006	1,000 510 µg/kg-d	1,000 510 µg/kg-d
Tamoxifen	Rat/M&F/GD 6–PND 21	0.00012 (NOAEL)	Developmental (day of preputial separation prolonged in male offspring and cleft phallus detected in female offspring)	Yamasaki et al., 2005	300 0.00040 µg/kg-d	1,000 × 10 [a] 0.000012 µg/kg-d
Triclosan	Rabbit/13 weeks	3 (NOAEL)	Systemic (no effect)	Barbolt, 2002	3,000 1.0 µg/kg-d	1,000 3.0 µg/kg-d
Trimethoprim	Rat/gestation	70 (NOAEL)	Reproductive (no effect)	Monarch Pharmaceuticals, 2006	1,000 70 µg/kg-d	1,000 70 µg/kg-d
EDCs						
Atrazine	Rat/6 months	1.8 (NOAEL)	Reproductive/ Endocrine (Attenuation of pre-ovulatory lutenizing hormone [LH] surge, as a biomarker indicative of hypothalamic function disruption)	U.S. EPA, 2006a	100 18 µg/kg-d	1,000 × 10 [d] 0.18 µg/kg-d
Bisphenol A	Rat/3-generation	5 (NOAEL)	Developmental (reduced body weights and body weight gains, reduced absolute and increased relative weanling and adult organ weights)	Tyl et al., 2002	100 50 µg/kg-d	1,000 × 10 [d] 0.5 µg/kg-d

Compound	Species/ Gender/Study Duration	Effect Dose (mg/kg-d)	Effect	Study Reference	Study-Specific Composite UF and Comparison Value (µg/kg-d)	Default UF and Comparison Value (µg/kg-d)
Butylbenzyl phthalate	Rat/(M&F) / 2-generation repro/devel study	100 (LOAEL)	Reproductive (softening of testes, atrophy of testicular seminiferous tubules, decreased spermatozoa and/or residual germ cells in the epididymal lumina observed in F1 generation)	Aso et al., 2005	1,000 100 µg/kg-d	3,000 × 10 [d] 3.3 µg/kg-d
DEHP	Rat/M/in utero and via lactation (GD 6–PND 21)	1.215 (NOAEL)	Developmental (higher incidence of cryptorchidism and higher testes weights in offspring)	Andrade et al., 2006a, 2006b	100 12 µg/kg-d	1,000 × 10 [d] 0.12 µg/kg-d
Dibutyl phthalate	Rat/F/GD 12–21	100 (NOAEL)	Developmental (malformations of the epidymous, retained nipples)	Mylchreest et al., 1999	100 1,000 µg/kg-d	1,000 × 10 [d] 10 µg/kg-d
17ß-Estradiol	Human/post-menopausal women trial study	0.005 (NOAEL)	Endocrine (changes in several hormone-dependent parameters in healthy postmenopausal women)	Mashchak et al., 1982; Moore et al., 1978	100 0.050 µg/kg-d	1,000 × 10 [d] 0.00050 µg/kg-d
Estrone	Human/post-menopausal women trial study	0.004 (NOAEL)	Endocrine (effects on several hormone and hormone-binding globulin capacities)	Mashchak et al., 1982	300 0.013 µg/kg-d	1,000 × 10 [d] 0.00040 µg/kg-d
Ethynylestradiol	Human/ therapeutic dose	0.0001 (LOAEL)	Minimal dose listed for any use	N/A	1,000 0.00010 µg/kg-d	3,000 × 10 [d] 0.0000033 µg/kg-d
Lindane	Rat/2-generation repro study	0.56 (LOAEL)	Systemic (increased liver weights, centrilobular hepatocellular hypertrophy)	Matsuura et al., 2005	1,000 0.56 µg/kg-d	3,000 × 10 [d] 0.019 µg/kg-d

Compound	Species/ Gender/Study Duration	Effect Dose (mg/kg-d)	Effect	Study Reference	Study-Specific Composite UF and Comparison Value (µg/kg-d)	Default UF and Comparison Value (µg/kg-d)
Linuron	Dog/2-years	0.625 (LOAEL)	Blood (abnormal blood pigment)	du Pont, 1962a, 1962b	300 2.0 µg/kg-d (same as EPA RfD)	3,000 × 10 [d] 0.021 µg/kg-d
Methoxychlor	Mouse/F/ GD11–17	0.020 (LOAEL)	Developmental (behavioral effects in dams and offspring)	Palanza et al., 2002	1,000 0.020 µg/kg-d	3,000 × 10 [d] 0.00067 µg/kg-d
Nonylphenol	Rat/(M&F)/ 3-generation repro/devel study	1.5 (NOAEL)	Systemic (renal histopathology)	Tyl et al., 2006	30 50 µg/kg-d	1,000 × 10 [d] 0.15 µg/kg-d
4-tert-Octylphenol	Rat/3-generation	15 (LOAEL)	Developmental (decreased body female weight gain)	Tyl et al., 1999; Nagao et al., 2001	100 150 µg/kg-d	3,000 × 10 [d] 0.50 µg/kg-d
Vinclozolin	Rat/M&F/ chronic dietary	1.2 (NOAEL)	Systemic (histopathological lesions in lungs [males], liver [males], ovaries [females] and eyes [both sexes])	U.S. EPA, 2000b	100 12 µg/kg-d (same as EPA FQPA RfD)	1,000 × 10 [d] 0.12 µg/kg-d

Note. GD = Gestational day; LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; PND = postnatal day; UF = uncertainty factor

[a]An additional UF of 10 was applied because the compound shows evidence of being a nongenotoxic carcinogen (see Table 4.2)

[b]Using the initial approach (i.e., assigning UFs on a study-specific basis), this point of departure yielded the lowest comparison value for doxycycline.

[c]Using the refined approach (i.e., assigning a default UF of 1,000 to NOAELs and 3,000 to LOAELs), this point of departure yielded the lowest comparison value.

[d]An additional UF of 10 was applied because the compound is a purported EDC.

4.3 DERIVATION OF COMPARISON VALUES BASED ON CANCER SLOPE FACTORS

For each case study compound, the project team determined the availability of evidence on carcinogenicity (Table 4.2). Tumor incidence data were identified where available, and SFs and corresponding comparison values were derived. Twenty-one of the case study compounds reportedly showed evidence of carcinogenicity in animal studies; for 10 of these compounds, tumor incidence data were located and SFs were derived using a linear extrapolation model (U.S. EPA, 2008c).

Of the pharmaceuticals for which tumor data were identified, ifosfamide appears to be the most potent, with a comparison value of 0.010 µg/kg-day. For the EDCs, the lowest SF-based comparison value was calculated for 17ß-Estradiol; the comparison value was 2.6E-5 µg/kg-day.

The panel agreed that when comparison values are set using the cancer slope factor approach, an acceptable lifetime excess cancer risk level of 1 in 1 million should be applied to be conservative, even though some agencies (e.g., WHO) use a default value of 1 in 100,000.

In addition, the panel discussed what to do in the event that a chemical shows evidence of carcinogenicity in animal studies, but no data can be readily located on tumor incidence for use in developing a cancer slope factor. The panel reached agreement that if the compound is a nongenotoxic carcinogen and no tumor incidence data are identified, an additional UF of 10 should be applied to the lowest therapeutic dose or the NOAEL/ LOAEL—this approach is consistent with the Gaylor and Gold (1998) virtually safe dose approach for nongenotoxic carcinogens. If the compound is a genotoxic carcinogen and no tumor incidence data are identified, the panel recommended that a comparison value be derived by dividing the maximum tolerated dose by 740,000 (the Gaylor and Gold approach for genotoxic carcinogens); this should be compared to the appropriate TTC, and the lower of the two values selected.

Three of the case study compounds—ifosfamide, methotrexate, and tamoxifen— are chemotherapeutic agents. Ifosfamide was carcinogenic in studies in mice (lung tumors and lymphomas of the hematopoietic system) and rats (uterine leiomyosarcomas and mammary tumors; NTP, 1977). Methotrexate does not show evidence of carcinogenicity in 23–28 month studies in mice, rats, and hamsters (Rustia and Shubik, 1973; Hall et al., 1988), but there have been case reports of subsequent neoplasms in humans following treatment (Drugs.com, 2007d). Tamoxifen showed increases in hepatocellular carcinomas in rats (e.g., Hard et al., 1993; Hirsimaki et al., 1993; Karki et al., 2000; Williams et al., 1993), increased granulose cell ovarian tumors and interstitial cell testicular tumors in mice (Drugs.com 2007d), and increased mammary tumors in female offspring of treated maternal rats (Halakivi-Clarke et al., 2000). Tamoxifen has also been associated with increased uterine malignancies, endometrial cancers, endometrial changes including hyperplasia, and other secondary cancers including liver cancer in humans (Drugs.com, 2007e).

Table 4.2. Evidence for Carcinogenicity of Case Study Compounds and Slope Factors (SFs) and Comparison Values Based on Those Data

Compound	Evidence	Genotoxicity Assumption*	Availability of Tumor Incidence Data	Cancer SF $(mg/kg\text{-}d)^{-1}$	Comparison Value Based on CSF (µg/kg-d)**
PPCPs					
Alendronate	Increased Harderian gland adenomas in female mice and parafollicular cell (thyroid) adenomas in male rats (Rxlist, 2008d) *Note*. Increasedtumor incidence seen in mice not likely relevant to humans because tumor site (Harderian gland) not present in humans.	Negative	Not located	NA	NA
Atenolol	Increased thyroid parafollicular cell carcinomas in male rats (Drugs.com, 2006)	Negative	Not located	NA	NA
Atorvastatin	Increased liver adenomas and carcinomas in mice, and rhabdomyosarcomas and fibrosarcomas in female rats (Pfizer, 2003)	Negative	Not located	NA	NA
Carbamazepine	Increased liver carcinomas in rats (Novartis, 2000, Singh et al., 2005)	Positive (Negative in Ames)	Not located	NA	NA
Desloratadine	Increased liver carcinomas in male mice and rats (Schering Corp, 2004)	Negative	Not located	NA	NA
Diazepam	No data	Positive (Positive in Ames)	NA	NA	NA
Diclofenac	No evidence of carcinogenicity in 2-yr studies of mice and rats (Novartis, 2002)	Negative	NA	NA	NA
Doxycycline	Increased uterine polyps in female rats (FDA, 2006) but no tumor formation.	Positive (No Ames test)	NA	NA	NA

Compound	Evidence	Genotoxicity Assumption*	Availability of Tumor Incidence Data	Cancer SF $(mg/kg\text{-}d)^{-1}$	Comparison Value Based on CSF (µg/kg-d)**
Enalapril	No evidence of carcinogenicity in 2-yr studies of mice and rats (FDA, 1985, Merck, 2001)	Negative	NA	NA	NA
Fluconazole	Increased hepatocellular adenomas in male rats (CPDB, 2007a)	Negative	CPDB, 2007a: 2 yr, rat (M) 0 mg/kg-d= 2/100 2.5 mg/kg-d = 0/50 5.0 mg/kg-d = 4/50 10 mg/kg-d = 5/50	0.011	0.091
Fluoxetine	No evidence of carcinogenicity in 2-yr studies of mice and rats (Bendele et al., 1992)	Negative	NA	NA	NA
Furosemide	Increased mammary gland tumors in female mice; increased C-cell adenomas in the thyroid in female rats; increased pituitary adenomas in male rats (NTP, 1989; Bucher et al., 1990) *Note*. Evidence of tumors in rats is equivocal: study authors determined increased tumors in female rats are not associated with exposure, and increased tumors seen at low dose in male rats were not seen at the next highest dose (NTP, 1989; Bucher et al., 1990)	Positive (Negative in Ames)	NTP, 1989; Bucher et al., 1990; CPDB, 2007a: 2 yr, mouse (F); Malignant mixed tumors (adenocarcinomas, type C) of the mammary gland 0 mg/kg-d = 0/50 89.3 mg/kg-d = 1/50 180 mg/kg-d = 5/48	0.0086	0.12
Gemfibrozil	Increased adrenal, pancreatic, liver, and teste tumors in male rats (Fitzgerald et al. 1981)	Negative	Fitzgerald et al., 1981; CPDB, 2007a: 2 yr, rat (M); Interstitial cell tumors of the testes 0 mg/kg-d = 1/50 30 mg/kg-d = 8/50 300 = 17/50	0.0018	0.56
HHCB	No data	Negative	NA	NA	NA

Compound	Evidence	Genotoxicity Assumption*	Availability of Tumor Incidence Data	Cancer SF $(mg/kg\text{-}d)^{-1}$	Comparison Value Based on CSF (µg/kg-d)**
Ifosfamide	Increased malignant lymphomas of the hematopoietic system in female mice and increased uterine leiomyosarcomas and mammary fibroadenomas in female rats (NTP, 1977)	Positive (Positive in Ames)	NTP, 1977: 52 week, rat (F); mammary fibroadenomas 0 mg/kg-d = 8/28 2.6 mg/kg-d = 28/33 5.1 mg/kg-d = 6/35	0.1	0.010
Iopamidol/ iopromide	No data	Negative	NA	NA	NA
Lansoprazole	Increased liver adenomas, testicular carcinomas, and adenomas in mice; marked hypergastrinemia and ECL cell proliferation and formation of carcinoid tumors in female rats (TAP, 2004)	Negative	Not located	NA	NA
Meprobamate	No data	Positive (Negative in Ames)	NA	NA	NA
Methotrexate	No evidence of carcinogenicity in 23–28 mo studies in mice, rats, and hamsters (Rustia and Shubik, 1973; Hall et al., 1988)	Positive	NA	NA	NA
Mirtazapine	Increased incidence of hepatocellular adenoma and carcinoma in male mice; increased hepatocellular adenoma in female rats; increased hepatocellular tumors and thyroid follicular adenoma/ cystadenoma and carcinoma in male rats (Drugs.com, 2007c)	Negative	Not located	NA	NA
Naproxen	No evidence of carcinogenicity in 2-yr study in rats (Roche, 2006)	Negative	NA	NA	NA

Compound	Evidence	Genotoxicity Assumption*	Availability of Tumor Incidence Data	Cancer SF $(mg/kg\text{-}d)^{-1}$	Comparison Value Based on CSF (µg/kg-d)**
Phenytoin	Liver neoplasms in female mice and male rats (NTP, 1993)	Positive (Positive in Ames)	NTP, 1993: 2 yr, mouse (F); liver adenomas and carcinomas in females 0 mg/kg-d = 5/48 50 mg/kg-d = 14/49 160 mg/kg-d = 30/50	0.0012	0.83
Risperidone	Mammary gland adenocarcinomas in female mice and rats (Drugs.com, 2007a)	Negative	Not located	NA	NA
Simvastatin	Liver carcinomas and adenomas and lung adenomas in mice; liver carcinomas and adenomas and thyroid follicular adenomas in male and female rats (Drugs.com, 2007b)	Negative	Not located	NA	NA
Sulfamethoxazole	No data	Negative	NA	NA	NA
Tamoxifen	Increased hepatocellular carcinomas in rats and increased granulose cell ovarian tumors and interstitial cell testicular tumors in mice (CPDB, 2007h).	Negative	Greaves et al., 1993, 2 yr, rat (F), liver tumors: 0 mg/kg-d = 0/105 5 mg/kg-d = 6/52 20 mg/kg-d = 37/52 35 mg/kg-d = 37/52	0.00041	2.4
Triclosan	No evidence of carcinogenicity in 2-yr study in rats (Barbolt, 2002)	Negative	NA	NA	NA
Trimethoprim	No data	Negative	NA	NA	NA

Compound	Evidence	Genotoxicity Assumption*	Availability of Tumor Incidence Data	Cancer SF $(mg/kg\text{-}d)^{-1}$	Comparison Value Based on CSF (µg/kg-d)**
EDCs					
Atrazine	Current California Public Health Goal (PHG) based on mammary tumors (adenocarcinoma and fibroadenoma) in female rats (Ciba-Geigy, 1986 as cited in CA EPA, 1999); SF = 0.23 (mg/kg-d)-1 (calculated by CA EPA, 1999), CA PHG = 0.15 µg/L calculated from the SF.	Negative	Ciba-Geigy, 1986 as cited in CA EPA, 1999: 2 yr, rat (F); mammary tumors: 0 mg/kg-d = 35/66 0.5 mg/kg-d = 39/64 3.5 mg/kg-d = 47/68 25 mg/kg-d = 47/65 50 mg/kg-d = 56/64	NA	NA
Note. The U.S. EPA determined that atrazine's cancer mode of action in the Sprague-Dawley rat is unlikely to be operative in humans. In a review by the FIFRA Scientific Advisory Panel of the toxicity of triazine pesticides, including atrazine, they recommended that development of mammary tumors in rodents not be considered relevant to humans (U.S. EPA, 2006c). Consequently, in accordance with the 1999 Draft Guidelines for Carcinogen Risk Assessment, the U.S. EPA classified atrazine as "not likely to be carcinogenic to humans" (US EPA, 2006c). The International Agency for Research on Cancer (IARC) has also classified atrazine as "not classifiable as to its carcinogenicity to humans" (Group 3) based on inadequate evidence in humans and sufficient evidence in experimental animals. (ATSDR, 2003)					
Bisphenol A	"No convincing evidence that bisphenol A was carcinogenic for F344 rats or B6C3F1 mice of either sex" (NTP, 1982a)	Negative	NA	NA	NA

Compound	Evidence	Genotoxicity Assumption*	Availability of Tumor Incidence Data	Cancer SF $(mg/kg\text{-}d)^{-1}$	Comparison Value Based on CSF (µg/kg-d)**
Butylbenzyl phthalate	Increased mononuclear cell leukemia in female rats (NTP, 1982b). Some evidence of carcinogenic activity in male rats based on increased incidences of pancreatic acinar cell adenoma and acinar cell adenoma or carcinoma (combined). Equivocal evidence of carcinogenic activity in female rats based on marginally increased pancreatic acinar cell adenoma and transitional epithelial papilloma of the urinary bladder (NTP, 1997).	Negative	NTP, 1982b, 2 yr, rat (F), leukemia: 0 mg/kg-d= 7/49 296 mg/kg-d = 7/49 589 mg/kg-d = 18/50 NTP, 1997, 2 yr, rat (M), pancreatic adenoma and carcinoma: 0 mg/kg-d= 3/50 120 mg/kg-d= 2/50 240 mg/kg-d= 3/50 480 mg/kg-d= 11/50	0.00067	1.5
DEHP	Increased liver tumors in rats and mice (U.S. EPA, 1987a)	Negative	U.S. EPA, 1987a, 2 yr, mouse (M), hepatocellular carcinoma and adenoma: 0 mg/kg-d = 14/50 32 mg/kg-d = 25/48 65 mg/kg-d = 29/50	0.014 (EPA IRIS, U.S. EPA, 1987a)	0.071
Dibutyl phthalate	No data	Positive (Positive in Ames)	NA	NA	NA

Compound	Evidence	Genotoxicity Assumption*	Availability of Tumor Incidence Data	Cancer SF $(mg/kg\text{-}d)^{-1}$	Comparison Value Based on CSF (µg/kg-d)**
17ß-Estradiol	Increased mammary gland tumors in mice (CPDB, 2007i)	Negative	CPDB, 2007i, 1 yr, mouse (F), mammary tumors: 0 mg/kg-d = 2/43 0.013 mg/kg-d = 1/34 0.13 mg/kg-d = 1/34 0.65 mg/kg-d = 7/45	39 (CA OEHHA, 1992, cancer potency factor)	0.000026
Estrone	May stimulate mammary gland tumors that have already developed; secondary sources (CPDB, U.S. EPA, etc.) have not found studies that are appropriate for derivation of cancer slope factors. Listed as a Proposition 65 carcinogen in California, but CA EPA has not derived a cancer slope factor.	Negative	NA	NA	NA
Ethynylestradiol	Increased liver tumors in rats; listed as a Proposition 65 carcinogen in California. NTP has completed a study that currently is in review (preliminary data indicate "equivocal" evidence of carcinogenicity).	Negative	CPDB, 2007d, 1 yr, rat (F), liver tumors: 0 mg/kg-d = 0/8 0.429 mg/kg-d = 4/13	0.19	0.0053

Compound	Evidence	Genotoxicity Assumption*	Availability of Tumor Incidence Data	Cancer SF $(mg/kg\text{-}d)^{-1}$	Comparison Value Based on CSF (µg/kg-d)**
Lindane	Increased liver tumors in mice (CPDB, 2007f; CA OEHHA, 2005)	Negative	CPDB, 2007f, 26 mo, mouse (M), liver tumors: 0 mg/kg-d= 11/45 48 mg/kg-d= 27/29	1.1 (CA OEHHA, 2005 potency factor)	0.00091
Linuron	Increased testicular hyperplasia and adenomas in male rats (U.S. EPA, 1987b)	Negative	Not located	NA	NA
Methoxychlor	No evidence of carcinogenicity in rats or mice (CPDB, 2007e)	Positive (Negative in Ames)	NA	NA	NA
Nonylphenol	No data	Negative	NA	NA	NA
4-tert-Octylphenol	No data	Positive (Positive in Ames)	NA	NA	NA
Vinclozolin	Increased testicular Leydig cell tumors and prostate adenomas in male rats and benign ovarian sex cord tumors, uterine carcinomas, and adrenal cortical tumors in female rats (IPCS, 1995)	Negative	Not located	NA	NA

Note. NA = not applicable.

*Genotoxicity test results are summarized in Appendix E.

**Calculated assuming an acceptable lifetime excess cancer risk of 1 in 1 million and that a person is exposed to the chemical at this dose daily for a lifetime; comparison value = 10^{-6} x 1000 µg/mg/ SF.

No tumor incidence data were available for methotrexate with which to develop a cancer slope factor and evidence suggests it is genotoxic; consequently, use of a TTC would be recommended. However, because structural alerts (e.g., polycyclic amines) suggest greater potential for carcinogenic potency, a chemical-specific toxicological investigation would be appropriate for this compound. Tumor incidence data were identified for ifosfamide and tamoxifen; consequently, development of comparison values based on the cancer slope factors is recommended. However, tamoxifen is also anti-estrogenic, suggesting that more careful evaluation of its toxicity is warranted. In general, the workshop panel recommended that chemotherapeutic agents be subject to compound-specific evaluation of their potential toxicity.

4.4 DERIVATION OF COMPARISON VALUES USING THE LOWEST THERAPEUTIC DOSE APPROACH

Table 4.3 lists the lowest therapeutic doses for case study PPCPs and for EDCs with therapeutic applications, and the UFs applied to these doses to calculate comparison values. In evaluating the case study compounds, the project team applied uncertainty factors in a manner consistent with the approach recommended by U.S. EPA (2002a; see Table 3.1), with consideration of parameters applied by Schwab et al. (2005).

The project team applied the following UFs:

- A pharmacologic effect in a nontarget population was considered to be a minimally toxic dose in humans; therefore, therapeutic doses were considered to be surrogate LOAELs and a minimum 10-fold uncertainty factor was applied to every therapeutic dose.
- A factor for intra-individual susceptibility of 10 was applied to account for possible sensitivities among exposed populations, consistent with U.S. EPA (2002a) guidance for developing RfDs.
- Although therapeutic doses can be taken chronically, it was assumed that subchronic exposure can produce the therapeutic effect. Therefore, a 10-fold uncertainty factor to extrapolate to a chronic dose was assumed to be appropriate, consistent with U.S. EPA (2002a).
- For new therapeutic agents, significant testing is required prior to marketing to evaluate the potential toxicity of therapeutic agents. For these compounds, a UF for database limitations may not be necessary. However, for some older compounds, less extensive toxicity testing may have been conducted. A UF for database limitations of 3 was considered appropriate for these compounds.

Based on these factors, a composite UF of 1000 to 3000 applied to each therapeutic dose was assumed to be reasonable.

The panel discussed the manner in which UFs were applied to therapeutic doses for case study compounds, and reached the same conclusion that was reached for developing screening values from LOAELs: A default cumulative UF of 3000 was proposed when the point of departure is a therapeutic dose. As discussed in Section 4.2, this UF is supported by the U.S. EPA's analysis of the 216 compounds with U.S. EPA RfDs, in which they concluded that an RfD could be approximated by dividing the NOAEL by 1000 or the LOAEL by 3000 (U.S. EPA, 2008b).

The panel also recommended that an additional UF of 10 be applied to the compound if it is either a nongenotoxic carcinogen or an EDC.

Most putative EDCs are not pharmaceuticals and, therefore, will not have a therapeutic dose. However, certain pharmaceuticals are used specifically because they are endocrine-active agents. For example, Ethynylestradiol (EE2) is used as a pharmaceutical in oral contraceptive formulations that are intentionally administered to disrupt reproductive endocrine function and, thus, can be considered to be an EDC in humans. EE2 is administered for this purpose only to women of child-bearing age who wish to avoid pregnancy. Obviously, the desired therapeutic effect is one that would not be relevant or desirable to non-target groups (men, pregnant women, women who do not desire contraception, post-menopausal women, and children and infants of both sexes). Also, numerous side effects have been documented in women receiving recommended therapeutic doses.

Adverse effects have been reported at or near therapeutic dose levels for some of the case study compounds. For example, phenytoin (an anti-convulsant used in the treatment of epilepsy) has a lowest therapeutic dose for adults of 300 mg/day, equivalent to a daily dose of 4.3 mg/kg-d, assuming exposure to a 70 kg adult. Phenytoin is not recommended for use during pregnancy (it is in FDA Pregnancy Category D), and data from humans (Hernandez-Diaz et al., 2000) suggest a potential for increased congenital defects in offspring of mothers who took phenytoin during pregnancy (i.e., at the therapeutic dose). A human equivalent dose (HED; extrapolated using differences in body surface area between test animals and humans) of 2.0 mg/kg-d caused developmental effects in mouse pups (reduced brain size and weight; Ohmori et al., 1997; Hatta et al., 1999). No effect was seen at a HED of 1.4 mg/kg-d.

However, if one divides the therapeutic dose for phenytoin by a composite UF of 3000, the resulting comparison value is 0.0014 mg/kg-d. This dose would appear to be health protective for noncarcinogenic effects based on available data. In addition, a HED of 4.1 mg/kg-d caused cancer in mice (NTP, 1993). Using a linear extrapolation model to calculate a cancer slope factor and assuming an acceptable lifetime excess cancer risk of 1 in 1 million, the resulting comparison value would be 0.00083 mg/kg-d; this level would be protective of all other effects.

Examination of the data in Appendix F shows that some adverse effects have been observed in animal studies at doses below the therapeutic dose. However, Table 4.6 shows that for most of the pharmaceuticals, the comparison level derived using the lowest therapeutic dose divided by a UF of 3000 is approximately the same as or lower than that derived from the NOAEL or LOAEL divided by a UF of 1000 or 3000. This suggests that using the therapeutic dose as the basis for a screening level will produce a health protective value. Two compounds produced clearly lower comparison levels using the NOAEL/ LOAEL: ifosfamide and tamoxifen. Because ifosfamide shows evidence of genotoxic carcinogenicity, the screening level for this compound would most appropriately be derived from data on its carcinogenicity (in this case, due to lack of tumor incidence data, a comparison value was derived from a TTC). Tamoxifen is a nongenotoxic carcinogen; the screening level for this compound would be most appropriately derived using the NOAEL/LOAEL using the default UF and an additional UF of 10. These comparisons demonstrate the utility of deriving comparison levels for a given compound using several methods, and selecting the lowest of these values as the screening level. This approach is the basis for the decision tree presented in Section 5.1.

Table 4.3. Lowest Therapeutic Doses for Case Study Compounds and Corresponding Comparison Values Assuming a UF of 3,000

Compound	Lowest Therapeutic Dose (mg/d)	Treatment Endpoint	Age Group and Assumed Body Weight (kg)	Minimum Therapeutic Dose (µg/kg-d)	Pregnancy Category & Adverse Human Effects at Therapeutic Dose	Comparison value (µg/kg-d)
Alendronate	5	Glucocorticoid-induced osteoporosis	Adult, 70	71	C	0.0024[a]
Atenolol	25	Hypertension	Adult, 70	360	D (low birth weight)	0.012 [a]
Atorvastatin	10	Hyper-cholesterolemia	Child, 30	300	X (risk of congenital abnormalities)	0.010 [a]
Carbamazepine	10	Epilepsy	Child <6, 10	1,000	D (developmental delays, congenital abnormalities); severe and sometimes fatal dermatologic reactions	0.33
Desloratadine	2.5	Relief of nasal and nonnasal symptoms of seasonal and perennial allergic rhinitis	Adult (w/ renal/hepatic impairment), 70	36	C	0.0012 [a]
Diazepam	2	Anxiety	Adult geriatric, 70	29	D (congenital abnormalities, respiratory difficulties)	0.0097
Diclofenac	100	Arthritis	Adult, 70	1,400	C; risk of serious cardiovascular events	0.47
Doxycycline	100	Malaria prophylaxis	Adult, 70	1,400	D (congenital abnormalities)	0.47
Enalapril	2.5	Hypertension (w/ renal impairment)	Adult, 70	36	C, D (congenital abnormalities)	0.012
Fluconazole	50	Candida urinary tract infection	Adult, 70	710	C (unconfirmed congenital abnormalities)	0.024 [a]

Compound	Lowest Therapeutic Dose (mg/d)	Treatment Endpoint	Age Group and Assumed Body Weight (kg)	Minimum Therapeutic Dose (µg/kg-d)	Pregnancy Category & Adverse Human Effects at Therapeutic Dose	Comparison value (µg/kg-d)
Fluoxetine	10	Depression, obsessive compulsive disorder	Pediatric (children & adolescents), 30	330	C (shortened gestation, reduced birth weight, poor neonatal adaptation)	0.11
Furosemide	20	Edema	Adult, 70	290	C	0.097
Gemfibrozil	1200	Lipid regulation	Adult, 70	17,000	C; gall bladder disease	0.57 [a]
HHCB (Galaxolide)	NA	NA	NA	NA	NA	NA
Ifosfamide	2400 (i.v.)	Germ cell testicular cancer	Adult, 70	34,000	D	11
Iopamidol/ iopromide	NA	NA	NA	NA	B	NA
Lansoprazole	15	Duodenal ulcer, GERD	Adult, 70	210	B	0.0070 [a]
Meprobamate	200	Anxiety	Child 6-12, 30	7,000	D (congenital abnormalities)	2.3
Methotrexate	0.7	Cutaneous T cell lymphoma	Adult, 70	10	X (abortifacient, teratogen); cancer	0.0033
Mirtazapine	15	Major depressive disorder	Adult, 70	210	C (spontaneous abortions)	0.0070 [a]
Naproxen	125	Juvenile arthritis	Child, 30	4,000	B (premature closure of ductus arteriosus)	1.3
Phenytoin	300	Epilepsy	Adult, 70	4,300	D (congenital abnormalities)	1.4
Risperidone	1.8	Schizophrenia	Adult, 70	26	C (tardive dyskinesia)	0.00087 [a]
Simvastatin	10	Hypercholesterol-emia	Child 10-17, 50	200	X (congenital abnormalities); myopathy; renal failure	0.0067 [a]

Compound	Lowest Therapeutic Dose (mg/d)	Treatment Endpoint	Age Group and Assumed Body Weight (kg)	Minimum Therapeutic Dose (µg/kg-d)	Pregnancy Category & Adverse Human Effects at Therapeutic Dose	Comparison value (µg/kg-d)
Sulfamethoxazole	400	Urinary tract infection	Child (>2 mo.), 30	13,000	C	4.3
Tamoxifen	20	Breast cancer	Adult, 70	290	D (expected fetal harm); cancer; pulmonary embolism; ocular disturbances	0.0097 [a]
Triclosan	NA	NA	NA	NA	NA	NA
Trimethoprim	80	Urinary tract infection	Pediatric, 10	8,000	C	2.7
EDCs						
17ß-Estradiol	0.5	Vulvar atrophy, atrophic vaginitis, ovary problems, symptoms of menopause	Adult, 70	7.1	X; Increased risk of myocardial infarction and stroke, endometrial cancer, gall bladder disease	0.00024 [b]
Estrone	0.014 (injected)	Ovary problems (female hypogonadism or failure or removal of both ovaries)	Adult, 70	0.20	X; Increased risk of myocardial infarction and stroke, endometrial cancer, breast cancer, and dementia	0.0000067 [b]
Ethynylestradiol	0.02	Symptoms of menopause	Adult, 70	0.29	X; Increased risk of thrombo-embolism, myocardial infarction and stroke, endometrial cancer, breast cancer	0.0000097 [b]

[a]An additional UF of 10 was applied because the compound shows evidence of being a nongenotoxic carcinogen (see Table 4.2).

[b]An additional UF of 10 was applied because the compound is a purported EDC.

4.5 DERIVATION OF COMPARISON VALUES USING THE THRESHOLD OF TOXICOLOGIC CONCERN (TTC) APPROACH

Table 4.4 lists relevant information for each case study compound compiled by the project team to support assignment of TTCs according to the schemes of Cheeseman et al. (1999) and Kroes et al. (2004). These include structural alerts identified as presenting genotoxicity potential by Cheeseman et al. (1999) and Kroes et al. (2004); the structural class assigned according to the decision tree approach outlined by Cramer et al. (1978) and applied to selecting the appropriate TTC under Kroes et al. (2004); the "genotoxicity assumption" based on results of genotoxicity tests applied to selecting appropriate TTCs under Cheeseman et al. (1999) and Kroes et al. (2004); and minimum oral LD_{50}s applied to selecting appropriate TTCs under Cheeseman et al. (1999).

Of note, the application of TTCs to pharmaceuticals is largely a hypothetical exercise, in that none of the TTC schemes evaluated explicitly considered in their derivation deliberately biologically active compounds such as pharmaceuticals. As such, the appropriateness of application of the TTCs to pharmaceuticals is highly uncertain. Further, both Cheeseman et al. (1999) and Kroes et al. (2004) caution against applying TTCs to EDCs, and thus no TTCs are assigned to any of the case study EDCs.

The genotoxicity assumptions listed in Table 4.4 are based on data gathered for the case study compounds for four different in vitro genotoxicity test types (the Ames test, mouse lymphoma assay (MLA), the in vitro micronucleus assay (MN), and the in vitro chromosomal aberration assay (CA)). These data are summarized in Appendix E. For purposes of determining genotoxic potential for application of appropriate TTCs, the following was assumed with regard to in vitro genotoxicity test results for the case study compounds:

- Case study compounds that tested negative in all tests for which data were available were assumed to be nongenotoxic (negative), and
- Case study compounds that tested positive in one or more tests for which data were available were assumed to be genotoxic (positive).

However, caution is recommended with regard to interpreting negative genotoxicity tests as indicative of noncarcinogenicity. Of the 20 PPCPs predicted to be nongenotoxic based on in vitro genotoxicity tests, 11 (alendronate, atenolol, atorvastatin, desloratadine, fluconazole, gemfibrozil, lansoprazole, mirtazapine, risperidone, simvastatin, and tamoxifen) showed positive evidence of carcinogenicity in animal bioassays (Table 4.2). These compounds may be carcinogenic via nongenotoxic mechanisms (e.g., liver enzyme induction, peroxisome proliferation, hormonal carcinogens). Of the eight PPCPs predicted to be genotoxic based on in vitro genotoxicity tests, five also showed positive evidence of carcinogenicity in animal bioassays (i.e., were genotoxic carcinogens; carbamazepine, doxycycline, furosemide, ifosfamide, and phenytoin) and two had no identified carcinogenicity data (diazepam and meprobamate). One compound—methotrexate—tested positive in in vitro genotoxicity tests but was negative in animal carcinogenicity assays. However, there are some case reports of subsequent neoplasms in patients following treatment with this compound.

Table 4.4. Structural Alerts or Classes, Genotoxicity Assumptions, and Minimum Oral LD_{50} Data for Rodents for Case Study Compounds and Threshold of Toxicologic Concern (TTC)-Based Comparison Values

Compound	CAS No.	Structural Alert or Cramer Class as Described by Cheeseman et al. (1999)/Kroes et al. (2004)[a]	Genotoxicity Assumption[b]	Minimum Oral LD_{50} (mg/kg)	TTC-Based Comparison Value (µg/kg-d)	
					Based on Scheme of Cheeseman et al. (1999)	Based on Scheme of Kroes et al. (2004)
PPCPs						
Alendronate	66376-36-1	NA/ III	Negative	27,800 (mouse)	0.43-0.64	1.3
Atenolol	29122-68-7	NA/ III	Negative	2,000 (mouse)	0.43-0.64	1.3
Atorvastatin	134523-00-5	NA/ III	Negative	NA	0.21	1.3
Carbamazepine	298-46-4	Polycyclic amine/ III	Positive (Negative in Ames)	529 (mouse)	NA (<0.021)	0.0021
Desloratadine	100643-71-8	Polycyclic amine/ III	Negative	NA	NA (<0.021)	1.3
Diazepam	439-14-5	Polycyclic amine/ III	Positive (Positive in Ames)	48 (mouse)	NA (<0.021)	0.0021
Diclofenac	15307-86-5	Polycyclic amine/ III	Negative	62.5 (rat)	NA (<0.021)	1.3
Doxycycline	564-25-0	NA/ III	Positive (No Ames test)	1,870 (mouse)	NA (<0.021)	0.0021
Enalapril	75847-73-3	NA/ III	Negative	2,000 (mouse)	0.43-0.64	1.3
Fluconazole	86386-73-4	Triazine/ III	Negative	1,271 (rat)	NA (<0.021)	1.3
Fluoxetine	54910-89-3	NA/ III	Negative	464 (mouse)	0.21	1.3

Compound	CAS No.	Structural Alert or Cramer Class as Described by Cheeseman et al. (1999)/Kroes et al. (2004)[a]	Genotoxicity Assumption[b]	Minimum Oral LD_{50} (mg/kg)	TTC-Based Comparison Value (µg/kg-d)	
					Based on Scheme of Cheeseman et al. (1999)	Based on Scheme of Kroes et al. (2004)
Furosemide	54-31-9	NA/ III	Positive (Negative in Ames)	2,000 (mouse)	NA (<0.021)	0.0021
Gemfibrozil	25812-30-0	NA/ II	Negative	1,414 (rat)	0.43-0.64	7.7
HHCB	1222-05-5	NA/ III	Negative	NA	0.21	1.3
Ifosfamide	3778-73-2	NA/ III	Positive (Positive in Ames)	143 (rat)	NA (<0.021)	0.0021
Iopamidol/ iopromide	73334-07-3	NA/ III	Negative	13,800 (i.v., rat)	0.43-0.64	1.3
Lansoprazole	103577-45-3	Polycyclic amine/ III	Negative	>5,000 (rat & mouse)	NA (<0.021)	1.3
Meprobamate	57-53-4	NA/ III	Positive (Negative in Ames)	750 (mouse)	NA (<0.021)	0.0021
Methotrexate	59-05-2	Polycyclic amine/ III	Positive	135 (rat)	NA (<0.021)	0.0021
Mirtazapine	61337-67-5	NA/ III	Negative	NA	0.21	1.3
Naproxen	22204-53-1	NA/ III	Negative	500 (rat)	0.21	1.3
Phenytoin	57-41-0	Polycyclic amine/ III	Positive (Positive in Ames)	150 (mouse)	NA (<0.021)	0.0021
Risperidone	106266-06-2	NA/ III	Negative	56.6 (rat)	0.21	1.3
Simvastatin	79902-63-9	NA/ III	Negative	3,000 (mouse)	0.43-0.64	1.3

Compound	CAS No.	Structural Alert or Cramer Class as Described by Cheeseman et al. (1999)/Kroes et al. (2004)[a]	Genotoxicity Assumption[b]	Minimum Oral LD_{50} (mg/kg)	TTC-Based Comparison Value (µg/kg-d)	
					Based on Scheme of Cheeseman et al. (1999)	Based on Scheme of Kroes et al. (2004)
Sulfamethoxazole	723-46-6	Polycyclic amine/ III	Negative	2,300 (mouse)	NA (<0.021)	1.3
Tamoxifen	10540-29-1	EDC/ III	Negative	2,150 (mouse)	NA (<0.021)	NA
Triclosan	3380-34-5	NA/ III	Negative	5,000 (rat)	0.43-0.64	1.3
Trimethoprim	738-70-5	Polycyclic amine/ III	Negative	2,764 (mouse)	NA (<0.021)	1.3
EDCs						
Atrazine	1912-24-9	EDC, Triazine/ III	Negative	850 (mouse)	NA (<0.021)	NA
Bisphenol A	80-05-7	EDC/ III	Negative	2,500 (mouse)	NA (<0.021)	NA
Butylbenzyl phthalate	85-68-7	EDC/ III	Negative	13,500 (rat)	NA (<0.021)	NA
DEHP	117-81-7	EDC/ I	Negative	>25,000 (rat)	NA (<0.021)	NA
Dibutyl phthalate	84-74-2	EDC/ I	Positive (Positive in Ames)	8,000 (rat)	NA (<0.021)	NA
17ß-Estradiol	50-28-2	EDC/ Steroid	Negative	NA	NA (<0.021)	NA (<0.0021)
Estrone	53-16-7	EDC/ Steroid	Negative	NA	NA (<0.021)	NA (<0.0021)
Ethynylestradiol	319-85-7	EDC/ Steroid	Negative	1,500 (mouse)	NA (<0.021)	NA (<0.0021)

Compound	CAS No.	Structural Alert or Cramer Class as Described by Cheeseman et al. (1999)/Kroes et al. (2004)[a]	Genotoxicity Assumption[b]	Minimum Oral LD_{50} (mg/kg)	TTC-Based Comparison Value (µg/kg-d)	
					Based on Scheme of Cheeseman et al. (1999)	Based on Scheme of Kroes et al. (2004)
Lindane (BHC-gamma)	58-89-9	EDC/ III	Negative	44 (mouse)	NA (<0.021)	NA
Linuron	330-55-2	EDC/ III	Negative	1,146 (rat)	NA (<0.021)	NA
Methoxychlor	72-43-5	EDC/ III	Positive (Negative in Ames)	2,900 (mouse)	NA (<0.021)	NA
Nonylphenol	104-40-5	EDC/ II	Negative	1,600 (rat)	NA (<0.021)	NA
Octylphenol (OP)	1806-26-4	EDC/ II	Positive (Positive in Ames)	3,210 (mouse)	NA (<0.021)	NA
Vinclozolin	50471-44-8	EDC/ III	Negative	>10,000 (rats)	NA (<0.021)	NA

[a]Roman numeral indicates Cramer structural class (Cramer et al., 1978). [b]Genotoxicity test results are summarized in Appendix E.

Note. NA = not available. With regard to EDCs, both Cheeseman et al. (1999) and Kroes et al. (2004) indicate that available data are insufficient to propose TTCs for compounds of this type.

As shown in Table 4.4, TTCs assigned according to the Cheeseman et al. (1999) scheme were generally lower than those assigned according to the Kroes et al. (2004) scheme.

In general, because of the uncertainties inherent in the application of the TTC approach, the panel recommended that use of this approach should be confined to compounds for which available toxicity data are limited. Because of the significant amount of data available for most pharmaceuticals, application of the TTC approach to most pharmaceuticals would therefore not be appropriate.

The panel discussed a number of concerns with specific TTC schemes. Specifically:

- Lack of a strong background in organic chemistry and the chemistry of natural products could easily lead to misclassification of compounds based on structure.However, implementation of the ToxTree open source software makes identifying Cramer classes a simple process.
- The Cramer classification and the TTC schemes did not use pharmaceuticals in the learning set for derivation of the TTC procedure. Consequently, the applicability of these approaches to pharmaceuticals, which are designed to be biologically active, has not been verified.
- The designation of "nongenotoxic" should be based on negative results from a defined set of studies.
- The Kroes et al. (2004) approach used the TD_{50} as a point of departure for linear extrapolation, a parameter felt to be rather high on the dose–response curve, therefore, yielding a tendency to result in a lower slope factor than a point of departure at the low end of the dose-response curve. In addition, a panelist suggested that use of the LD_{50} in deriving comparison levels (e.g., in the Cheeseman et al., 1999, approach) is not recommended, as these data are generally of low quality for predicting chronic toxicity.
- The Dolan et al. (2005) approach evaluated non-pharmacologically active ingredients of pharmaceuticals but did not consider the potential for reproductive toxicity. During the development of the original health effects data requirements for NSF/ANSI Standard 60, Drinking Water Treatment Chemicals, the 1, 10, and 100 µg/day doses were suggested as thresholds for required doses in toxicity studies for different types of chemicals. However, a study was conducted using the FDA toxicity data summaries on food additives for chemicals found in the EPA drinking water database, and the100 µg/day threshold was lowered to 50 µg/day because the FDA data indicated a number of chemicals had reproductive effects in the 50 to 100 µg/day range.
- Based on the Australian experience in developing guidelines (Australia EPHC, 2008), values obtained using the Kroes et al. (2004) approach, which uses the Cramer classification system, required adjustment to arrive at guidelines that are consistent with those developed by more conventional risk assessment methodologies. They concluded that a factor of 15 should be applied to values determined using the Kroes et al. (2004) approach. In addition, the Australia EPHC utilized a default for genotoxic chemicals of 0.15 µg/person/day, representing an adoption of a recommendation by the European branch of the International Life Sciences Institute (i.e., as reported in Kroes et al., 2004).

Overall, the panel recommended that the TTC approach should be applied only when no NOAEL/LOAEL data or lowest therapeutic doses are available, or when the compound

shows evidence of being a genotoxic carcinogen and sufficient tumor incidence data are not available to calculate a cancer slope factor.

The panel agreed that, in general, the Cheeseman et al. (1999) TTC scheme should be applied, because it is more conservative than the other approaches discussed at the meeting, avoids the use of the complicated Cramer structural classes, and includes some specific compound information. The panel also noted that although the Kroes et al. (2004) approach excludes metals, most metals in water are addressed with standards, and good databases are generally available for establishing MCLs for those that are not regulated.

4.6 GAYLOR AND GOLD (1998) VIRTUALLY SAFE DOSE APPROACH FOR CARCINOGENS

Table 4.5 lists relevant information for each case study compound to support development of comparison values using the Gaylor and Gold (1998) "virtually safe dose" (VSD) approach for carcinogens, including the maximum tolerated dose from 90-day studies in rodents or the maximum dose from cancer studies for different species. For genotoxic carcinogens, the lowest identified maximum tolerated dose for each compound was divided by a factor of 740,000 to derive a VSD assumed to correspond to a cancer risk of 1 in 1 million. For nongenotoxic carcinogens, the lowest maximum tolerated dose for each compound was divided by a factor of 7000 (7 to extrapolate to a LTD_{10} combined with a composite UF of 1000).

Overall, four of the comparison values calculated using this approach assumed genotoxic carcinogenicity (carbamazepine, furosemide, ifosfamide, and phenytoin) and the remaining 19 assumed nongenotoxic carcinogenicity (see Table 4.6). Three of the four genotoxic carcinogens also had comparison values based on cancer slope factors; for these compounds, the comparison values calculated using the VSD approach were lower, but only by 2- to 17-fold. Of the 19 nongenotoxic carcinogens, 8 also had comparison values derived from cancer slope factors; in all of these cases, the comparison value based on the VSD approach was higher, as would be expected, and in some cases substantially higher. However, deriving slope factors for nongenotoxic carcinogens is not recommended.

The panel recommended that if the compound is a genotoxic carcinogen and no tumor incidence data are identified, a comparison value should be derived using the Gaylor and Gold (1998) VSD approach. Then this value should be compared to the appropriate TTC, and the lower of the two values selected. For compounds that are nongenotoxic carcinogens, an additional UF of 10 should be applied to the minimum therapeutic dose or the NOAEL/LOAEL.

Table 4.5. Comparison Values Calculated for Case Study Compounds With Evidence of Carcinogenicity, Based on the Gaylor and Gold (1998) Virtually Safe Dose Approach

Compound	Genotoxicity Assumption [a]	Maximum Tolerated Doses in Animal Studies (mg/kg-d)	Source of Maximum Tolerated Doses	Comparison Value (µg/kg-d) [b]
PPCPs				
Alendronate	Negative	5 (mouse, F) 10 (mouse, M) 3.75 (rat, M)	RxList, 2008d, highest doses from cancer studies	0.54
Atenolol	Negative	1,500 (rat)	RxList, 2008e, highest doses from cancer studies	210
Atorvastatin	Negative	400 (mouse) 100 (rat)	Pfizer, 2003, highest doses from cancer studies	14
Carbamazepine	Positive	250 (rat)	Novartis, 2000, highest doses from cancer studies	0.34
Desloratadine	Negative	96 (mouse, F) 48 (mouse, M) 3 (rat, F) 30 (rat, M)	Schering Corp, 2004, 90 d studies	0.43
Fluconazole	Negative	10 (mouse & rat)	CPDB, 2007a, highest doses from cancer studies	1.4
Furosemide	Positive	180 (mouse, F) 166 (mouse, M) 34.5 (rat, F) 27.7 (rat, M)	NTP, 1989, 90 d studies	0.037
Gemfibrozil	Negative	300 (mouse & rat)	Fitzgerald, 1981, highest doses from cancer studies	43

Compound	Genotoxicity Assumption [a]	Maximum Tolerated Doses in Animal Studies (mg/kg-d)	Source of Maximum Tolerated Doses	Comparison Value (µg/kg-d) [b]
Ifosfamide	Positive	5.6 (mouse) 3.3 (rat)	CPDB, 2007g, highest doses from cancer studies	0.0045
Lansoprazole	Negative	600 (mouse) 150 (rat)	TAP, 2004, highest doses from cancer studies	21
Mirtazapine	Negative	200 (mouse) 60 (rat)	Drugs.com, 2007c, highest doses from cancer studies	8.6
Phenytoin	Positive	78 (mouse, F) 36 (mouse, M) 120 (rat, F) 96 (rat, M)	NTP, 1993, highest doses from cancer studies	0.049
Risperidone	Negative	10 (mouse & rat)	Drugs.com, 2007a, highest doses from cancer studies	1.4
Simvastatin	Negative	400 (mouse) 100 (rat)	Drugs.com, 2007b, highest doses from cancer studies	14
Tamoxifen	Negative	50 (mouse, F&M) 45 (rat, F) 35 (rat, M)	CPDB, 2007h, highest doses from cancer studies	5.0
EDCs				
Butylbenzyl phthalate	Negative	1,530 (mouse, F) 1,410 (mouse, M) 1,200 (rat, F) 480 (rat, M)	CPDB, 2007c, highest doses from cancer studies	69

Compound	Genotoxicity Assumption [a]	Maximum Tolerated Doses in Animal Studies (mg/kg-d)	Source of Maximum Tolerated Doses	Comparison Value (µg/kg-d) [b]
DEHP	Negative	773 (mouse, F) 713 (mouse, M) 619 (rat, F) 800 (rat, M)	CPDB, 2007d, highest doses from cancer studies	88
17ß-Estradiol	Negative	0.650 (mouse, F) 0.650 (mouse, F) 0.650 (mouse, F)	CPDB, 2007i, highest doses from cancer studies	0.093
Estrone	Negative	NA	NA	NA
Ethynylestradiol	Negative	0.429 (rat, F)	CPDB, 2007i, highest doses from cancer studies	0.061
Lindane	Negative	52.0 (mouse, F) 17.0 (mouse, M) 9.8 (rat, F) 13.6 (rat, M)	CPDB, 2007f, highest doses from cancer studies	1.4
Linuron	Negative	31 (rat)	U.S.EPA, 1987b, highest doses from cancer studies	4.4
Vinclozolin	Negative	225 (rat)	IPCS, 1995, highest doses from cancer studies	32

[a]Genotoxicity test results are summarized in Appendix E.

[b]Calculated by dividing the lowest maximum tolerated dose by a factor of 740,000 for genotoxic carcinogens or 7,000 for nongenotoxic carcinogens, and multiplying by a conversion factor of 1000 (µg/mg).

Table 4.6. Summary of Comparison Values (µg/kg-d) Developed Using Different Methods*

Compound	Category	Mode of Action	Based on NOAEL/ LOAEL and Default UF	Based on Lowest Therapeutic Dose and Default UF	TTC-based		Based on CSF	Based on VSD for Carcin -ogens	Existing Toxicity Criterion
					Using Scheme of Cheeseman et al. (1999)	Using Scheme of Kroes et al. (2004)			
PPCPs									
Alendronate	Drug	Bisphonate inhibitor of bone resorption (nongenotoxic carcinogen)	0.017**	0.0024**	0.43-0.64	1.3	NA	0.54	NA
Atenolol	Drug	Beta-blocker (nongenotoxic carcinogen)	0.027**	0.012**	0.43-0.64	1.3	NA	210	NA
Atorvastatin	Drug	Antilipidemic (nongenotoxic carcinogen)	0.67**	0.010**	0.21	1.3	NA	14	NA
Carbamazepine	Drug	Anticonvulsant and mood stabilizer (genotoxic carcinogen)	1.0	0.33	NA (<0.021)	0.0021	NA	0.34	NA
Desloratadine	Drug	Antihistamine (nongenotoxic carcinogen)	0.30**	0.0012**	NA (<0.021)	1.3	NA	0.43	NA
Diazepam	Drug	Benzodiazapine antianxiety	0.33	0.0097	NA (<0.021)	0.0021	NA	NA	NA
Diclofenac	Drug	NSAID	4.0	0.47	NA (<0.021)	1.3	NA	NA	NA
Doxycycline	Drug	Tetracycline antibiotic	1.0	0.47	NA (<0.021)	0.0021	NA	NA	NA
Enalapril	Drug	ACE inhibitor	0.023	0.012	0.43-0.64	1.3	NA	NA	NA

Compound	Category	Mode of Action	Based on NOAEL/ LOAEL and Default UF	Based on Lowest Therapeutic Dose and Default UF	TTC-based		Based on CSF	Based on VSD for Carcin -ogens	Existing Toxicity Criterion
					Using Scheme of Cheeseman et al. (1999)	Using Scheme of Kroes et al. (2004)			
Fluconazole	Drug	Antifungal (nongenotoxic carcinogen)	0.17**	0.024**	NA (<0.021)	1.3	NA***	1.4	NA
Fluoxetine	Drug	SSRI	0.097	0.11	0.21	1.3	NA	NA	NA
Furosemide	Drug	Loop diuretic (genotoxic carcinogen)	8.3	0.097	NA (<0.021)	0.0021	0.12	0.037	NA
Gemfibrozil	Drug	Antilipidemic (nongenotoxic carcinogen)	3.1**	0.57**	0.43-0.64	7.7	NA***	43	NA
HHCB	Musk	Musk	50	NA	0.21	1.3	NA	NA	NA
Ifosfamide	Drug	Chemotherapy agent (genotoxic carcinogen)	1.0	11	NA (<0.021)	0.0021	0.010	0.0045	NA
Iopamidol/ iopromide	X-ray contrast media	X-ray contrast media	50	NA	0.43-0.64	1.3	NA	NA	NA
Lansoprazole	Drug	Antacid/ proton pump inhibitor (nongenotoxic carcinogen)	0.11**	0.0070**	NA (<0.021)	1.3	NA	21	NA
Meprobamate	Drug	Antianxiety agent	75	2.3	NA (<0.021)	0.0021	NA	NA	NA
Methotrexate	Drug	Chemotherapy agent (potential genotoxic carcinogen)	0.0033	0.0033	NA (<0.021)	0.0021	NA	NA	NA

Compound	Category	Mode of Action	Based on NOAEL/ LOAEL and Default UF	Based on Lowest Therapeutic Dose and Default UF	TTC-based		Based on CSF	Based on VSD for Carcin -ogens	Existing Toxicity Criterion
					Using Scheme of Cheeseman et al. (1999)	Using Scheme of Kroes et al. (2004)			
Mirtazapine	Drug	Tetracyclic antidepressant (nongenotoxic carcinogen)	0.0070**	0.0070**	0.21	1.3	NA	8.6	NA
Naproxen	Drug	NSAID	20	1.3	0.21	1.3	NA	NA	NA
Phenytoin	Drug	Anti-convulsant (genotoxic carcinogen)	1.4	1.4	NA (<0.021)	0.0021	0.83	0.049	NA
Risperidone	Drug	Antipsychotic (nongenotoxic carcinogen)	0.0053**	0.00087**	0.21	1.3	NA	1.4	NA
Simvastatin	Drug	Antilipidemic (nongenotoxic carcinogen)	0.0067**	0.0067**	0.43-0.64	1.3	NA	14	NA
Sulfamethoxazole	Drug	Antibacterial	510	4.3	NA (<0.021)	1.3	NA	NA	NA
Tamoxifen	Drug	Chemotherapy agent (nongenotoxic carcinogen, estrogen agonist)	0.000012**	0.0097**	NA (<0.021)	NA	NA***	5.0	NA
Triclosan	Antibacterial	Antibacterial	3.0	NA	0.43-0.64	1.3	NA	NA	NA
Trimethoprim	Drug	Antiinfective	70	2.7	NA (<0.021)	1.3	NA	NA	NA
EDCs									

Compound	Category	Mode of Action	Based on NOAEL/ LOAEL and Default UF	Based on Lowest Therapeutic Dose and Default UF	TTC-based		Based on CSF	Based on VSD for Carcin -ogens	Existing Toxicity Criterion
					Using Scheme of Cheeseman et al. (1999)	Using Scheme of Kroes et al. (2004)			
Atrazine	Herbicide	Neuro-endocrine (nongenotoxic animal carcinogen; not likely carcinogenic in humans)	0.18**	NA	NA (<0.021)	NA	NA	NA	35 (noncancer, EPA IRIS); 0.1 (noncancer, based on 3 µg/L EPA MCL)
Bisphenol A	Industrial chemical	Estrogenic / Anti-estrogenic	0.5**	NA	NA (<0.021)	NA	NA	NA	50 (noncancer, EPA IRIS)
Butylbenzyl phthalate	Industrial chemical	Estrogenic / Anti-estrogenic (nongenotoxic carcinogen)	3.3**	NA	NA (<0.021)	NA	NA***	69	200 (noncancer, EPA IRIS)
DEHP	Industrial chemical	Estrogenic / Anti-estrogenic, Androgenic / Anti-androgenic (nongenotoxic carcinogen)	0.12**	NA	NA (<0.021)	NA	NA***	88	0.071 (CSF, EPA IRIS) 20 (noncancer, EPA IRIS)
Dibutyl phthalate	Industrial chemical	Estrogenic / Anti-estrogenic, Androgenic / Anti-androgenic	10**	NA	NA (<0.021)	NA	NA	NA	100 (noncancer, EPA IRIS)

Compound	Category	Mode of Action	Based on NOAEL/ LOAEL and Default UF	Based on Lowest Therapeutic Dose and Default UF	TTC-based		Based on CSF	Based on VSD for Carcin -ogens	Existing Toxicity Criterion
					Using Scheme of Cheeseman et al. (1999)	Using Scheme of Kroes et al. (2004)			
17ß-Estradiol	Endogenous hormone	Estrogenic / Anti-estrogenic (nongenotoxic carcinogen)	0.00050**	0.00024**	NA (<0.021)	NA (<0.0021)	NA***	0.093	0.000026 (cancer, CalEPA) 0.05 (noncancer, JECFA)
Estrone	Endogenous hormone	Estrogenic / Anti-estrogenic (nongenotoxic carcinogen)	0.00040**	0.0000067**	NA (<0.021)	NA (<0.0021)	NA	NA	NA
Ethynylestradiol	Pharmaceutical	Estrogenic / Anti-estrogenic (nongenotoxic carcinogen)	0.0000033**	0.0000097**	NA (<0.021)	NA (<0.0021)	NA***	0.061	0.43 (15 ug/L; noncancer, Australia EPHC)
Lindane	Pesticide	Estrogenic / Anti-estrogenic, Androgenic / Anti-androgenic (nongenotoxic carcinogen)	0.019**	NA	NA (<0.021)	NA	NA***	1.4	0.00091 (cancer, CA OEHHA PHG) 0.3 (noncancer, EPA IRIS)
Linuron	Herbicide	Androgenic / Anti-androgenic (nongenotoxic carcinogen)	0.021**	NA	NA (<0.021)	NA	NA	4.4	2.0 (noncancer, EPA IRIS)

Compound	Category	Mode of Action	Based on NOAEL/ LOAEL and Default UF	Based on Lowest Therapeutic Dose and Default UF	TTC-based		Based on CSF	Based on VSD for Carcin -ogens	Existing Toxicity Criterion
					Using Scheme of Cheeseman et al. (1999)	Using Scheme of Kroes et al. (2004)			
Methoxychlor	Pesticide	Estrogenic / Anti-estrogenic, Androgenic / Anti-androgenic	0.00067**	NA	NA (<0.021)	NA	NA	NA	5 (noncancer, EPA IRIS)
Nonylphenol	Industrial chemical	Estrogenic / Anti-estrogenic	0.15**	NA	NA (<0.021)	NA	NA	NA	NA
4-tert-Octylphenol	Industrial chemical	Estrogenic / Anti-estrogenic	0.50**	NA	NA (<0.021)	NA	NA	NA	NA
Vinclozolin	Fungicide	Androgenic / Anti-androgenic (nongenotoxic carcinogen)	0.12**	NA	NA (<0.021)	NA	NA	32	25 (noncancer, EPA IRIS) 12 (noncancer, EPA FQPA)

*The value that would be selected for each compound according to the decision tree approach is enclosed in a box.

**An additional UF of 10 was applied because the compound was identified as a nongenotoxic carcinogen and/or an endocrine disrupting compound.

***A slope factor was calculated based on tumor incidence data (see Table 4.2), but was judged not applicable because the compound is a nongenotoxic carcinogen.

CHAPTER 5

EXPERT PANEL DISCUSSION AND FINAL RECOMMENDATIONS

5.1 RECOMMENDED DECISION TREE APPROACH FOR DERIVATION OF SCREENING LEVELS

On Wednesday, November 5, 2008, an Expert Panel Workshop was convened at the Southern Nevada Water Authority's River Mountain Water Treatment Facility to discuss the development of procedures and guidelines for developing screening levels of current and future contaminants of interest in water intended for indirect potable reuse. The workshop was attended by 23 experts including toxicologists, chemists, biologists, policy analysts, and pharmaceutical company and drinking water utility representatives (Table 5.1). The goal of the meeting was to reach consensus regarding the procedural details of a process for rapidly deriving health-protective screening levels, in the event that "new" chemicals are found in source or reuse water and to discuss how the information gathered from the process should be presented to the public. The presentations and discussion provided the Project Team with constructive feedback about how to modify the proposed schema and present the information in a manner that minimizes the potential for its misuse by the public. Though there were minor disagreements on details of the report, the group reached consensus at each stage of the process and, in the end, assisted the Project Team in producing a simplified decision tree for developing screening values. At the end of the expert panel discussion on November 6, 2008, the Project Team presented an overview of the workshop and revised procedures and guidelines to a small group of stakeholders. Many of the comments and questions posed by the stakeholders were similar to those raised during the expert panel.

Table 5.1: List of Expert Panel Attendees

Expert Panelist/Attendee	Agency/Role
David Cunliffe	Department of Health, South Australia
Katharine Cupps	WA Dept of Ecology
Joyce Donohue	Environmental Protection Agency (U.S. EPA)
Andrew Humpage	Australian Water Quality Centre
Roger Meyerhoff	Lilly Research Labs
Michael Narotsky	Environmental Protection Agency (U.S. EPA)
Tony Priestly	Australian Water Quality Centre
Craig Riley	WA Dept of Health
Richard Sakaji	East Bay MUD
James Stevens	Wake Forest University
Joe Cotruvo	Cotruvo & Associates/Technical Advisor
James Crook	Consulting Engineer/Technical Advisor
Brian Bernados	California Dept. of Health Services / PAC
Richard Bull	MoBull Consulting/PAC
Gary Ginsberg	Connecticut Dept. of Public Health / PAC
Djanette Khiari	Water Research Foundation / PAC
Dan Gerrity	Southern Nevada Water Authority (SNWA)
Shane Snyder	Southern Nevada Water Authority (SNWA)/Principal Investigator
Ben Stanford	Southern Nevada Water Authority (SNWA)
Gretchen Bruce	Intertox
Rick Pleus	Intertox/Co-PI
Jorg Drewes	Colorado School of Mines/Co-PI
Anna Durden	WRF/Project Manager

In general, the comparisons from the previous chapters illustrate that a single method for developing screening values that can be applied across all chemical types and classes would not be appropriate. Table 4.6 in Chapter 4 summarized comparison values derived using each of the methodologies. As shown, comparison values can range by several orders of magnitude depending on the method. Based on these findings, the Expert Panel recommended a decision tree approach for determining screening levels for emerging compounds in drinking water and reuse water (Figure 5.1). Using the approach suggested in this report, it is possible to rapidly establish conservative health risk-based screening level values. However, it is critical to note that the screening level values are not the same as regulatory standards, nor should they be interpreted as levels above which adverse human health effects are likely. In order to develop a regulatory value, significantly more information will be required including more detailed evaluation of the toxicological database and possibly additional toxicological studies, collection of additional occurrence data, and cost-benefit analysis.

The panel further emphasized that application of the decision tree in the development of screening values should be performed in consultation with appropriate experts in toxicology and risk assessment.

Although this decision tree was developed based on analysis of the case study compounds that consisted primarily of pharmacologically active compounds and EDCs, the scheme can

reasonably be applied to non-pharmacologically active ingredients of pharmaceuticals (e.g., preservatives, coloring agents, surfactants), in that the decision tree follows generally accepted toxicological principles. It should be noted, however, that a number of non-pharmacologically active ingredients of pharmaceuticals (e.g., parabens, phthalates) are suspected endocrine disruptors and, therefore, may require evaluation as EDCs.

The steps in the process for chemicals of interest without existing drinking water guidelines or other criteria (e.g., values developed and published by federal, state, or international regulatory agencies such as U.S. EPA RfDs, cancer SFs, or MCLs; California public health goals; or values developed by the WHO, the European Union, or other international agencies, if such values are derived using comparable methodologies to those discussed here) include:

1) If the chemical is a pharmaceutical, select the lowest value from among comparison values derived using the following processes:

    a) Divide the therapeutic dose (on a milligram per kilogram body weight basis, based on the range of doses and age groups for which the pharmaceutical is prescribed) by a default UF of 3000; divide by an additional UF of 10 if the compound is either a non-genotoxic carcinogen or an EDC.

    b) Divide the the literature-based NOAEL by a default UF of 1000 or the LOAEL by a default UF of 3000; divide by an additional UF of 10 if the compound is either a non-genotoxic carcinogen or an EDC.

    c) If the compound is a genotoxic carcinogen and tumor incidence data are available, develop a slope factor and establish a comparison value assuming a *de minimis* cancer risk of 1 in 1,000,000.

    d) If the compound is a genotoxic carcinogen and no tumor incidence data are available, use the lower of the VSD derived using the method of Gaylor and Gold (1998) or the TTC.

2) If the chemical is not a pharmaceutical and either a literature-based NOAEL or LOAEL can be identified or the chemical is a genotoxic carcinogen, set guidelines based on toxicological data following (b), (c), and (d) from No. 1 above.

3) If the chemical is not a pharmaceutical but does not have either a literature-based NOAEL or LOAEL or there is no evidence it is a genotoxic carcinogen, derive a screening level based on the TTC.

With regard to EDCs, the Panel agreed that if an existing toxicity criterion is available for an EDC, that criterion should be used. Otherwise, if a compound is an EDC and has a NOAEL or a LOAEL, that value should be divided by an additional UF of 10 (in addition to the default UF of 1000 or 3000). If the compound is a nongenotoxic carcinogen and an EDC, only one additional 10-fold UF should be applied to the default UF of 1000 or 3000 (not an additional 10-fold UF for both nongenotoxic carcinogenicity and EDC status).

A positive genotoxic compound was defined as one that is positive in at least one standard genotoxicity test. A compound should be described as having “equivocal” genotoxicity only if the result of the test itself is reported as “equivocal.”

The panel also recommended that if the risk assessor/toxicologist notes potential for unique toxicity (e.g., evidence from toxicity studies suggests the compound is a frank teratogen at the lowest dose or the compound is a chemotherapeutic), then the compound should be subject to a compound-specific risk analysis rather than using the screening approach presented here.

The recommended approach is similar to that developed for establishing drinking water guidelines for chemicals found in recycled water by the Australian Natural Resource Management Ministerial Council and Environment Protection and Heritage Council (Australia EPHC, 2008). Appendix A of the document "Australian Guidelines for Water Recycling: Managing Health and Environmental Risks (Phase 2). Augmentation of Drinking Water Supplies" provides a decision tree for establishing drinking water guidelines for a range of compounds, including pharmaceuticals, pesticides, and other organic compounds. Similarities and differences in the approaches for deriving screening levels for compounds without existing criteria are:

- For pharmaceuticals, the Australian approach recommends that screening levels be derived from the therapeutic dose divided by a UF of 1000. In contrast, the approach herein recommends that screening levels for pharmaceuticals be based on the lowest value derived from the therapeutic dose divided by a UF of 3000; the NOAEL divided by a UF of 1000 or the LOAEL divided by a UF of 3000; or, if the compound is a genotoxic carcinogen, the cancer slope factor and an assumption of a 10^{-6} acceptable lifetime excess cancer risk if tumor incidence data are available, or the lower of the VSD or TTC of 0.0021 µg/kg-d if no tumor incidence data are available. The Australian approach recommends application of an additional UF of 10 if the compound is cytotoxic or 10 if the compound is a hormonally active steroid. A similar approach was recommended herein: An additional UF of 10 was applied if the compound was a nongenotoxic carcinogen or an EDC.

- For nonpharmaceuticals, the Australian approach recommends that for "threshold" compounds with sufficient toxicity data, screening levels be derived by dividing the NOAEL from animal studies by a compound-specific UF, which ranged from 100 to 1000 in their examples. The approach herein recommends that screening levels for these types of compounds be based on a NOAEL or a LOAEL divided by a default UF of 1000 or 3000, respectively, with an additional UF of 10 if the compound was a nongenotoxic carcinogen or an EDC. For "nonthreshold" compounds (e.g., genotoxic carcinogens) with sufficient toxicity data, the Australian approach recommends that screening levels be derived based on the slope factor—where available—and the assumption of a 10^{-6} acceptable lifetime excess cancer risk. This is the same as the approach recommended herein.

- For genotoxic compounds without sufficient toxicity data to derive a slope factor, the Australian approach recommends that screening levels be based on the TTC proposed by Kroes et al. (2004) for genotoxic compounds of 0.15 µg/day (or 0.002 µg/kg-d)—this is the 5th percentile of the 10^{-6} risk level calculated from the database of compounds used in the derivation of the value. In converting this dose to a drinking water guideline, the Australian guidelines recommend applying an additional UF of 15 to the 100-fold UF already assumed to be incorporated by analogy to the 100-fold UF applied to NOELs in deriving TTCs for noncarcinogens (see the following bullet). Application of a combined 1500-fold factor is based on observation that compound-specific Australian Drinking Water Guidelines differ from their NOELs by a factor of 1570 at the 95th percentile and WHO Guidelines for Drinking-Water

Quality differ by a factor of 1660 at the 95th percentile. Application of a TTC of 0.0021 µg/kg-d is recommended herein—additional factors may be considered if the screening level is extrapolated to a drinking water guideline as discussed in Section 5.2.

- For nongenotoxic compounds without sufficient toxicity data to calculate a screening level from a NOAEL, the Australian approach recommends that screening levels be based on the following TTCs: for Cramer class I—30 µg/kg-d; for Cramer class II—9 µg/kg-d; and for for Cramer class III—1.5 µg/kg-d; these are assumed to correspond to the 5th percentile NOEL for the class divided by a UF of 100. The Australian guidelines recommend incorporating an additional UF of 15 to derive a drinking water guideline, as previously discussed. The screening levels recommended herein based on TTCs for these Cramer classes are 26, 7.7, and 1.3 µg/kg-d, respectively (Kroes et al., 2004). Again, application of additional factors may be considered if the screening level is extrapolated to a drinking water guideline as discussed in Section 5.2. The slight difference between these TTCs and those recommended in the the Australian guidelines are due to differences in the assumed body weight (60 kg in the Australian approach vs. 70 kg herein). The Australian approach recommends application of a TTC of 0.3 µg/kg-d for cholinesterase inhibitors; a specific TTC for cholinesterase inhibitors is not recommended herein because the focus of the review was on PPCPs and EDCs.

One final item worth noting is also mentioned here: Often, when setting toxicity-based standards for contaminants in surface water systems, regulatory agencies incorporate an additional factor into the prior equations to account for the possibility that, on any given day, a person could be exposed to the substance through some other source than drinking water ingestion. This factor, called a relative source contribution or RSC, typically ranges in value from 20 to 80% of the RfD or other acceptable daily intake based on knowledge about likely alternative sources of exposure to the chemical (U.S. EPA, 2000c; CDPH, 2007; U.S. EPA, 2006b). Thus, if this RSC approach is used in combination with the approach proposed in this Report, the resulting guideline value would be 20 to 80% of the screening value based solely on ingestion of drinking water. For example, residues of certain pesticides (e.g., acetochlor) can be found on food products, lowering the safety margin associated with an acceptable daily intake or drinking water equivalent level (DWEL) based solely on intake from drinking water. Thus, policymakers and risk assessors would need to incorporate the RSC to make an appropriate adjustment the drinking water guidline value to account for the additional exposure to those compounds. Again, it is emphasized that the approach described in this report is meant to assist in developing screening values, but is not meant to be a standalone approach to make specific recommendations regarding potential regulatory actions.

5.2 RECOMMENDATIONS FOR APPLICATION AND COMMUNICATION OF PROJECT CONCLUSIONS

At the end of the expert panel discussion on November 6, 2008, the project team presented an overview of the workshop and revised procedures and guidelines to a small group of stakeholders. Many of the comments and questions posed by the stakeholders were similar to those raised during the expert panel. During the Stakeholder Meeting, several key questions were raised about the application of these methodologies. These included:

1) Is this project meant to develop or recommend levels at which utilities should monitor for a given compound?

2) How should the "comparison values" shown in this report be interpreted, in the event that they are interpreted as "bright lines" indicative of levels that do or don't present a significant health risk?

3) How should values be presented to regulators?

4) Is it possible to turn the intent of the report toward trying to find a target detection limit rather than a safe/not safe exposure threshold?

In response to several of these questions, some of the attendees familiar with the draft Australian guidelines commented that the public has converted many of the screening levels presented in those guidelines into DWELs. Members of the Project Team have done a similar exercise in a previously published AwwaRF report (Snyder et al., 2008, AwwaRF Project 3085,) and used the calculated DWELs to suggest minimum reporting limits for emerging contaminants (Table 5.2). However, the minimum reporting limits calculated were not meant to suggest a maximum contaminant level or health effect level, but were instead meant to illustrate the link between public perception of risk (i.e., if the reporting limits are low enough and scientists can measure a compound, then there must be a risk), actual risk, and how the use of analytical techniques can be used to drive the argument. In many cases the actual method reporting limit is several orders of magnitude lower than the suggested reporting limit calculated from dividing the DWEL by a factor of 100.

In general, the panelists argued, the public is less concerned with the details of the risk analysis process than knowing that a system is in place that it is working to protect them. All attendees agreed that it is important to emphasize that the process proposed here has been peer reviewed, was intensively and rigorously evaluated and is conservative compared to other approaches, and that the end result is that we have provided water utilities, together with their toxicologists and risk assessors, with a means to efficiently evaluate potential risk associated with new contaminants in drinking water and communicate those risks to the public.

Table 5.2: Suggested Method Reporting Limits Based on Dividing the DWEL by 100 and Rounding to One Significant Figure

	Max Drinking Water Conc. (µg/L)	DWEL (µg/L)	Liters Per Day to Meet DWEL*	Current MRL (µg/L)	Recommended MRL (µg/L)
Phenytoin	0.019	6.8	700	0.001	0.1
Carbamazepine	0.018	12	1,300	0.0005	0.1
Fluoxetine	0.0082	34	82,000	0.0005	0.3
Diazepam	0.00033	35	210,000	0.00025	0.4
Gemfibrozil	0.0021	45	43,000	0.00025	0.5
Atenolol	0.018	70	7,800	0.00025	0.7
Meprobamate	0.042	260	13,000	0.00025	3
Bisphenol A	0.025	1,800	140,000	0.005	20
4-Nonylphenol	0.1	1,800	35,000	0.08	20
Sulfamethoxazole	0.003	18,000	12,000,000	0.00025	200

Note. Adapted from Snyder et al. (2008), AwwaRF Project 3085

*The equivalent amount of water in 8-ounce glasses of water per day can be computed by multiplying the amount in L/day by 4.23.

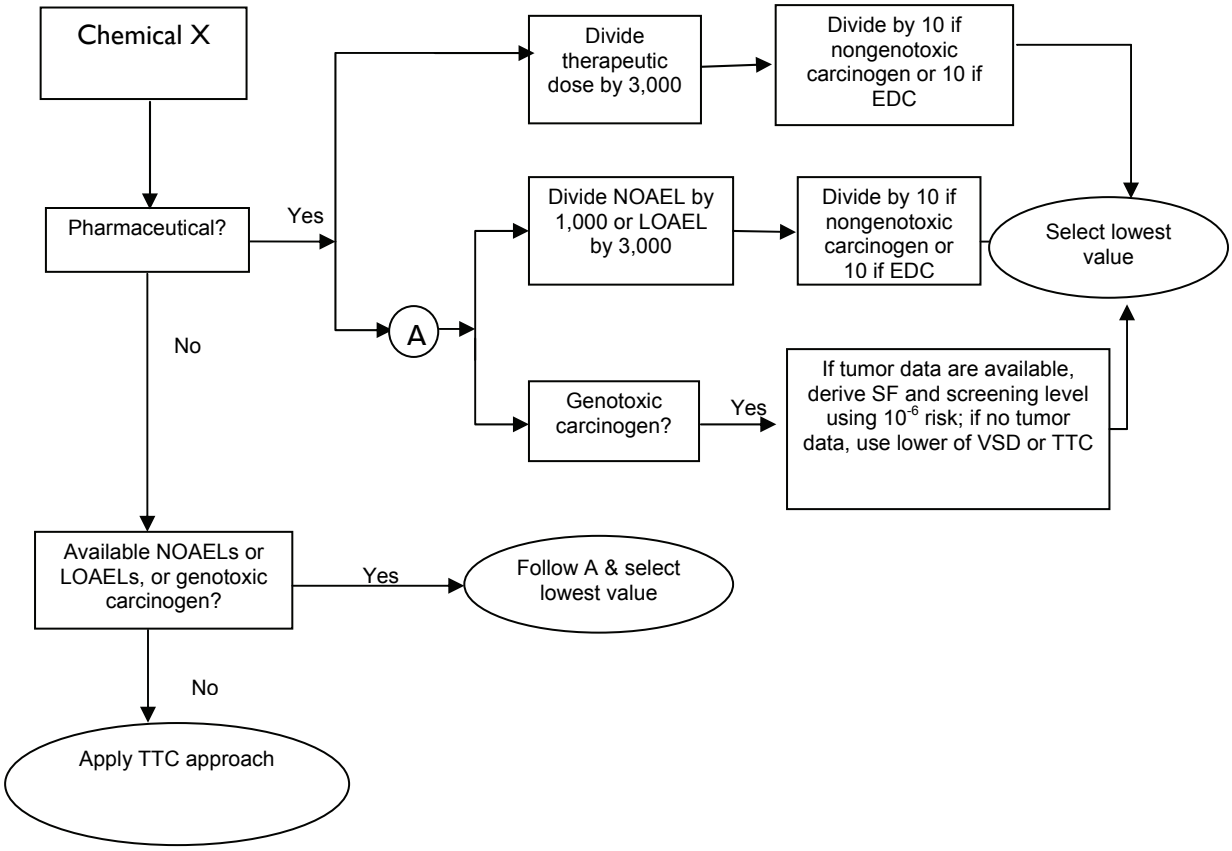

Figure 5.1: Final Decision Tree for Determination of Screening Levels for New and Emerging Contaminants

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APPENDIX A

COMPOUNDS CONSIDERED FOR AND SELECTED FOR EVALUATION IN CASE STUDIES

Table A-1. PPCPs Evaluated in AwwaRF/WRF 3085/04-003 (Snyder et al., 2008)

Generic name	Brand name	Group
Atenolol	Tenormin	Beta-blocker (treatment of high cholesterol)
Atorvastatin	Lipitor	Antilipidemic (treatment of high cholesterol)
Carbamazepine	Tegretol	Anticonvulsant and mood stabilizer
Diazepam	Valium	Benzodiazapine antianxiety
Diclofenac	Cataflam, Voltaren	NSAID
Enalapril	Enalaprit	ACE inhibitor (treatment of high blood pressure)
Fluoxetine	Prozac	SSRI (anti-depressant)
Gemfibrozil	Lopid	Antilipidemic (treatment of high cholesterol)
Meprobamate	Equanil, Miltown	Antianxiety agent
Naproxen	Aleve	NSAID
Phenytoin	Dilantin	Anticonvulsant
Risperidone	Risperidal	Antipsychotic
Simvastatin	Zocor	Antilipidemic
Sulfamethoxazole	Cotrim	Antibacterial
Triclosan	*Numerous including soap, toothpaste, shaving cream, cosmetics, deodorant, first aid cream	Antibacterial
Trimethoprim	Cotrim	Antiinfective

Table A-2. EDCs Evaluated in AwwaRF/WRF 3085/04-003 (Snyder et al., 2008)

Chemical	Occurrence in Drinking Water	Available Analytical Method	Mode of Action	Public & Scientific Interest
Atrazine	✓	✓	N	GWRC, EDSP, IEH
Bisphenol A	✓	✓	E	Ca DHS, GWRC, EDSP, IEH
Butylbenzyl phthalate	✓	✓	E	IEH
DEHP†	✓	✓	E, A	GWRC, IEH
17ß-Estradiol	✓	✓	E	GWRC, EDSP, IEH
Estrone	✓	✓	E	GWRC, IEH
Ethynylestradiol	✓	✓	E	GWRC, EDSP, IEH
Lindane (BHC-gamma)	✓	✓	E, A	GWRC, IEH
Linuron	✓	✓	A	EDSP, IEH
Methoxychlor	✓	✓	E, A	GWRC, EDSP, IEH
Nonylphenol	✓	✓	E	Ca DHS, GWRC, EDSP, IEH
Octylphenol	✓	✓	E	Ca DHS, IEH
Vinclozolin	✓	✓	A	EDSP, GWRC, IEH

Note. Ca DHS = Recommended for monitoring under California Department of Health Services Draft Groundwater Recharge Reuse Regulations (Ca DHS, 2008)

GWRC = Global Water Research Coalition, Priority List of EDCs (GWRC, 2003)

EDSP = reference chemical used in the Endocrine Disrupter Screening Program Tier 1 Prevalidation Studies (December 10, 2003) (U.S.EPA, 2003)

IEH = Institute for Environmental Health (IEH), Chemicals Purported to Be Endocrine Disrupters (IEH, 2005)

E = Estrogenic/Anti-estrogenic; A = Androgenic/Anti-androgenic; N = Neuroendocrine

†Synonyms: dioctylphthalate or diethylhexylphthalate. Also called DEPH (GWRC, 2003).

Table A-3. Top-Selling Pharmaceuticals Not Evaluated in AwwaRF/WRF 3085/04-003 (Snyder et al., 2008) but Identified as of Possible Toxicological Interest if Present in Indirect Potable Reuse Water

Drug Group	Compound	U.S. Brand Name(s)	2003 Rx Rank	FDA Pregnancy Category	Toxicity Classification	Detected in Environmental Water Samples
Analgesic/antipyretic	Tramadol / Acetaminophen	Ultracet®	123	C	Carcinogenic; Developmental toxicant	NA
Antacid/proton pump inhibitor	Lansoprazole	Prevacid®	17	B	Carcinogenic; Developmental toxicant	NA
Antacid/proton pump inhibitor	Esomeprazole	Nexium®	27	B	Carcinogenic; Developmental toxicant	NA
Antacid/proton pump inhibitor	Pantoprazole	Protonix®	47	B	Carcinogenic	NA
Antacid/proton pump inhibitor	Omeprazole	Omeprazole®; Prilosec®	62	C	Carcinogenic; Developmental toxicant	NA
Antacid/proton pump inhibitor	Rabeprazole	Aciphex®	81	B	Carcinogenic	NA
Anticonvulsant	Gabapentin	Neurontin®	36	C	Carcinogenic; Developmental toxicant	NA
Anticonvulsant	Topiramate	Topamax®	127	C	Carcinogenic; Developmental toxicant	NA
Antidiabetic agent	Pioglitazone	Actos®	70	C	Carcinogenic; Developmental toxicant	NA
Antidiabetic agent	Rosiglitazone maleate	Avandia®	77	C	Developmental toxicant	NA
Antifungal	Fluconazole	Diflucan®	65	C	Carcinogenic; Developmental toxicant	NA
Antihistamine	Desloratadine	Clarinex®	105 (in 2004)	C	Carcinogenic; Developmental toxicant	NA
Antihypertensive/angiotensin II antagonist	Irbesartan	Avapro®	116	C, D	Developmental toxicant	NA

Drug Group	Compound	U.S. Brand Name(s)	2003 Rx Rank	FDA Pregnancy Category	Toxicity Classification	Detected in Environmental Water Samples
Antihypertensive/angiotensin II antagonist	Candesartan	Atacand®	175	C, D	Developmental toxicant	NA
Antihypertensive/angiotensin II antagonist; thiazide diuretic	Losartan/ HCTZ	Hyzaar®	94	C	Carcinogenic; Developmental toxicant	NA
Anti-infective	Nitrofurantoin	Macrobid®	139	C	Carcinogenic; Developmental toxicant	NA
Bisphosphonate inhibitor of bone resorption	Alendronate	Fosamax®	28	C	Carcinogenic	NA
BPH therapy agent	Tamsulosin	Flomax®	80	B	Carcinogenic	NA
Central nervous system stimulant	Methyl-phenidate XR	Concerta®	102	C	Carcinogenic; Developmental toxicant	NA
Fluoroquinolone antibiotic	Moxifloxacin	Avelox®	178	C	Developmental toxicant	NA
Loop diuretic	Furosemide	Furosemide (any form)	7	C	Carcinogenic; Developmental toxicant	Yes
Nitrate	Nitroglycerin	Generics	186	C	Carcinogenic	NA
Selective norepinephrine reuptake inhibitor (SNRI)	Atomoxetine	Strattera®	164	C	Developmental toxicant	NA
Tetracyclic antidepressant	Mirtazapine	Remeron®	194	C	Carcinogenic; Developmental toxicant	NA
Tetracycline antibiotic	Doxycycline	Doxycycline Hyclate®	141	D	Developmental toxicant	NA
Topical eczema drug	Pimecrolimus	Elidel®	166	C	Carcinogenic; Developmental toxicant	NA

Note. Pregnancy Categories: A = Possibility of fetal harm appears remote. B = Animals show no risk, or animal studies suggest risk but human studies show no risk. C = Animal studies show risk but human studies are inadequate, or no adequate studies are available. D = Human studies show some evidence of risk. E = Animal or human studies show fetal harm, and risks clearly outweigh benefits.

Table A-4. Veterinary Drugs, Cancer Agents, Personal Care Products, and X-ray Contrast Agents Detected in U.S. Environmental Water Samples

Drug Group	Compound	U.S. Brand Name(s)	Usage				Detections			
			Prescrip-tion Drug	OTC Drug	Personal Care Product	Veterin-ary Drug	Waste-water Effluent	Treat-ment Plant Outflow	Surface Water	Drinking Water
Anthelmintic [human and veterinary]	Thiabendazole	Mintezol®	✓			✓		✓		
Antibacterial [human and veterinary]	Trimethoprim	Numerous (generics)	✓			✓	✓	✓	✓	✓
Antibacterial [human and veterinary]	Sulfamethazine	Numerous (generics)	✓			✓	✓	✓	✓	✓
Antibacterial [human and veterinary]	Triclosan	Irgasan DP 300	✓	✓	✓	✓	✓	✓	✓	
Antibiotic [human and veterinary]	Chlortetracycline	Numerous (generics)	✓			✓	✓	✓	✓	✓
Antibiotic [human and veterinary]	Erythromycin	Numerous (generics)	✓			✓		✓	✓	✓
Antibiotic [human and veterinary]	Lincomycin	Lincocin®	✓			✓	✓	✓	✓	✓
Antibiotic [human and veterinary]	Norfloxacin	Noroxin®	✓			✓	✓	✓	✓	✓
Antibiotic [human and veterinary]	Oxytetracycline	Numerous (generics)	✓			✓	✓	✓	✓	✓
Antibiotic [human and veterinary]	Tetracycline	Numerous (generics)	✓			✓	✓	✓	✓	✓
Antibiotic [veterinary]	Enrofloxacin	Baytril®				✓	✓	✓	✓	✓
Antibiotic [veterinary]	Sulfadimethoxine	Albon®				✓	✓	✓	✓	✓

Drug Group	Compound	U.S. Brand Name(s)	Usage				Detections			
			Prescrip-tion Drug	OTC Drug	Personal Care Product	Veterin-ary Drug	Waste-water Effluent	Treat-ment Plant Outflow	Surface Water	Drinking Water
Antibiotic [veterinary]	Tilmicosin	Pulmotil®				✓			✓	✓
Antibiotic [veterinary]	Tylosin	Tylan®				✓	✓	✓	✓	✓
Antineoplastic [human]	Cyclophos-phamide	Cyclophosphane®; Cytoxan®	✓						✓	✓
Antineoplastic [human]	Ifosfamide	Ifex/Mesnex®	✓				✓	✓		
Chemotherapy agent [human]	Tamoxifen	Nolvadex®	✓					✓		
Musk	Galaxolide	[musk fragrance]			✓		✓	✓		
Musk	Tonalide	[musk fragrance]			✓		✓	✓		
Skin care product ingredient	Salicylic acid	[ingredient of numerous skin care products]		✓	✓		✓	✓		
X-ray contrast agent	Iopamidol	Isovue®	✓				✓			
X-ray contrast agent	Iopromide	Ultravist®	✓				✓	✓	✓	

Table A-5. Top 300 Most Prescribed Drugs in 2005, Sorted by Drug Group [a,b]

Group (specific)	Generic Name	Brand Name	Rank
Analgesic			
Analgesic	Acetaminophen	Tylenol, Acetaminophen, APAP	23, 112, 226
Analgesic	Aspirin	Aspirin	24
Analgesic (COX-2 inhibitor)	Celecoxib	Celebrex	55
Analgesic (COX-2 inhibitor)	Rofecoxib	Vioxx	240
Analgesic (COX-2 inhibitor)	Valdecoxib	Bextra	295
Analgesic (narcotic)	Hydrocodone	Hydrocodone, Vicodin, Lortab, Norco	3, 6, 48, 119
Analgesic (narcotic)	Tramadol	Ultram, Ultracet	5, 132
Analgesic (narcotic)	Oxycodone	Oxycodone, Percocet, Oxycontin, Endocet	8, 12, 46, 236
Analgesic (narcotic)	Morphine	Morphine	20
Analgesic (narcotic)	Propoxyphene napsylate	Darvocet	27
Analgesic (narcotic)	Tramadol	Ultram	36
Analgesic (narcotic)	Codeine	Codeine	65
Analgesic (narcotic)	Methadone	Methadone	67
Analgesic (narcotic)	Fentanyl	Fentanyl, Duragesic	84, 294
Analgesic (narcotic)	Tramadol	Ultracet	132
Analgesic (narcotic)	Propoxyphene	Propoxyphene	147
Analgesic (narcotic)	Hydromorphone	Dilaudid	164
Analgesic (narcotic)	Meperidine	Demerol	206
Analgesic (NSAID)	Naproxen	Naproxen	21
Analgesic (NSAID)	Diclofenac	Diclofenac, Voltaren	70, 192
Analgesic (NSAID)	Meloxicam	Mobic	72
Analgesic (NSAID)	Ibuprofen	Ibuprofen, Motrin	79, 208
Analgesic (NSAID)	Etodolac	Etodolac, Lodine	179, 250
Analgesic (NSAID)	Naprosyn	Naprosyn	189
Analgesic (NSAID)	Nabumetone	Nabumetone, Relafen	200, 233

Group (specific)	Generic Name	Brand Name	Rank
Analgesic (NSAID)	Ketorolac	Toradol	202
Analgesic (NSAID)	Indomethacin	Indomethacin, Indocin	221, 300
Analgesic (NSAID)	Piroxicam	Piroxicam	281
Migraine drug	Sumatriptan	Imitrex	167
Antibiotic/Antiviral			
Antibiotic	Levofloxacin	Levaquin	40
Antibiotic	Ciprofloxacin	Cipro, Ciprofloxacin	45, 124
Antibiotic	Amoxicillin	Amoxicillin	59
Antibiotic	Doxycycline	Doxycycline, Zetia	73, 82
Antibiotic	Amoxicillin/ clavulanate	Augmentin	74
Antibiotic	Cephalexin	Cephalexin, Keflex	75, 120
Antibiotic	Sulfamethoxazole/ trimethoprim	Bactrim, Septra	76
Antibiotic	Clindamycin	Clindamycin	94
Antibiotic	Metronidazole	Metronidazole, Flagyl	104, 121
Antibiotic	Azithromycin	Zithromax, Azithromycin	114, 177
Antibiotic	Clarithromycin	Biaxin	127
Antibiotic	Penicillin	Penicillin	143
Antibiotic	Moxifloxacin	Avelox	158
Antibiotic	Erythromycin	Erythromycin	163
Antibiotic	Nystatin	Nystatin	201
Antibiotic	Vancomycin	Vancomycin	207
Antibiotic	Cefdinir	Omnicef	228
Antibiotic	Tetracycline	Tetracycline	246
Antibiotic	Nitrofurantoin	Macrobid	277
Antibiotic	Ampicillin	Ampicillin	292
Antifungal	Fluconazole	Diflucan, Fluconazole	195, 252
Antifungal	Terbinafine	Lamisil	279
Antiviral	Oseltamivir	Tamiflu	133

Group (specific)	Generic Name	Brand Name	Rank
Antiviral	Valacyclovir	Valtrex	159
Antiviral	Acyclovir	Acyclovir	176
Antimalarial	Quinine	Quinine	222
Bone			
Inhibitor of bone resorption	Alendronate	Fosamax	97
Inhibitor of bone resorption	Risedronate	Actonel	178
Inhibitor of bone resorption	Ibandronate	Boniva	213
Cancer Drug			
Cancer drug	Conjugated estrogens	Premarin	151
Cancer drug	Methotrexate	Methotrexate	153
Cancer drug	Allopurinol	Allopurinol	161
Cancer drug	Leuprolide	Lupron	253
Cardiovascular			
ACE inhibitor	Lisinopril	Prinivil, Zestril	9, 286
ACE inhibitor	Ramipril	Altace	105
ACE inhibitor	Olmesartan medoxomil	Benicar	110
ACE inhibitor	Amlodipine/benazepril	Lotrel	117
ACE inhibitor	Enalapril	Enalapril, Vasotec	130, 267
ACE inhibitor	Valacyclovir	Avapro	162
ACE inhibitor	Donepezil	Aricept	165
ACE inhibitor	Quinapril	Accupril	262
ACE inhibitor	Captopril	Captopril	275
Alpha-adrenergic blocker	Tamsulosin	Flomax	91
Alpha-adrenergic blocker	Terazosin	Terazosin	247
Alpha-adrenergic blocker	Doxazosin	Cardura	296
Alpha-agonist hypotensive agent	Clonidine	Clonidine	64
Angiotensin II receptor antagonist	Valsartan	Diovan	30

Group (specific)	Generic Name	Brand Name	Rank
Angiotensin II receptor antagonist	Losartan	Cozaar	149
Angiotensin II receptor antagonist	Irbesartan	Avalide	249
Angiotensin II receptor antagonist	Candesartan	Atacand	268
Antiarrhythmic	Amiodarone	Amiodarone	194
Anticoagulant	Warfarin	Coumadin, Warfarin	90, 135
Anticoagulant	Heparin	Heparin	199
Antilipidemic	Fenofibrate	Tricor	116
Beta blocker	Atenolol	Atenolol	18
Beta blocker	Metoprolol	Toprol, Metoprolol, Lopressor	26, 39, 173
Beta blocker	Carvedilol	Coreg	107
Beta blocker	Propranolol	Inderal, Propanolol	125, 185
Calcium channel blocker	Amlodipine	Norvasc, Amlodipine	25, 259
Calcium channel blocker	Verapamil	Verapamil	111
Calcium channel blocker	Diltiazem	Diltiazem, Cardizem	134, 193
Calcium channel blocker	Nifedipine	Nifedipine	215
Cardiac glycoside	Digoxin	Digoxin, Lanoxin	108, 225
Heparin, for thrombosis	Enoxaparin	Lovenox	181
HMG-CoA reductase inhibitor	Atorvastatin	Lipitor	11
HMG-CoA reductase inhibitor	Simvastatin	Zocor, Simvastatin	37, 168
HMG-CoA reductase inhibitor	Ezetimibe	Vytorin	56
HMG-CoA reductase inhibitor	Rosuvastatin	Crestor	106
HMG-CoA reductase inhibitor	Lovastatin	Lovastatin	138
HMG-CoA reductase inhibitor	Pravastatin	Pravachol	211
Inhibitor of platelet aggregation	Clopidogrel	Plavix	52
Vasodilator	Isosorbide	Isosorbide, Imdur	196
Vasodilator	Hydralazine	Hydralazine	297

Group (specific)	Generic Name	Brand Name	Rank
Endocrine			
Antidiabetic	Metformin	Metformin, Glucophage	14, 155
Antidiabetic	Pioglitazone	Actos	103
Antidiabetic	Rosiglitazone	Avandia	122
Antidiabetic	Glyburide	Glyburide	156
Antidiabetic	Glipizide	Glipizide	174
Antidiabetic	Exenatide	Byetta	197
Antidiabetic	Glimepiride	Amaryl	263
Contraceptive	Ethynylestradiol/ norelgestromin	Ortho Evra	141
Contraceptive	Drospirenone/ Ethynylestradiol	Yasmin	269
Corticosteroid	Prednisone	Prednisone	17
Corticosteroid	Fluticasone	Advair, Flonase, Flovent	78, 191, 271
Corticosteroid	Methylprednisolone	Medrol, Methylprednisolone	142, 257
Corticosteroid	Triamcinolone	Triamcinolone	170
Corticosteroid	Dexamethasone	Decadron, Dexamethasone	227, 238
Corticosteroid	Hydrocortisone	Hydrocortisone	241
Corticosteroid	Mometasone	Nasonex	244
Corticosteroid	Prednisolone	Prednisolone	280
Erectile dysfunction	Sildenafil	Viagra	42
Erectile dysfunction	Tadalafil	Cialis	175
Erectile dysfunction	Vardenafil	Levitra	291
Estrogen replacement	Estradiol	Estradiol	169
Hormone	Medroxyprogesterone	Provera	248
Hormone analog	Leuprolide	Lupron	273
Insulin	Insulin	Insulin	95
Selective estrogen receptor modulator	Raloxifene	Evista	212
Synthetic steroid	Finasteride	Proscar	270

Group (specific)	Generic Name	Brand Name	Rank
Thyroid hormone	Levothyroxine	Synthroid, Levothyroxine, Levoxyl	51, 152, 204
Thyroid hormone	Thyroid, desiccated	Thyroid	256
GI tract			
Anticholinergic/ Antispasmodic	Atropine	Atropine	231
Anticholinergic/ Antispasmodic	Dicyclomine	Bentyl	283
Antisecretory	Lansoprazole	Prevacid	54
Antisecretory	Omeprazole	Omeprazole, Prilosec	80, 92
Antisecretory	Rabeprazole	Aciphex	129
For overactive bladder	Tolterodine	Detrol	190
Gastroesophogeal reflux	Esomeprazole	Nexium	28
GI reflux agent	Metoclopramide	Reglan	145
Histamine receptor antagonist (ulcer treatment)	Famotidine	Famotidine, Pepcid	261, 274
Proton pump inhibitor	Pantoprazole	Protonix	35
Treatment of irritable bowel syndrome	Tegaserod	Zelnorm	239
Immune			
Antiarthritec/ Antiinflammatory	Etanercept	Enbrel	299
Antihistamine	Cetirizine	Zyrtec	61
Antihistamine	Promethazine	Promethazine	71
Antihistamine	Fexofenadine	Allegra, Fexofenadine	93, 258
Antihistamine	Ranitidine	Ranitidine, Zantac	100, 131
Antihistamine	Diphenhydramine	Benadryl, Diphenhydramine	144, 254
Antihistamine	Loratadine	Claritin, Loratadine	166, 203
Antihistamine	Meclizine	Meclizine	172
Antihistamine	Desloratadine	Clarinex	288
Muscle			
Muscle relaxant	Carisoprodol	Soma	29
Muscle relaxant	Metaxalone	Skelaxin	87

Group (specific)	Generic Name	Brand Name	Rank
Muscle relaxant	Baclofen	Baclofen	136
Muscle relaxant	Methocarbamol	Robaxin, Methocarbamol	180, 220
Muscle relaxant	Tizanidine	Zanaflex, Tizanidine	198, 224
Nervous			
5-HT3 receptor antagonist	Ondansetron	Zofran	187
Amphetamine	Amphetamine	Adderall	34
Anesthetic	Lidocaine	Lidocaine, Lidoderm	137, 285
Antianxiety agent	Buspirone	Buspar	154
Anticonvulsant	Divalproex	Depakote	63
Anticonvulsant	Topiramate	Topamax	69
Anticonvulsant	Phenytoin	Dilantin, Phenytoin	115, 265
Anticonvulsant	Carbamazepine	Tegretol	209
Antidepressant	Venlafaxine	Effexor	15
Antidepressant	Bupropion	Wellbutrin, Bupropion	19, 188
Antidepressant	Trazodone	Trazodone	60, 126
Antidepressant	Mirtazapine	Remeron, Mirtazapine	146, 243
Antidepressant (SSNRI)	Duloxetine	Cymbalta	10
Antidepressant (SSRI)	Paroxetine	Paxil, Paroxetine	1, 157
Antidepressant (SSRI)	Escitalopram	Lexapro	2
Antidepressant (SSRI)	Sertraline	Zoloft	13
Antidepressant (SSRI)	Fluoxetine	Prozac, Fluoxetine	43, 101
Antidepressant (SSRI)	Citalopram	Celexa, Citalopram	50, 99
Antidepressant (tricyclic)	Amitriptyline	Elavil, Amitriptyline	88, 89
Antidepressant (tricyclic)	Doxepin	Doxepin	276
Antiepileptic	Gabapentin	Neurontin	33
Antiepileptic	Lamotrigine	Lamictal	66
Antiepileptic	Oxcarbazepine	Trileptal	182
Antiepileptic	Levetiracetam	Keppra	216

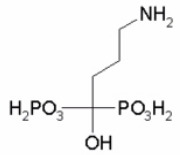
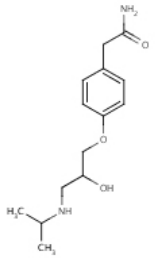
Group (specific)	Generic Name	Brand Name	Rank
Antipsychotic	Risperidone	Risperdal	85
Antipsychotic	Olanzapine	Zyprexa	98
Antipsychotic	Haloperidol	Haldol	214
Antiseizure	Pregabalin	Lyrica	7
Antispasmodic	Oxybutynin	Ditropan	260
Antispasmotic	Cyclobenzaprine	Cyclobenzaprine, Flexeril	53, 68
Atypical antipsychotic	Quetiapine	Seroquel	31
Atypical antipsychotic	Aripiprazole	Abilify	86
Atypical antipsychotic	Ziprasidone	Geodon	184
Barbiturate	Butalbital	Fioricet, Butalbital	232, 289
Benzodiazepine	Alprazolam	Xanax, Alprazolam	4, 44
Benzodiazepine	Lorazepam	Ativan, Lorazepam	38, 58
Benzodiazepine	Diazepam	Valium, Diazepam	41, 83
Benzodiazepine	Clonazepam	Clonazepam, Klonopin	49, 62
Benzodiazepine	Temazepam	Temazepam, Restoril	186, 235
Benzodiazepine	Midazolam	Versed	293
CNS stimulant	Methylphenidate	Ritalin, Concerta	123, 148
Dopamine agonist	Ropinirole	Requip	210
Hypnotic agent	Eszopiclone	Lunesta	96
Hypnotic agent	Zolpidem	Ambien	16
Mania treatment	Lithium	Lithium	113
Neurotransmitter	Dopamine	Dopamine	284
NMDA receptor antagonist	Memantine	Namenda	171
Antitremor	Carbidopa/ levodopa	Sinemet	282
Phenothiazine	Prochlorperazine	Compazine	234
Sedative	Ramelteon	Rozerem	223
Sedative	Hydroxyzine	Hydroxyzine, Atarax	102, 183
Sedative	Promethazine	Phenergan	109

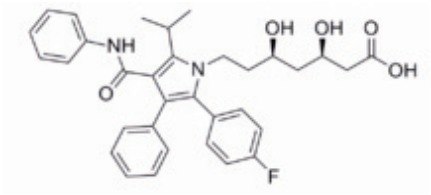
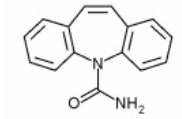
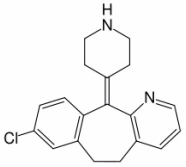
Group (specific)	Generic Name	Brand Name	Rank
Selective norepinephrine reuptake inhibitor	Atomoxetine	Strattera	230
Sympathomimetic amine (antiobesity)	Phentermine	Phentermine	22
Wakefulness promoting agent	Modafinil	Provigil	140
Renal			
Diuretic	Furosemide	Lasix	57
Diuretic	Hydrochlorothiazide	Hydrochlorothiazide, HCTZ, Hyzaar	77, 150, 245
Diuretic	Furosemide	Furosemide	81
Diuretic	Spironolactone	Spironolactone, Aldactone	218, 251
Diuretic	Triamterene	Triamterene	229
Respiratory			
Antiasthmatic	Montelukast sodium	Singulair	128
Beta-adrenergic agonist	Albuterol	Albuterol, Combivent	32, 290
Bronchodilator	Ipratropium	Atrovent, Combivent	264, 290
Bronchospasm treatment	Tiotropium	Spiriva	237
Cough/ cold medication	Guaifenesin/ pseudoephedrine	Entex	278
Cough/ cold medication	Pseudoephedrine	Pseudoephedrine	298
Vitamin/ Mineral			
Vitamin/ Mineral	Potassium	Potassium	118
Vitamin/ Mineral	Calcium	Calcium	160
Vitamin/ Mineral	Magnesium	Magnesium	205
Vitamin/ Mineral	Niacin	Niaspan	242
Other			
Gout treatment	Colchicine	Colchicine	266

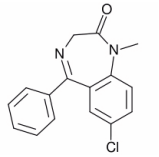
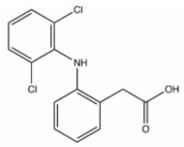
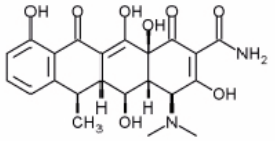
[a]Source: RxList.com, 2007. Top 300 Prescriptions for 2005. WebMd. San Clemente, CA. Available at: www.rxlist.com/script/main/art.asp?articlekey=79509

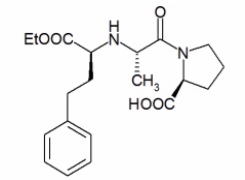
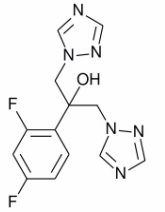
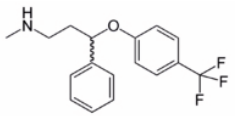
[b]For drugs listed more than once, all brands and their associated rank are listed under the generic drug name.

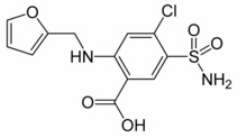
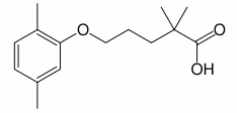
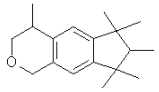
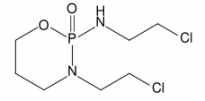
Table A-6. Structure, IUPAC Nomenclature, and SMILES Code of Compounds Selected as Case Studies

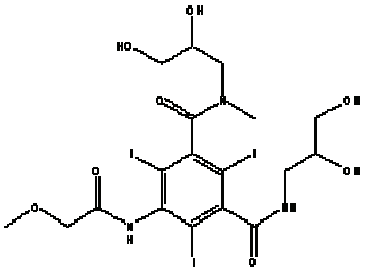
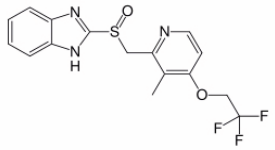
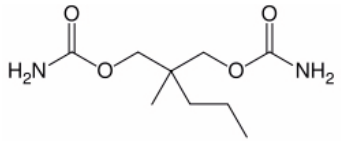
Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
PPCPs			
Alendronate (Fosamex®)	66376-36-1	Bisphonate inhibitor of bone resorption	 (4-amino-1-hydroxy-1-phosphonobutyl)phosphonic acid NCCCC(O)(P(O)(O)=O)P(O)(O)=O
Atenolol (Tenormin®)	29122-68-7	Beta-blocker	 2-[4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl]acetamide CC(C)NCC(O)COC1=CC=C(CC(N)=O)C=C1

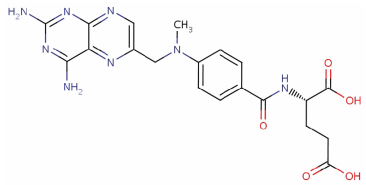
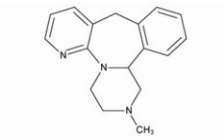
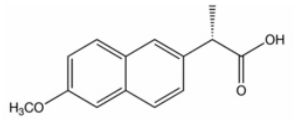
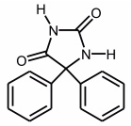
Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Atorvastatin (Lipitor®)	134523-00-5	Antilipidemic	 (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid CC(C)C1=C(C(=O)NC2=CC=CC=C2)C(C2=CC=CC=C2)=C(N1CCC(O)CC(O)CC(O)=O)C1=CC=C(F)C=C1
Carbamazepine (Tegretol®)	298-46-4	Anticonvulsant and mood stabilizer	 benzo[b][1]benzazepine-11-carboxamide NC(=O)N1C2=CC=CC=C2C=CC2=CC=CC=C12
Desloratadine (Clarinex®)	100643-71-8	Antihistamine	 IUPAC name not available ClC1=CC2=C(C=C1)C(=C1CCNCC1)C1=C(CC2)C=CC=N1

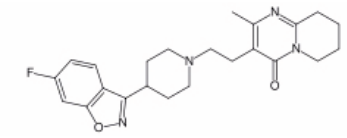
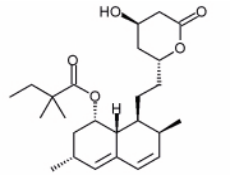
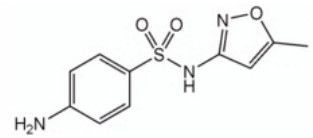
Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Diazepam (Valium®)	439-14-5	Benzodiazapine antianxiety	 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one CN1C(=O)CN=C(C2=CC=CC=C2)C2=C1C=CC(Cl)=C2
Diclofenac (Cataflam®, Voltaren®)	15307-86-5	NSAID	 2-[2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid OC(=O)CC1=CC=CC=C1NC1=C(Cl)C=CC=C1Cl
Doxycycline (generics)	564-25-0	Tetracycline antibiotic	 (2Z,4S,4aR,5S,5aR,6R,12aS)-2-(amino-hydroxymethylidene)-4-dimethylamino-5,10,11,12a-tetrahydroxy-6-methyl-4a,5,5a,6-tetrahydro-4H-tetracene-1,3,12-trione CC1C2C(O)C3C(N(C)C)C(=O)C(C(=O)C3(O)C(=O)C2=C(O)C2=C1C=CC=C2O)=C(N)O

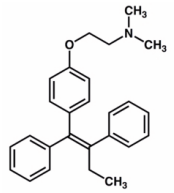
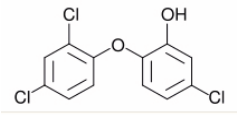
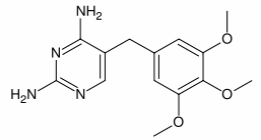
Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Enalapril (Enalaprit®)	75847-73-3	ACE inhibitor	 (2S)-1-[(2S)-2-[[(2R)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]pyrrolidine-2-carboxylic acid CCOC(=O)C(CCC1=CC=CC=C1)NC(C)C(=O)N1CCCC1C(O)=O
Fluconazole (Diflucan®)	86386-73-4	Antifungal	 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol OC(CN1C=NC=N1)(CN1C=NC=N1)C1=C(F)C=C(F)C=C1
Fluoxetine (Prozac®)	54910-89-3	SSRI anti-depressant	 N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine CNCCC(OC1=CC=C(C=C1)C(F)(F)F)C1=CC=CC=C1

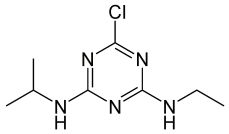
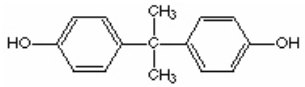
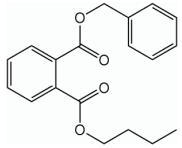
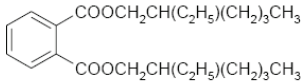
Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Furosemide (Lasix®)	54-31-9	Loop diuretic	 4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid NS(=O)(=O)C1=C(Cl)C=C(NCC2=CC=CO2)C(=C1)C(O)=O
Gemfibrozil (Lopid®)	25812-30-0	Antilipidemic	 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid CC1=CC(OCCCC(C)(C)C(O)=O)=C(C)C=C1
HHCB (Galaxolide®)	1222-05-5	Musk	 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran CC1COCC2=CC3=C(C=C12)C(C(C3(C)C)C)(C)C
Ifosfamide (NA)	3778-73-2	Chemotherapy agent	 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro -2H-1,3,2-oxazaphosphorine 2-oxide ClCCNP1(=O)OCCCN1CCCl

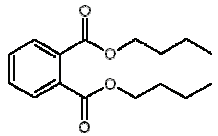
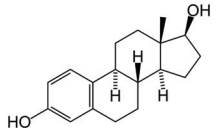
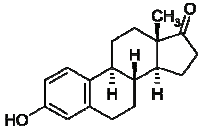
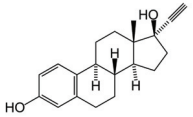
Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Iopamidol/ iopromide (Isovue®)	73334-07-3	X-ray contrast media	 IUPAC name not available Ic1c(c(I)c(c(I)c1NC(=O)COC)C(=O)NCC(O)CO)C(=O)N(CC(O)CO)C
Lansoprazole (Prevacid®)	103577-45-3	Antacid/ proton pump inhibitor	 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1H-benzimidazole CC1=C(OCC(F)(F)F)C=CN=C1CS(=O)C1=NC2=CC=CC=C2N1
Meprobamate (Equanil®, Miltown®)	57-53-4	Antianxiety agent	 2-(carbamoyloxymethyl)-2-methylpentyl] carbamate CCCC(C)(COC(N)=O)COC(N)=O

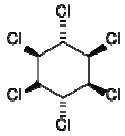
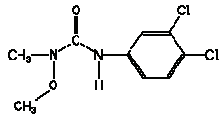
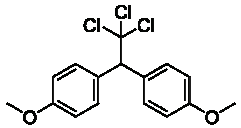
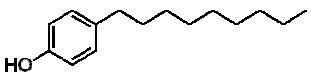
Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Methotrexate (NA)	59-05-2	Chemotherapy agent	 (2S)-2-[[4-[(2,4-diaminopteridin-6-yl)methyl-methylamino]benzoyl]amino]pentanedioic acid CN(CC1=CN=C2N=C(N)N=C(N)C2=N1)C1=CC=C(C=C1)C(=O)NC(CCC(O)=O)C(O)=O
Mirtazapine (Remeron®)	61337-67-5	Tetracyclic antidepressant	 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine CN1CCN2C(C1)C1=CC=CC=C1CC1=C2N=CC=C1
Naproxen (Aleve®)	22204-53-1	NSAID	 2-(6-methoxynaphthalen-2-yl)propanoic acid COC1=CC2=C(C=C1)C=C(C=C2)C(C)C(O)=O
Phenytoin (Dilantin®)	57-41-0	Anticonvulsant	 5,5-di(phenyl)imidazolidine-2,4-dione O=C1NC(=O)C(N1)(C1=CC=CC=C1)C1=CC=CC=C1

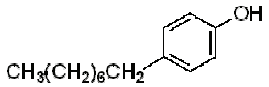
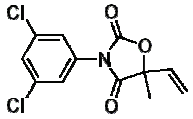
Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Risperidone (Risperidal®)	106266-06-2	Antipsychotic	 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[2,1-b]pyrimidin-4-one CC1=C(CCN2CCC(CC2)C2=NOC3=C2C=CC(F)=C3)C(=O)N2CCCCC2=N1
Simvastatin (Zocor®)	79902-63-9	Antilipidemic	 [(1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl] 2,2-dimethylbutanoate CCC(C)(C)C(=O)OC1CC(C)C=C2C=CC(C)C(CCC3CC(O)CC(=O)O3)C12
Sulfamethoxazole (Cotrim®)	723-46-6	Antibacterial	 4-amino-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide CC1=CC(NS(=O)(=O)C2=CC=C(N)C=C2)=NO1

Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Tamoxifen (NA)	10540-29-1	Chemotherapy agent	 2-[4-[(Z)-1,2-di(phenyl)but-1-enyl]phenoxy]-N,N-dimethylethanamine CCC(C1=CC=CC=C1)=C(C1=CC=CC=C1)C1=CC=C(OCCN(C)C)C=C1
Triclosan	3380-34-5	Antibacterial	 5-chloro-2-(2,4-dichlorophenoxy)phenol C1=CC(=C(C=C1Cl)O)OC2=C(C=C(C=C2)Cl)Cl
Trimethoprim (Cotrim®)	738-70-5	Antiinfective	 5-[(3,4,5-trimethoxyphenyl)methyl]pyrimidine-2,4-diamine COC1=CC(CC2=CN=C(N)N=C2N)=CC(OC)=C1OC

Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
EDCs			
Atrazine	1912-24-9	Herbicide	 1-chloro-3-ethylamino-5-isopropylamino-2,4,6-triazine CCNC1=NC(=NC(=N1)Cl)NC(C)C
Bisphenol A	80-05-7	Industrial chemical	 4,4''-dihydroxy-2,2-diphenylpropane CC(C)(C1=CC=C(C=C1)O)C2=CC=C(C=C2)O
Butylbenzyl phthalate	85-68-7	Industrial chemical; PPCP ingredient	 butyl benzyl benzene-1,2-dicarboxylate CCCCOC(=O)C1=CC=CC=C1C(=O)OCC2=CC=CC=C2
DEHP	117-81-7	Industrial chemical; ; PPCP ingredient	 bis(2-ethylhexyl) benzene-1,2-dicarboxylate CCCCC(CC)COC(=O)C1=CC=CC=C1C(=O)OCC(CC)CCCC

Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Dibutyl phthalate	84-74-2	Industrial chemical; PPCP ingredient	 dibutyl benzene-1,2-dicarboxylate CCCCOC(=O)C1=CC=CC=C1C(=O)OCCCC
17ß-Estradiol	50-28-2	Endogenous hormone	 (8S,9S,13S,14S,17S)-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydro cyclopenta[a]phenanthrene-3,17-diol CC12CCC3C(C1CCC2O)CCC4=C3C=CC(=C4)O
Estrone	53-16-7	Endogenous hormone	 3-hydroxy-13-methyl- 6,7,8,9,11,12,13,14,15,16- decahydrocyclopenta[a]phenanthren- 17- one CC12CCC3C(C1CCC2=O)CCC4=C3C=CC(=C4)O
Ethynylestradiol	319-85-7	Pharmaceutical	 17-ethynyl-13-methyl-7,8,9,11,12,13,14,15,16,17- decahydro-6H-cyclopenta[a] phenanthrene-3,17-diol CC12CCC3C(C1CCC2(C#C)O)CCC4=C3C=CC(=C4)O

Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
Lindane (BHC-gamma)	58-89-9	Pesticide	 1,2,3,4,5,6-hexachlorocyclohexane C1(C(C(C(C(C1Cl)Cl)Cl)Cl)Cl)Cl
Linuron	330-55-2	Herbicide	 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea CN(C(=O)NC1=CC(=C(C=C1)Cl)Cl)OC
Methoxychlor	72-43-5	Pesticide	 1-methoxy-4-[2,2,2-trichloro-1-(4-methoxyphenyl)ethyl]benzene COC1=CC=C(C=C1)C(C2=CC=C(C=C2)OC)C(Cl)(Cl)Cl
4-Nonylphenol	104-40-5	Industrial chemical; PPCP ingredient	 4-nonylphenol CCCCCCCCCC1=CC=C(C=C1)O

Compound	CAS No.	Category	Structure, IUPAC Nomenclature, and SMILES Code
4-tert-Octylphenol	1806-26-4	Industrial chemical; PPCP ingredient	 4-octylphenol CCCCCCCCC1=CC=C(C=C1)O
Vinclozolin	50471-44-8	Fungicide	 3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-1,3-oxazolidine-2,4-dione CC1(C(=O)N(C(=O)O1)C2=CC(=CC(=C2)Cl)Cl)C=C

APPENDIX A REFERENCES

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APPENDIX B

UNCERTAINTY FACTORS APPLIED TO THERAPEUTIC DOSES BY SCHWAB ET AL. (2005) AND ACCEPTABLE DAILY INTAKES DEVELOPED BY WEBB ET AL. (2003) AND SCHWAB ET AL. (2005) BASED ON THERAPEUTIC DOSES

Table B-1. Summary of Uncertainty Factors Applied by Schwab et al. (2005) in Developing Screening Levels from Lowest Therapeutic Doses

Category	Value
Interspecies Differences	• 10 when no human data are available unless considerations that follow apply • 3 when ADME data are similar for multiple species, including humans or non-human primates • 1 when derivation is based on human data
Intra-individual Susceptibility	• 10 when NOAEL is from a general adult population and/or animal study, with no multigenerational study of toxicity • 3 when effect is therapeutic and there is little difference between the median and minimally effective dose • 3 when using an adjusted LOEL, NOEL or therapeutic dose specific to a sensitive sub-population • 1 when sufficient post-marketing data indicate the absence of specific and particularly sensitive individuals or when using a LOEL or NOEL for a specifically identified sensitive human population based on a large post-marketing study
LOAEL to NOAEL	• 10 when a NOAEL is not available • 3 when the LOAEL is a therapeutic response, operative only in a disease state • 1 when the LOEL is associated with a homeostatic response or an equivocal effect (i.e., the LOEL is a NOAEL)
Duration of Exposure	• 10 when no relevant chronic data are available • 3 when no chronic data are available, but PK or PD analyses suggest little persistence of compound or effect • 1 when adequate chronic data are available
Data Quality	• 10, 3, or 1, or a number smaller than 1, are recommended based on professional judgment on the quality of data available on a compound • >1 if critical studies used small number of animals or groups • >1 if results are poorly described or analyzed • Data require route-to-route extrapolation to be relevant to the exposure condition (UF < or >1 depending on the relevance and relative sensitivity to the effect by alternate dosing routes) • >1 if important specialized studies were not conducted (e.g., reproductive, teratogenicity, carcinogenicity) when positive genetic toxicity data is available • The absence of data is mitigated (UF <1) or exacerbated (UF >1) by results on a compound of similar structure and responses • Non-standard study designs (UF < or > 1 depending on the nature of the study) • Esoteric or extreme effects (UF < or > 1 depending on the nature of the study) • NOEL is the highest dose tested (possibly a UF <1)

Table B-2. ADIs Developed by Webb et al. (2003) and Schwab et al. (2005) Based on Therapeutic Doses of Pharmaceuticals

Substance	POD (mg/kg/day)	UFs[a]	ADI (µg/kg/day)	Critical effect and Basis for POD[b]
Webb et al. (2003)				
Clenbuterol	0.00029	10 (interindividual differences)	0.029	Therapeutic effect. POD is lowest single effective therapeutic dose in adults of 20 mcg/day or 0.00029 mg/kg/day in a 70-kg adult.
Schwab et al. (2005)				
Acetaminophen	9.3	27 (1,3,3,3,1)	340	Therapeutic effect. POD is the lowest single effective therapeutic dose in adults of 650 mg, or 9.3 mg/kg in a 70-kg adult, when taken once in a day (Goodman and Gilman, 2001)
Albuterol	0.029	10.2 (1,3.2,3.2,1,1)	2.8	Therapeutic effect. POD is the lowest single therapeutic oral dose in adults of 2 mg/day or 0.029 mg/kg/day taken three to four times per day (HSDB, 2005; PDR, 2005b)
Cimetidine	2.9	100 (1,10,10,1,1)	29	Therapeutic effect. POD is the lowest single therapeutic dose for over-the-counter use for reducing gastric acid secretion in adults of 200 mg/day or 2.9 mg/kg/day taken once or twice daily (GSK, 2002; Martindale, 2005)
Ciprofloxacin	NA	NA	1.6	Sensitivity of human intestinal microflora. ADI of 1.6 mcg/kg/day is based on minimum inhibitory concentration (MIC) values for ciprofloxacin (lowest MIC50D 0.0016 mcg/ml) against human intestinal flora following EMEA methodology (EMEA, 1998)
Codeine	0.21	100 (1,10,10,1,1)	2	Therapeutic effect. POD is the lowest single therapeutic dose for pain relief in adults of 15 mg/day or 0.21 mg/kg/day taken four to six times per day (PDR, 2005c)
Dehydronifedipine	100	100 (10,10,1,10,1)	100	Animal study NOEL. POD is the NOEL in the longest term data available for the metabolite that is 100 mg/kg/day in rodent studies of up to four weeks in duration (Bayer HealthCare, private communication, March, 28, 2005)

Substance	POD (mg/kg/day)	UFs[a]	ADI (µg/kg/day)	Critical effect and Basis for POD[b]
Digoxigenin	0.0007	10 (1,1,10,1,1)	0.07	Therapeutic effect of parent compound. Digoxigenin is a metabolite of digoxin and has similar properties but reduced activity when compared to the parent compound (ASHP, 2003; Hoffman and Bigger, 1990). Digoxigenin is assumed to be pharmacologically equipotent with digoxin for purposes of this ADI
Digoxin	0.0007	10 (1,1,10,1,1)	0.07	Therapeutic effect. POD is the lowest maintenance dose to regulate heart rate and increase cardiac output in a very sensitive population (i.e., persons with congestive heart failure and renal impairment) of 0.05 mg/day or 0.0007 mg/kg/day taken once daily (PDR, 2005a)
Diltiazem	0.43	30 (1,10,3,1,1)	14	Therapeutic effect. POD is the lowest single therapeutic dose to lower blood pressure in adults of 30 mg or 0.43 mg/kg taken four times per day (Hoechst et al., 1999)
Doxycycline	NA	NA	30	Sensitivity of human intestinal microflora. ADI of 30 mcg/kg/day was established by WHO based on antimicrobial sensitivity of human intestinal microflora (JECFA, 1998)
Enalaprilat	0.6	9 (1,3,3,1,1)	70	Therapeutic effect. POD is based on an initial dose to lower blood pressure in adults of 1.25 mg given intravenously every 6 h (Goodman and Gilman, 2001). POD calculated using a bodyweight of 70 kg and 3% oral bioavailability (Merck, 2005)

Substance	POD (mg/kg/day)	UFs[a]	ADI (µg/kg/day)	Critical effect and Basis for POD[b]
Erythromycin-H2O	3.6	90 (1,3,3,10,1)	40	Therapeutic effect of parent compound. POD is the lowest single therapeutic dose in adults of 250 mg/day or 3.6 mg/kg/day taken four times per day (Goodman and Gilman, 2001). ADI established by EMEA based on antimicrobial activity of the parent is not applicable because the erythromycin-H2O metabolite is not active as an antibiotic (Roth and Fenner, 1994)
Fluoxetine	0.29	100 (1,10,10,1,1)	2.9	Therapeutic effect. POD is the lowest therapeutic dose for depression in adults of 20 mg/day or 0.29 mg/kg/day taken once daily (PDR, 2005c)
Gemfibrozil	8.6	150 (1,5,3,1,10)	55	Therapeutic effect. POD is the lowest single therapeutic dose for reducing cholesterol in adults of 600 mg/day or 8.6 mg/kg/day taken twice daily (Pfizer, 2003)
Ibuprofen	2.9	27 (1,3,3,1,3)	110	Therapeutic effect. POD is the lowest single therapeutic dose for pain relief in adults of 200 mg/day or 2.9 mg/kg/day taken four to six times per day (PDR, 2005b)
Lincomycin	2.5	100 (1,10,1,1,10)	25	Sensitivity of human intestinal microflora. POD was established by WHO based on correlation to clindamycin, which had a human intestinal microflora NOEL of 2.5 mg/kg/day (JECFA, 2000)
Metformin	5.6	90 (1,10,3,1,3)	62	Therapeutic effect. POD is the lowest effective dose on blood glucose in adults of 500 mg/day of metformin HCl (390 mg/day or 5.6 mg/kg/day of metformin free base) taken once daily (Goodman and Gilman, 2001)
Norfloxacin	5.7	30 (1,10,3,1,1)	190	Gastrointestinal upset. POD is the GI effect associated with the lowest clinical dose, 400 mg/day or 5.7 mg/kg/day (Merck, 2004)

Substance	POD (mg/kg/day)	UFs[a]	ADI (µg/kg/day)	Critical effect and Basis for POD[b]
Oxytetracycline	NA	NA	30	Sensitivity of human intestinal microflora. ADI of 30 mcg/kg/day was established by WHO based on antimicrobial sensitivity of human intestinal microflora (JECFA, 1998)
Paroxetine metabolite	0.29	100 (1,10,10,1,1)	2.9	Therapeutic effect of parent compound. POD is the lowest therapeutic dose of the parent compound relative to antidepressant effects in adults of 20mg/day or 0.29mg/kg/day taken once daily (PDR, 2005c)
Ranitidine	1.1	100 (1,10,10,1,1)	11	Therapeutic effect. POD is the lowest therapeutic dose for over-the-counter use to reduce gastric acid secretion in adults of 75 mg/day or 1.1mg/kg/day taken once daily (PDR, 2005b)
Sulfamethoxazole	25	200 (10,10,1,1,2)	130	Animal study NOEL. POD is based on NOEL for thyroid tumors in rats that may have no relevance for humans. POD is the 25mg/kg/day dose of the rat studies (Swarm et al., 1973)
Sulfathiazole	5	100 (10,10,1,1,1)	50	Changes in thyroid tissue. Established by reference to the WHO assessment of sulfamethazine that had a NOEL of 5mg/kg for thyroid effects in animal studies. POD is the thyroid tissue NOEL of 5mg/kg/day (JECFA, 1994)
Tetracycline	NA	NA	30	Sensitivity of human intestinal microflora. ADI of 30 mcg/kg/day was established by WHO based on antimicrobial sensitivity of human intestinal microflora (JECFA, 1998)
Trimethoprim	NA	NA	4.2	Sensitivity of human intestinal microflora. ADI of 4.2mcg/kg/day was established by EMEA (1997) based on the in vitro minimum inhibitory concentration (MIC) of the most sensitive species in a study of trimethoprim activity against human gut flora

Substance	POD (mg/kg/day)	UFs[a]	ADI (μg/kg/day)	Critical effect and Basis for POD[b]
Warfarin sodium	0.014	90 (1,3,3,1,10)	0.16	Therapeutic effect. POD is a low fixed therapeutic dose (converted to free acid) that is sometimes effective in selected patients and is also sometimes used in more susceptible populations (e.g., Asians) of 1mg/day or 0.014mg/kg/day (Bern et al., 1997; Yu et al., 1996)

[a]Values in parentheses indicate uncertainty factor assigned in each of the following five areas: extrapolation from animal data to human, intra-individual susceptibility, LOAEL to NOAEL, study duration, database.

[b]References are as cited in Schwab et al. (2005).

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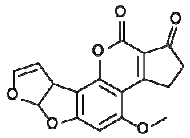
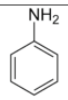
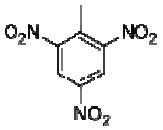
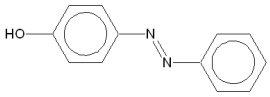
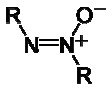
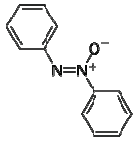
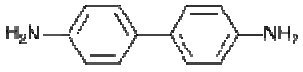
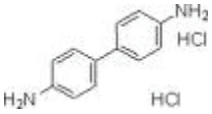
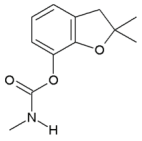
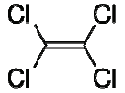
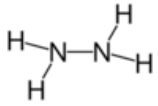
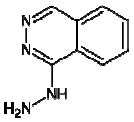
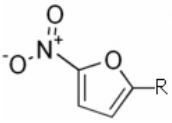
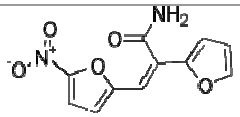
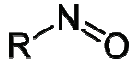
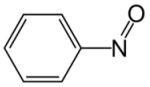
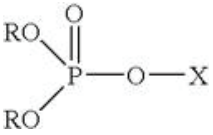
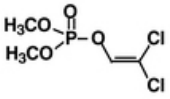
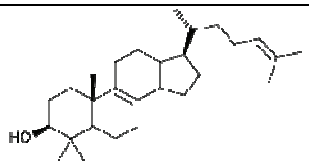
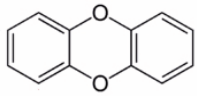
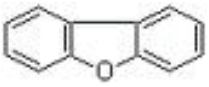
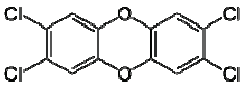
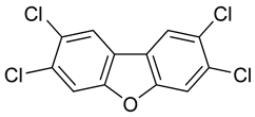
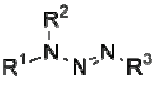
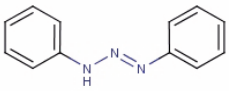
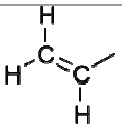
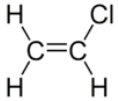
APPENDIX C

STRUCTURAL GROUPS IDENTIFIED BY CHEESEMAN ET AL. (1999) AND KROES ET AL. (2004) AS PRESENTING GENOTOXICITY POTENTIAL

Table C-1. Structural Groups Identified by Cheeseman et al. (1999) and Kroes et al. (2004) as Presenting Genotoxicity Potential

Structural Group	General Structure/ Functional Group	Example
*Aflatoxin-like compounds (Kroes et al., 2004)	Naturally occurring mycotoxins that are produced by many species of *Aspergillus*	 Aflatoxin B_1
Aromatic amines (Kroes et al., 2004)	-NH2, -NH- or nitrogen group(s) attached to an aromatic hydrocarbon	 Aniline
Aromatic nitrates (Kroes et al., 2004)	-NO2 attached to an aromatic hydrocarbon	 Trinitrotoluene
Azo compounds (Cheeseman et al., 1999 ; Kroes et al., 2004)	R-N=N-R', R and R' can be either aryl or alkyl	 Yellow azo dye
*Azoxy compounds (Cheeseman et al., 1999; Kroes et al., 2004)		 Azoxybenzene
Benzidine derivatives (Cheeseman et al., 1999; Kroes et al., 2004)		 Benzidine dihydrochloride
Carbamates (Kroes et al., 2004)	H O | || R_1-N- C-O-R_2	 Carbofuran
*Heavy metal containing compounds (Kroes et al., 2004)	Definitions vary, but include compounds containing mercury, lead, and cadmium	NA
Highly chlorinated compounds (Kroes et al., 2004)	$Cl_2C=CCl_2$	 Perchloroethylene

Structural Group	General Structure/ Functional Group	Example
Hydrazines (Cheeseman et al., 1999; Kroes et al., 2004)		 Hydralazine
α-Nitro furyl compounds (Kroes et al., 2004)		 Furylfuramide
*N-Nitroso compounds (Cheeseman et al., 1999 ; Kroes et al., 2004)		 Nitrosobenzene
Organophosphorus compounds (Kroes et al., 2004)		 Dichlorvos
Steroids (Kroes et al., 2004)	Terpenoid lipid characterized by a carbon skeleton with four fused rings, generally arranged in a 6-6-6-5 fashion	 Lanosterol
*Tetrahlogenated dibenzodioxins and dibenzofurans (Kroes et al., 2004)	 	 TCDD  TCDF
Triazenes (Cheeseman et al., 1999)		 1,3-diphenyl-1-triazene
Vinyl containing compounds (Kroes et al., 2004)		 Vinyl chloride

*Kroes et al. (2004) recommends not applying TTCs to these compounds because of their high potency for carcinogenicity.

APPENDIX C REFERENCES

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APPENDIX D

SUMMARY OF TOXICITY DATA FOR PPCPS AND EDCS

Table D-1. Summary of Toxicity Data for Alendronate

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Minsker, Manson, and Peter, 1993	NA	10	Unknown	Rat (F)	Reproductive (tremors, dystocia, and death at parturition)	NA, 23x	3,000 (10,3,10,3,3)= 0.0033
Rxlist, 2008d	5	NA	Unknown	Rat (M&F)	Reproductive (no effect on fertility)	11x, NA	300 (10,3,1,3,3)= 0.017
Merck, 2006	NA	0.5	Before mating-gestation	Rat (F)	Reproductive (protracted parturition due to maternal hypocalcemia)	NA, 1.1x	3,000 (10,3,10,3,3)= 0.00017
Rxlist, 2008d	35	NA	Gestation	Rabbit	Reproductive/developmental (no significant reproductive or teratogenic effects)	155x, NA	300 (10,3,1,3,3)= 0.12
Rxlist, 2008d	NA	1	Gestation	Rat	Developmental (decreased body weight gain in normal pups)	NA, 2.3x	3,000 (10,3,10,3,3)= 0.00033
Patlas et al., 1999	NA	10**	GD 11–20	Rat (F)	Developmental (changes in fetal bone structure)	NA, 23x	3,000 (10,3,10,3,3)= 0.0033
Rxlist, 2008d	2	5	92 weeks	Mouse (F)	Cancer(increased Harderian gland [a retro-orbital gland not present in humans] adenomas)	2.3x, 5.8x	NA
Rxlist, 2008d	10	NA	92 weeks	Mouse (M)	Cancer (no significant increase in tumors)	1.1x, NA	NA
Rxlist, 2008d	1	3.75	2 years	Rat (M)	Cancer (increased parafollicular cell [thyroid] adenomas)	2.3x, 8.5x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.071 mg/kg-d (glucocorticoid-induced osteoporosis).

**Subcutaneous dose adjusted to an oral dose assuming a relative oral bioavailability of 1% (Gertz et al., 1995)

Table D-2. Summary of Toxicity Data for Atenolol

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Bayliss et al., 2002, Lip et al., 1997, Lydakis et al., 1999	NA	0.8	Gestation	Human (F)	Developmental (decreased infant birth weights)	NA, 2.2x	300 (1,3,10,3,3)= 0.0027
McGuiness et al., 1997	NA	0.8	Chronic	Human	Immune (not specified)	NA, 2.2x	300 (1,10,10,1,3)= 0.0027
el-Sayed et al., 1998	NA	9	60 days	Rat (M)	Reproductive (decreased percent of progressive motility of sperm; decreased testosterone)	NA, 4.2x	3,000 (10,3,10,3,3)= 0.0030
Drugs.com, 2006c	200	NA	NA	Rat (M&F)	Reproductive (fertility)	89x, NA	300 (10,3,1,3,3)= 0.67
Drugs.com, 2006c	25	50	Gestation	Rat (F)	Developmental (increased embryo/ fetal resorptions)	11x, 23x	300 (10,3,1,3,3)= 0.083
Drugs.com, 2006c	150	300	NA	Rat	Systemic (atrial degeneration of heart)	67x, 133x	NA (10,10,1,NA,3)= NA
Drugs.com, 2006c	NA	15	NA	Dog	Systemic (vacuolation of epithelial cells of duodenum)	NA, 23x	NA (10,10,10,NA,3)= NA
Zavanella et al., 1994	300**	NA	Up to 21 months	Rat	Cancer (no effects)	133x, NA	NA
Zavenella et al., 1994	300**	NA	Up to 21 months	Mouse	Cancer (no effects)	67x, NA	NA
Drugs.com, 2006c	NA	500	Chronic	Rat	Cancer (thyroid parafollicular cell carcinomas in males)	NA, 225x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.36 mg/kg-d (hypertension in adults).

**Animals were initiated with a single dose of diethylnitrosamine (DEN, 200 mg/kg, i.p.) and, after 17 days of recovery, treated with atenolol (oral).

Table D-3. Summary of Toxicity Data for Atorvastatin

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
Dostal et al., 2001	120	NA	2 years	Dog (M)	Reproductive (semen parameters; reproductive organs)	220x, NA	100 (10,3,1,1,3)= 1.2
Dostal et al., 1996	175	NA	~27 weeks	Rat (M)	Reproductive (fertility & general)	93x, NA	100 (10,3,1,1,3)= 1.75
Dostal et al., 1996	225	NA	~27 weeks	Rat (F)	Reproductive (fertility & general)	120x, NA	100 (10,3,1,1,3)= 2.25
Pfizer, 2003	NA	100	11 weeks	Rat (M)	Reproductive (decreased sperm motility and spermatid head concentration, and increased abnormal sperm)	NA, 53x	10,000 (10,3,10,10,3)= 0.010
Pfizer, 2003	NA	30	3 months	Rat (M)	Reproductive (reduced testes weight)	NA, 16x	1,000 (10,3,1,10,3)= 0.030
Dostal et al., 1994	100	NA	GD 6–15	Rat (F)	Developmental (teratogenic effects)	53x, NA	300 (10,3,1,3,3)= 0.33
Henck et al., 1998	NA	20	GD 7–PND 21	Rat (M)	Developmental (behavioral effects—reduced acoustic startle; reduced pup weight at 100 mg/kg-d and higher)	NA, 11x	3,000 (10,3,10,3,3)= 0.0067
Dostal et al., 1994	50	NA	GD 6–18	Rabbit (F)	Developmental (teratogenic effects)	53x, NA	300 (10,3,1,3,3)= 0.17
Henck et al., 1998	20	100	~27 weeks	Rat (M)	Systemic (decreased body weight gain)	11x, 53x	300

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
							(10,10,1,1,3)= 0.067
Pfizer, 2003	200	400	2 years	Mouse (M&F)	Cancer (liver adenomas and carcinomas)	53x, 110x	NA
Pfizer, 2003	30	100	2 years	Rat (F)	Cancer (rhabdomyosarcoma and fibrosarcoma)	16x, 53x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.3 mg/kg-d (hypercholesterolemia in children).

Table D-4. Summary of Toxicity Data for Carbamazepine

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration*	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
Hernandez-Diaz et al., 2000, 2001; Samren et al., 1997, 1999	NA	3	Gestation	Human (F)	Developmental (increased neural tube defects, cardiovascular defects, oral clefts, and urinary tract defects)	NA, 3x	300 (1,3,10,3,3)= 0.010
Artama et al., 2005	3	NA	Gestation	Human (F)	Developmental (no effect)	3x, NA	30 (1,3,1,3,3)= 0.10
FDA, 1968	300	400	Gestation	Mouse (F)	Reproductive (decreased fertility, increased resorptions)	24x, 33x	300 (10,3,1,3,3)= 1.0
FDA, 1968	NA	225	Gestation	Rabbit (F)	Reproductive (decreased fertility and number of fetuses, increased resorptions)	NA, 73x	3,000 (10,3,10,3,3)= 0.075
FDA, 1968	48	192	Gestation	Rat (M&F)	Developmental and reproductive (decreased body weight increase in pups)	7.7x, 31x	300 (10,3,1,3,3)= 0.16
FDA, 1968	NA	250	GD 7–16	Rat (F)	Developmental (rib kinking in pups)	NA, 40x	3,000 (10,3,10,3,3)= 0.083
FDA, 1968	NA	650	Gestation	Rat (F)	Developmental (cleft palate, clubfoot, absence of one or both eyes)	NA, 105x	3,000 (10,3,10,3,3)= 0.22
FDA, 1968	192	NA	Gestation	Mouse (M&F)	Developmental and reproductive (no effect)	16x, NA	300 (10,3,1,3,3)= 0.64
FDA, 1968	100	NA	5 days/wk for 52	Dog (F)	Systemic (no effect)	56x, NA	300 (10,10,1,1,3)=

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration*	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
			weeks				0.33
Vorhees et al., 1990	NA	200	GD 7–18	Rat (F)	Developmental (decreased fetal weight)	NA, 32x	3,000 (10,3,10,3,3)= 0.067
Novartis, 2000, Singh et al., 2005	NA	25	2 years	Rat	Cancer (liver carcinomas)	NA, 4x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 1.0 mg/kg-d (epilepsy in children).

Table D-5. Summary of Toxicity Data for Desloratadine

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
FDA, 2001	24	NA	14 days prior to mating to GD 7	Rat (F)	Reproductive (no effect on female fertility)	108x, NA	300 (10,3,1,3,3)= 0.080
FDA, 2001	3	12	70 days prior to mating–mating period	Rat (M)	Reproductive (M decrease in fertility demonstrated by reduced (F) conception rates, decreased sperm numbers and motility, and histopathologic testicular changes)	13x, 53x	300 (10,3,1,3,3)= 0.010
RxList, 2008e	9	24	During gestation	Rat (F)	Reproductive/developmental (increased pre-implantation loss)	42x, 108x	300 (10,3,1,3,3)= 0.030
FDA, 2001	6	24	GD 6–15	Rat (F)	Developmental (reduced fetal weight, skeletal variations)	27x, 108x	300 (10,3,1,3,3)= 0.020
FDA, 2001	3	9	GD 6–PND21	Rat (F)	Developmental (reduced pup body weight and slow righting reflex)	13x, 42x	300 (10,3,1,3,3)= 0.010
FDA, 2001	60	NA	GD 7–19	Rabbit	Developmental (no significant teratogenic effects)	530x, NA	300 (10,3,1,3,3)= 0.20
RxList, 2008e	16/32 (M/F)	NA	2 years	Mouse (M&F)	Cancer (no significant increases in any tumors)	36/72x, NA	NA
FDA, 2002	NA	40 (loratadine)	18 months	Mouse (M)	Cancer (increased hepatocellular tumors)	NA, 181x	NA
FDA, 2002	NA	10	60	Rat (M)	Cancer (increased hepatocellular	NA, 44x	NA

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
		(loratadine)	2 years		tumors)		
FDA, 2002	NA	25 (loratadine)	2 years	Rat (F)	Cancer (increased hepatocellular tumors)	NA, 110x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.036 mg/kg-d (relief of nasal and nonnasal symptoms of seasonal and perennial allergic rhinitis).

Table D-6. Summary of Toxicity Data for Diazepam

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
IARC, 1996	0.06	NA	Gestation	Human (F)	Developmental (no effect)	2.1x, NA	10 (1,3,1,3,1)= 0.0060
Chapin et al., 1992	NA	26	2-Generation	Rat (M&F)	Reproductive (decreased live pups per litter, first generation)	NA, 140x	300 (10,3,10,1,1)= 0.087
Drugs.com, 2006a	80	100	Before and during gestation	Rat	Reproductive (decreased pregnancies and surviving offspring)	450x, 550x	100 (10,3,1,3,1)= 0.80
Chapin et al., 1992	84	240	2-Generation	Rat (M&F)	Developmental (decreased pup body and organ weights)	480x, 1300x	30 (10,3,1,1,1)= 2.8
Drugs.com, 2006a	80	NA	NA	Rat	Developmental (no effect)	450x, NA	100 (10,3,1,3,1)= 0.80
Frieder et al., 1984	NA	10	Gestation (16 days)	Rat	Developmental (extensive pathological changes in brain histology)	NA, 69x	1,000 (10,3,10,3,1)= 0.010
Hernandez-Alvarez et al. 1998	NA	2.5**	GD 6–17	Rat (M)	Developmental/Reproductive (altered adult male sexual behavior)	NA, 14x	1,000 (10,3,10,3,1)= 0.0025
Kellogg et al., 1991	NA	1**	GD 14–20	Rat	Developmental (behaviorial changes in offspring)	NA, 5.5x	1,000 (10,3,10,3,1)= 0.0010
Kellogg and Retell, 1986	NA	1**	GD 13–20	Rat	Developmental (decreased release of [3H] norepinephrine from the hippocampus)	NA, 5.5x	1,000 (10,3,10,3,1)= 0.0010

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
Miranda et al., 1989	NA	1**	GD 14–20	Rat	Developmental (elevated levels of brain thiobarbituric acid [TBA] reactive material)	NA, 5.5x	1,000 (10,3,10,3,1)= 0.0010
Miranda et al., 1990	NA	1**	Gestation	Rat	Developmental (altered utilization of brain high energy phosphate compounds)	NA, 5.5x	1,000 (10,3,10,3,1)= 0.0010
Ryan and Pappas, 1986	NA	1**	GD 14–20	Rat	Developmental (decreased pup viability, neurobehavioral alterations)	NA, 5.5x	1,000 (10,3,10,3,1)= 0.0010
Silva and Palermo-Neto, 1999	NA	1**	Gestation	Rat	Developmental (immune)	NA, 5.5x	1,000 (10,3,10,3,1)= 0.0010
Silva and Palermo-Neto, 1999	NA	2**	GD 14–20	Rat	Developmental (effects on testes or vaginal opening, increased locomotor activity)	NA, 11x	300 (10,3,10,1,1)= 0.0067
Tocco et al., 1987	NA	400	Gestation (2 days)	Rat	Developmental (cleft palate)	NA, 2200x	1,000 (10,3,10,3,1)= 0.40
Weber and Schmahl, 1983	1	5**	Gestation (5 days)	Rat	Developmental (reduced brain enzyme activity after 16 days of age)	5.5x, 28x	100 (10,3,1,3,1)= 0.010

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.029 mg/kg-d (anxiety in adults, geriatric).

**Subcutaneous or IV dose not adjusted because oral bioavailability is nearly complete, ranging from about 97–100% (Ochs et al., 1982).

Table D-7. Summary of Toxicity Data for Diclofenac

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
Novartis, 2002	4	NA	NA	Rat (M&F)	Reproductive (no effect on fertility or reproductive performance)	0.5x, NA	300 (10,3,1,3,3)= 0.013
Novartis, 2002	20	NA	Gestation	Mouse (F)	Developmental (no effect)	1.1x, NA	300 (10,3,1,3,3)= 0.067
Novartis, 2002	10	NA	Gestation	Rat (F)	Developmental (no effect)	1.1x, NA	300 (10,3,1,3,3)= 0.033
Novartis, 2002	10	NA	Gestation	Rabbit (F)	Developmental (no effect)	2.3x, NA	300 (10,3,1,3,3)= 0.033
Novartis, 2002	2	NA	2 years	Rat	Cancer (no effect)	0.23x, NA	NA
Novartis, 2002	1	NA	2 years	Mouse (F)	Cancer (no effect)	0.058x, NA	NA
Novartis, 2002	0.3	NA	2 years	Mouse (M)	Cancer (no effect)	0.017x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 1.4 mg/kg-d (arthritis in adults).

Table D-8. Summary of Toxicity Data for Doxycycline

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and associated dose (mg/kg-d)
FDA, 2006	100	250	Prior to mating until GD 7 (F)	Rat (F)	Reproductive (decreased mean number of implantations)	11x, 56x	300 (10,3,1,3,3)= 0.33
FDA, 2006	NA	50 (low dose)	Prior to mating until mating	Rat (M)	Reproductive (decreased sperm velocity)	NA, 5.8x	3,000 (10,3,10,3,3)= 0.017
FDA, 2006	100	400	13 weeks (oral, gavage)	Rat	Systemic (trend toward decreased weight gain, suppressed erythrocyte parameters, reduced plasma protein, mild GI irritation)	11x, 46x	1,000 (10,3,1,10,3)= 0.10
RxList, 2008f	NA	~3.0	During pregnancy	Human (F)	Developmental (weak but marginally statistically significant association with total malformations)	NA, 2.1x	300 (1,3,10,3,3)= 0.010
Siddiqui and Janjua, 2002	NA	8 **	GD 15–19; PND 1 (pups)	Rat	Developmental (delayed skeletal differentiation in long bones)	NA, 0.93x	3,000 (10,3,10,3,3)= 0.0027
FDA, 2006	75	200	2 years	Rat (F)	Cancer (increased uterine polyps)	8.6x, 23x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 1.4 mg/kg-d (malaria prophylaxis).

**Intraperitoneal dose; because reported oral bioavailabilities of doxycycline range widely, from about ~40– 100% depending on fasting conditions, pH, and other factors, no adjustment to the dose was made.

Table D-9. Summary of Toxicity Data for Enalapril

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Tabacova and Kimmel, 2001; Tabacova et al., 2003	NA	0.07	Gestation	Human (F)	Developmental (congenital malformations)	NA, 1.9x	300 (1,3,10,3,3)= 0.00023
al-Harbi et al., 1992	3	10	GD 6–12	Rat (F)	Reproductive/Developmental (decreased implants and litter size, increased resorbed fetuses, reduced growth)	13x, 44x	300 (10,3,1,3,3)= 0.010
Valdes et al., 1992	NA	15	GD 1–9 or 10–20	Rat (F)	Reproductive/Developmental (reduced placental/ fetal size)	NA, 67x	3,000 (10,3,10,3,3)= 0.0050
FDA, 1985	NA	1	GD 6–18	Rabbit (F)	Reproductive/Developmental (increased resorbed fetuses, decreased live fetuses per litter)	NA, 8.9x	3,000 (10,3,10,3,3)= 0.00033
FDA, 1985	120	1200	GD 6–17	Rat	Reproductive/Developmental (decreased fetal weight)	530x, 5300x	300 (10,3,1,3,3)= 0.40
FDA, 1985	90	NA	15 days <mating-gest (14 weeks)	Rat (F)	Reproductive (no effect)	420x, NA	300 (10,3,1,3,3)= 0.30
FDA, 1985	90	NA	70 days <mating-gest (14 weeks)	Rat (M)	Reproductive (no effect)	420x, NA	300 (10,3,1,3,3)= 0.30
Harewood et al., 1994	NA	7.5	Chronic, from < conception	Baboon (F)	Developmental (fetal death, growth retardation)	NA, 210x	1,000 (10,3,10,1,3)= 0.0075

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
FDA, 1985	NA	30	14 week incl gestation	Rat (M&F)	Developmental (growth retardation)	NA, 58x	3,000 (10, 3,10,3,3)= 0.010
FDA, 1985	NA	10	GD 15–PND 20	Rat	Developmental (growth retardation, developmental delay)	NA, 44x	3,000 (10,3,10,3,3)= 0.0033
FDA 1985	200	NA	GD 6–17	Rat	Developmental (no effect)	890x, NA	300 (10,3,1,3,3)= 0.67
FDA, 1985; Minsker et al., 1990	30	NA	GD 6–18	Rabbit	Developmental (no effect)	280x, NA	300 (10,3,1,3,3)= 0.10
Minsker et al., 1990	NA	1.0	13 days	Rabbit (F)	Liver (nephrotoxicity- elevated serum urea nitrogen concentrations)	NA, 8.9x	3,000 (3,3,10,10,3)= 0.00033
FDA, 1985	NA	30	3 months	Dog	Kidney (functional changes)	NA, 470x	10,000 (10,3,10,10,3)= 0.0030
FDA, 1985	10	30	3 months	Rat	Systemic (decreased body weight gains)	44x, 130x	1,000 (10,3,1,10,3)= 0.010
FDA 1985	30	NA	3 months	Monkey	Systemic (no effect)	58x, NA	1,000 (10,3,1,10,3)= 0.030
FDA, 1985	NA	10	1 year	Rat (M&F)	Systemic (decreased body weight)	NA, 44x	1,000 (10,3,10,1,3)= 0.010

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
FDA, 1985	15	NA	1 year	Dog (M&F)	Systemic (no effect)	230x, NA	100 (10,3,1,1,3)= 0.15
FDA, 1985, Merck, 2001	90	NA	106 weeks	Rat	Cancer (no effects)	420x, NA	NA
FDA, 1985, Merck, 2001	180	NA	94 weeks	Mouse (F)	Cancer (no effects)	420x, NA	NA
FDA, 1985, Merck, 2001	90	NA	94 weeks	Mouse (M)	Cancer (no effects)	203x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.036 mg/kg-d (hypertension, in adults with renal impairment).

Table D-10. Summary of Toxicity Data for Fluconazole

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Mastroiacovo et al., 1996	~2.1–5.7**	NA	Exposure during first trimester	Human (F)	Reproductive/developmental (no increase in the prevalence of miscarriages, congenital anomalies, and low birth weight)	3.0-8.0x, NA	30 (1,3,1,3,3)= 0.19
Sorensen et al., 1999	~2.1–5.7**	NA	Exposure just before or during pregnancy	Human (F)	Reproductive/developmental (no increased risk of congenital malformations, low birth weight, or preterm birth)	3.0-8.0x, NA	30 (1,3,1,3,3)= 0.19
RxList, 2008a	10	20	Mating/ gestation	Rat (F)	Reproductive (slightly delayed onset of parturition)	2.3x, 4.5x	300 (10,3,1,3,3)= 0.033
RxList, 2008a	20	NA	Mating/ gestation	Rat (M)	Reproductive (no evidence of fertility effects)	4.5x, NA	300 (10,3,1,3,3)= 0.067
RxList, 2008a	5	20	Mating/ gestation	Rat (F)	Reproductive (dystocia and prolongation of parturition)	1.1x, 4.5x	300 (10,3,1,3,3)= 0.017
el-Medany and Hagar, 2002	NA	50	1 month	Rat (M)	Reproductive (decreased serum testosterone, semen volume, count and percentage of motile sperms; increased serum prolactin, follicle stimulating hormone, and luteinizing hormone)	NA, 11x	3,000 (10,3,10,3,3)= 0.017
RxList, 2008a	25	75	Gestation during organo-genesis	Rabbit (F)	Reproductive (spontaneous abortions)	11x, 34x	300 (10,3,1,3,3)= 0.083
Tiboni and Giampietro 2005	87.5	175	GD 10	Mouse (F)	Developmental (increased incidence of cleft palate)	10x, 20x	300 (10,3,1,3,3)=

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
							0.29
RxList, 2008a	10	25	Gestation during organo genesis	Rat (F)	Developmental (increased fetal anatomical variants [supernumerary ribs, renal pelvis dilation] and delays in ossification)	2.3x, 5.6x	300 (10,3,1,3,3)= 0.033
RxList, 2008a	10	25	Gestation during organo genesis	Rat (F)	Systemic/reproductive (reduced maternal weight gain)	2.3x, 5.6x	300 (10,3,1,3,3)= 0.033
RxList, 2008a	NA	5	Gestation during organo genesis	Rabbit (F)	Systemic/reproductive (reduced maternal weight gain)	NA, 2.3x	3,000 (10,3,10,3,3)= 0.0017
RxList, 2008a, CPDB, 2007	10	NA	2 years	Mouse	Cancer (no evidence of carcinogenicity)	1.1x, NA	NA
RxList, 2008a, CPDB, 2007	2.5	5	2 years	Rat (M)	Cancer (increased incidence of hepatocellular adenomas)	0.56x, 1.1x	NA
RxList, 2008a, CPDB, 2007	10	NA	2 years	Rat (F)	Cancer (no evidence of carcinogenicity)	2.3x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.71 mg/kg-d (urinary tract infection in adults).
**Assuming a daily dose of 150–400 mg/day, based on recommended therapeutic doses, and a body weight of 70 kg.

Table D-11. Summary of Toxicity Data for Fluoxetine

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration*	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
NTP, 2004	NA	0.29	Gestation	Human (F)	Developmental (shortened gestation, reduced birth weight, poor neonatal adaptation)	NA, 1.1x	300 (1,3,10,3,3)= 0.00097
da-Silva et al., 1999	16	NA	GD 15–20	Rat (F)	Reproductive/ Developmental (no effects)	7.9x, NA	300 (10,3,1,3,3)= 0.053
Vorhees et al., 1994	5	12	GD 7–20	Rat (F)	Reproductive/ Developmental (increased stillborn pups, decreased pup weight, increased pup deaths)	2.5x, 5.8x	300 (10,3,1,3,3)= 0.017
Byrd and Markham, 1994	15	NA	GD 6–18	Rabbit (F)	Developmental (no effects)	15x, NA	300 (10,3,1,3,3)= 0.050
Byrd and Markham, 1994	12.5	NA	GD 6–15	Rat (F)	Developmental (no effects)	61x, NA	300 (10,3,1,3,3)= 0.042
NTP, 2004	NA	25	Postnatally	Rat (M)	Developmental (behavioral effects)	NA, 12x	3,000 (10,3,10,3,3)= 0.0083
Vorhees et al., 1994	12	NA	GD 7–20	Rat (F)	Developmental (no behavioral effects)	5.8x, NA	300 (10,3,1,3,3)= 0.040
Bendele et al., 1992	10	NA	2 years	Rat	Cancer (no effects)	4.8x, NA	NA
Bendele et al., 1992	10	NA	2 years	Mouse	Cancer (no effects)	2.4x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.33 mg/kg-d (depression and obsessive compulsive disorder in children).

Table D-12. Summary of Toxicity Data for Furosemide

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
RxList, 2008b	NA	25	Gestation	Rabbit (F)	Reproductive/developmental (unexplained maternal deaths and abortions)	NA, 28x	3,000 (10,3,10,3,3)= 0.0083
RxList, 2008b	NA	50	GD 12–17	Rabbit (F)	Reproductive/developmental (maternal deaths and abortions)	NA, 55x	3,000 (10,3,10,3,3)= 0.017
RxList, 2008b	100	NA	NA	Rat (M&F)	Reproductive (no impairment of fertility observed)	55x, NA	300 (10,3,1,3,3)= 0.33
HSDB, 2008	NA	300	GD 6–17	Rat (F)	Reproductive/developmental (increased resorption rates, decreased fetal weight, wavy ribs)	NA, 166x	3,000 (10,3,10,3,3)= 0.10
Gerber et al., 1978	3.3**	NA	One day during gestation	Dog (F)	Reproductive (no effect on production or metabolism of prostaglandin E2)	62x, NA	300 (10,3,1,3,3)= 0.011
NTP, 1989; Bucher et al., 1990	NA	89.3	2 years	Mouse (F)	Cancer (increased mammary gland tumors)	NA, 25x	NA
NTP, 1989; Bucher et al., 1990	NA	17.2	2 years	Rat (F)	Cancer (increased C-cell adenomas in the thyroid, though authors determined not associated with exposure)	NA, 9.7x	NA
NTP, 1989; Bucher et al. 1990	NA	13.7	2 years	Rat (M)	Cancer (increased pituitary adenomas at low dose; this increase was not seen at the next higher dose)	NA, 76x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.29 mg/kg-d (edema in adults).
**Intravenous dose adjusted to an oral dose assuming a relative oral bioavailability of 60% (RxList, 2008b).

Table D-13. Summary of Toxicity Data for Gemfibrozil

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration*	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Hall et al., 1981; Leiss et al., 1985	NA	17	NA	Human	Gallbladder disease/gallstones	NA, 1x	300 (1,10,10,1,3)= 0.057
Fitzgerald et al., 1987	94	318	Before, t/o gestation to weaning	Rat (M&F)	Reproductive (decreased fertility rates)	1x, 3x	300 (10,3,1,3,3)= 0.31
Fitzgerald et al., 1987	101	339	Before, t/o gestation to weaning	Rat (F)	Developmental (reduced offspring body weight)	1x, 3x	300 (10,3,1,3,3)= 0.34
Fitzgerald et al., 1987	92	310	15 days prior to mating	Rat (M)	Reproductive (decrease in male fertility)	1x, 3x	300 (10,3,1,3,3)= 0.31
Fitzgerald et al., 1987	281	NA	GD6– 15	Rat (F)	Developmental (no effect on fetuses)	2.6x, NA	300 (10,3,1,3,3)= 0.94
Fitzgerald et al., 1987	NA	92	GD 15– PND21	Rat (F)	Developmental (reduced offspring body weight)	NA, 1x	3,000 (10,3,10,3,3)= 0.031
Fitzgerald et al., 1987	200	NA	GD 6– 15	Rabbit (F)	Developmental (no effect on fetuses)	3.8x, NA	300 (10,3,1,3,3)= 0.67
Fitzgerald et al., 1981	0.3	300	2 years	Rat	Cancer (liver carcinomas)	0.003x, 2.8x	NA
Fitzgerald et al., 1981	300	NA	1.5 years	Mouse	Cancer (no effect)	1.4x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 17 mg/kg-d (lipid regulation in adults).

Table D-14. Summary of Toxicity Data for HHCB (galaxolide)

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Christian et al., 1999	150	500	GD 7–17	Rat (M&F)	Developmental (axial skeletal malformations)	NA	300 (10,3,1,3,3)= 0.50
Api and Ford, 1999	150	NA	90 days	Rat (M&F)	Systemic/reproductive (no histopathological changes of sex organs noted)	NA	300 (10,3,1,3,3)= 0.50
Christian et al., 1999	50	150	GD 7–17	Rat (F)	Systemic (maternal; clinical signs, reduced weight gain)	NA	3,000 (10,10,1,10,3)= 0.017

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = NA.

Table D-15. Summary of Toxicity Data for Ifosfamide

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Ypsilantis et al., 2003	NA	60**	1 day	Rabbit (M)	Reproductive (transient oligospermia)	NA, 0.56x	3,000 (10,3,10,3,3)= 0.020
RxList, 2008c	NA	10	GD 11	Mouse (F)	Developmental (resorptions increased and anomalies present)	NA, 0.024x	3,000 (10,3,10,3,3)= 0.0033
NTP, 1977	5**	10**	GD 11 (single dose)	Mouse (F)	Developmental (growth retardation)	0.012x, 0.024x	300 (10,3,1,3,3)= 0.017
RxList, 2008c	NA	3	GD 6–15	Rat (F)	Developmental (embryotoxic effects)	NA, 0.088x	3,000 (10,3,10,3,3)= 0.0010
RxList, 2008c	NA	7.3	GD 6–18	Rabbit (F)	Developmental (embryotoxic effects and increase in anomalies)	NA, 0.071x	3,000 (10,3,10,3,3)= 0.0024
NTP, 1977	NA	8.1**	8 weeks	Mouse	Cancer (increased lung tumors)	NA, 0.019x	NA
NTP, 1977	NA	4.3**	52 weeks	Mouse (F)	Cancer (increased malignant lymphomas of hematopoietic system)	NA, 0.010x	NA
NTP, 1977	8.6**	NA	52 weeks	Mouse (M)	Cancer (negative)	0.021x, NA	NA
NTP, 1977	NA	2.6**	52 weeks	Rat (F)	Cancer (increased uterine leiomyosarcomas and mammary fibroadenomas)	NA, 0.076x	NA
NTP, 1977	5.1**	NA	52 weeks	Rat (M)	Cancer (tumors of the hematopoietic system but not statistically significant)	0.15x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993), and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 34 mg/kg-d (germ cell testicular cancer in adults).

**Intravenous or intraperitoneal doses. Doses were not adjusted because reported oral bioavailabilities range from 92 to 100%, and a relative oral bioavailability of 100% was conservatively assumed.

Table D-16. Summary of Toxicity Data for Iopamidol / Iopromide

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Parravicini et al., 1996	NA	150**	1 dose between PND 3–7	Human (M&F)	Higher mean thyrotropin and lower free triiodothyronine and thyroxine levels in infants	NA	300 (1,3,10,3,3)= 0.50
Drugs.com, 2008	2.7x recom-mended human dose	NA	1 dose	Rat (M&F)	Reproductive/developmental (no effect on fertility or harm to the fetus)	NA	1,000 (10,3,1,10,3)= NA
Drugs.com, 2008	1.4x recom-mended human dose	NA	1 dose	Rabbit (M&F)	Reproductive/developmental (no effect on fertility or harm to the fetus)	NA	1,000 (10,3,1,10,3)= NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = NA.

**Assuming a recommended human dose of 150 mg/kg-d.

Table D-17. Summary of Toxicity Data for Lansoprazole

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
RxList, 2008g	15–60	NA	1 year	Human (M&F)	Reproductive (no clinically significant effects on the endocrine system or sexual function)	290, NA	10 (1,3,1,1,3)= 6.0
Fort et al., 1995	NA	1,200	3 months	Mouse (M)	Reproductive (reduced sperm in epididymides and atrophy of seminiferous tubules)	NA, 470x	3,000 (10,3,10,3,3)= 0.40
Fort et al., 1995	600	NA	2 years	Mouse (M)	Reproductive (no Leydig cell hyperplasia or tumors)	230x, NA	100 (10,3,1,1,3)= 6.0
TAP, 2004	33**	NA	9 weeks before thru mating	Rat (M)	Reproductive (no effect on fertility and mating performance)	25x, NA	300 (10,3,1,3,3)= 0.11
Fort et al., 1995	NA	300	3 months	Rat (M)	Reproductive (testicular atrophy)	NA, 230x	3,000 (10,3,10,3,3)= 0.10
Fort et al., 1995	NA	15	2 years	Rat (M)	Reproductive (increased Leydig cell hyperplasia and benign Leydig cell tumors)	NA, 11x	1,000 (10,3,10,1,3)= 0.015
Fort et al., 1995	NA	50	2 years	Rat (M)	Reproductive (increased seminiferous tubule degeneration/ atrophy)	NA, 39x	1,000 (10,3,10,1,3)= 0.050
TAP, 2004	33**	NA	GD 6–17	Rat (F)	Reproductive/ Developmental (no embryotoxicity/ teratogenicity)	25x, NA	300 (10,3,1,3,3)= 0.11
TAP, 2004	33**	NA	GD 6–18	Rabbit (F)	Reproductive/ Developmental (no embryotoxicity/ teratogenicity)	52x, NA	100 (10,3,1,1,3)=

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
							0.11
Fort et al., 1995	50	150	1 month	Cynomolgus monkey (M)	Reproductive (decreased plasma testosterone)	45x, 130x	300 (10,3,1,3,3)= 0.17
Diav-Citrin et al., 2005	0.21***	NA	During pregnancy	Human (F)	Developmental (no effect on congenital anomalies)	1x, NA	30 (1,3,1,3,3)= 0.0070
TAP, 2004	33**	NA	GD 15–PND 21	Rat (F)	Developmental (no effect)	25x, NA	300 (10,3,1,3,3)= 0.11
Fort et al., 1995	50	NA	6 months	Dog	Systemic (no changes in prostate weight)	130x, NA	300 (10,10,1,1,3)= 0.17
TAP, 2004	11**	NA	2 weeks	Dog	Systemic (no effect)	29x, NA	3,000 (10,10,1,10,3)= 0.0037
TAP, 2004	3.3**	11**	4 weeks	Dog	Systemic (necrosis and hypertrophy of parietal cells of stomach)	8.6x, 29x	3,000 (10,10,1,10,3)= 0.0011
TAP, 2004	NA	3.3**	13 weeks	Dog	Systemic (inflammation, fibrosis of vein wall, hyper-plasia of fundic glands, atrophy of parietal cells of stomach)	NA, 8.6x	10,000 (10,10,10,3,3)= 0.00033
Youssef et al., 2003	5	15	21–60 days old	Rat (M&F)	Systemic (increased absolute and relative duodenal and stomach weight and chronic adhesions to the spleen)	3.9x, 11x	1,000 (10,3,1,10,3)= 0.0050
TAP, 2004	11**	NA	2 weeks	Rat	Systemic (no effect)	8.6x, NA	3,000 (10,10,1,10,3)= 0.0037

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
TAP, 2004	33**	NA	4 weeks	Rat	Systemic (no effect)	25x, NA	3,000 (10,10,1,10,3)= 0.011
TAP, 2004	11**	33**	13 weeks	Rat	Systemic (decreased body weight gain, serum kinase activity, thymus weight)	8.6x, 25x	1,000 (10,10,1,3,3)= 0.011
TAP, 2004	NA	15	2 years	Mouse (M&F)	Cancer (increased liver tumors—adenoma & carcinoma and adenoma of rete testes)	NA, 5.7x	NA
TAP, 2004	NA	5	2 years	Rat (M&F)	Cancer (hypergastrinemia followed by ECL cell proliferation and formation of carcinoid tumors of the gastric mucosa, especially in F)	NA, 2.0x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.21 mg/kg-d (duodenal ulcer and GERD in adults).

**Based on IV dose. Adjusted to oral dose equivalent assuming an oral bioavailability of 90% (Gerloff et al., 1996).

*** Assumes a dose of 15 mg/day and a body weight of 70 kg.

Table D-18. Summary of Toxicity Data for Meprobamate (based on studies using carisoprodol)

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Grizzle et al., 1995	750	1200	14 weeks	Mouse	Developmental/reproductive (decreased pups born live and absolute and relative live pup weight, increased time in proestrous and estrous, increased epididymis weight)	8.7x, 14x	300 (10,3,1,3,3)= 2.5
NTP, 2000	100	200	13 weeks	Rat	Systemic (increased kidney weight and nephrotoxicity)	2.3x, 4.6x	3,000 (10,10,1,10,3)= 0.033
NTP, 2000	75	150	13 weeks	Mouse	Systemic (increased liver weight)	0.87x, 1.7x	3,000 (10,10,1,10,3)= 0.025

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 7 mg/kg-d (anxiety in children).

Table D-19. Summary of Toxicity Data for Methotrexate

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Janssen and Genta, 2000	NA	0.010 (Ther dose)	Pregnancy	Human (F)	Reproductive/ developmental (abortion, fetal malformations)	NA, 1x	300 (1,3,10,3,3)= 0.000033
Jordan et al., 1977	NA	0.33**	One dose during gestation	Rat (F)	Developmental (embryo lethality and malformation)	NA, 5.3x	3,000 (10,3,10,3,3)= 0.00011
Jordan et al., 977	NA	21**	GD10–15	Rabbit (F)	Developmental (embryo lethality and malformation)	NA, 680x	3,000 (10,3,10,3,3)= 0.0070
Freeman-Narrod and Narrod, 1977	2	3	12–18 months	Mouse (M)	Systemic (hematopoietic and gastrointestinal damage leading to early death)	16x, 24x	300 (10,10,1,1,3)= 0.0067
Hall et al., 1988	0.1	0.2	23 months (5 day on, 9 day off)	Rat (M&F)	Systemic (increased myeloid and erythroid bone marrow hypoplasia)	1.6x, 3.2x	300 (10,10,1,1,3)= 0.00033
Rustia and Shubik, 1973	0.65	NA	28 months	Mouse	Cancer (no increase in tumors)	5.3x, NA	NA
Rustia and Shubik, 1973	1.05	NA	23 months	Hamster	Cancer (no increase in tumors)	14x, NA	NA
Hall et al., 1988	0.4	NA	23 months (5 day on, 9 day off)	Rat (M&F)	Cancer (no evidence of increased tumors; however, there was increased mortality at this dose)	6.5x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.010 mg/kg-d (cutaneous T cell lymphoma in adults).

**Intraperitoneal (rat) and intravenous (rabbit) doses adjusted to an equivalent oral dose assuming a relative oral bioavailability of 90%.

Table D-20. Summary of Toxicity Data for Mirtazapine

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Djulus et al., 2006	NA	0.21**	95% during first trimester, 25% t/o pregnancy	Human (F)	Reproductive/developmental (increased spontaneous abortions)	NA, 1x	300 (1,3,10,3,3)= 0.00070
Drugs.com, 2007c	100	NA	During pregnancy	Rat (F)	Developmental (no teratogenic effects)	76x, NA	300 (10,3,1,3,3)= 0.33
Drugs.com, 2007c	15	100	During pregnancy	Rat (F)	Developmental (increased post-implantation losses; increased pup deaths during the first 3 d of lactation and decrease in pup birth weight)	11x, 76x	300 (10,3,1,3,3)= 0.050
Drugs.com, 2007c	40	NA	During pregnancy	Rabbit (F)	Developmental (no teratogenic effects)	62x, NA	300 (10,3,1,3,3)= 0.13
Drugs.com, 2007c	20	200	NA	Mouse (M)	Cancer (increased incidence of hepatocellular adenoma and carcinoma)	7.6x, 0.46x	NA
Drugs.com, 2007c	2 (F)/ 20 (M)	20 (F)/ 60 (M)	NA	Rat (M&F)	Cancer (increased hepatocellular adenoma in females, increased hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males)	15x, 15x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.21 mg/kg-d (major depressive disorder in adults).
**Based on a dose of 15 mg/day and a body weight of 70 kg.

Table D-21. Summary of Toxicity Data for Naproxen

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Roche, 2006	20	NA	Gestation	Rat	Reproductive/ Developmental (no evidence of impaired fertility or harm to fetus)	0.8x, NA	300 (10,3,1,3,3)= 0.067
Roche, 2006	20	NA	Gestation	Rabbit	Reproductive/ Developmental (no evidence of impaired fertility or harm to fetus)	1.6x, NA	300 (10,3,1,3,3)= 0.067
Roche, 2006	170	NA	Gestation	Mouse	Reproductive/ Developmental (no evidence of impaired fertility or harm to fetus)	3.5x, NA	300 (10,3,1,3,3)= 0.57
Roche, 2006	24	NA	2 years	Rat	Cancer (no effect)	1x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 4 mg/kg-d (juvenile arthritis in children).

Table D-22. Summary of Toxicity Data for Phenytoin

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Hernandez-Diaz et al., 2000; Ornoy, 2006	NA	4.3	Gestation	Human (F)	Developmental (congenital defects)	NA, 0.4x	300 (1,3,10,3,3)= 0.014
Artama et al., 2005; Samren et al., 1999	4.3	NA	Gestation	Human (F)	Developmental (no effect)	0.4x, NA	30 (1,3,1,3,3)= 0.14
Drugs.com, 2006b	NA	75	Gestation	Rabbit (F)	Reproductive/ Developmental (increased resorption/malformation rates)	NA, 2.4x	3,000 (10,3,10,3,3)= 0.025
Bittigau et al., 2002	11**	22**	PND 0–30	Rat	Developmental (increased brain cell degeneration)	0.18x, 0.36x	300 (10,3,1,3,3)= 0.037
Danielson et al., 1992	NA	150	GD 14–16	Rabbit (F)	Developmental (limb effects)	NA, 4.8x	3,000 (10,3,10,3,3)= 0.050
Danielsson et al., 1995	50	100	GD 14–16	Rabbit (F)	Developmental (digital hypoplasia)	1.6x, 3.2x	300 (10,3,1,3,3)= 0.17
Ohmori et al., 1992	NA	50	PND 2–14	Mouse (F)	Developmental (reduced brain size/ weight)	NA, 0.41x	3,000 (10,3,10,3,3)= 0.017
Ohmori et al., 1997; Hatta et al., 1999	17.5	25	PND 2–4	Mouse (F)	Developmental (reduced brain size/ weight)	0.14x, 0.2x	300 (10,3,1,3,3)= 0.058
Tsutsumi et al., 1998	NA	50	GD 7–18	Rat (F)	Developmental (effects on learning and memory)	NA, 0.81x	3,000 (10,3,10,3,3)=

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
							0.017
Minck et al., 1991; Vorhees, 1987; Vorhees and Minck, 1989; Weisenburger et al., 1990	NA	100	Gestation	Rat (F)	Developmental (abnormal circling behaviors in offspring)	NA, 1.6x	3,000 (10,3,10,3,3)= 0.033
Maeda et al., 1988	16	NA	78 weeks	Mouse (M&F)	Cancer (no effects)	0.13x, NA	NA
Jang et al., 1987	23	NA	2 years	Rat (M&F)	Cancer (no effects)	0.37x, NA	NA
NTP, 1993	NA	32	2 years	Rat (M)	Cancer (liver neoplasms, primarily adenomas)	NA, 0.56x	NA
NTP, 1993	NA	50	2 years	Mouse (F)	Cancer (liver neoplasms)	NA, 0.41x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M) = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 10 mg/kg-d (epilepsy in children).

**Intraperitoneal dose. Dose adjusted assuming a relative oral bioavailability of 90% (Lander et al., 1984).

Table D-23. Summary of Toxicity Data for Risperidone

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Drugs.com, 2007a	NA	0.16	NA	Rat (F)	Reproductive (impaired mating)	NA, 1x	3,000 (10,3,10,3,3)= 0.000053
Drugs.com, 2007a	NA	2.5	Gestation	Rat	Reproductive/ Developmental (increased stillborn pups)	NA, 15x	3,000 (10,3,10,3,3)= 0.00083
Drugs.com, 2007a	NA	0.31	Subchronic	Dog (M)	Reproductive (decreased sperm motility and concentration; decreased serum testosterone)	NA, 6.5x	3,000 (10,3,10,3,3)= 0.00010
Drugs.com, 2007a	NA	0.16	Gestation/ Lactation	Rat	Developmental (increased pup death 4 days postnatal)	NA, 1x	3,000 (10,3,10,3,3)= 0.000053
Drugs.com, 2007a	10	NA	Gestation	Rat	Developmental (no increase in malformations)	62x, NA	300 (10,3,1,3,3)= 0.033
Drugs.com, 2007a	NA	5	Gestation (cross-fostering study)	Rat	Developmental (increase in live pups & decrease in dead pups at birth; decrease in birth weight)	NA, 31x	3,000 (10,3,10,3,3)= 0.0017
Drugs.com, 2007a	5	NA	Gestation	Rabbit	Developmental (no increase in malformations)	62x, NA	300 (10,3,1,3,3)= 0.017
Drugs.com, 2007a	NA	0.63	18 months	Mouse (F)	Cancer (mammary gland adenocarcinomas)	NA, 1.7x	NA
Drugs.com, 2007a	NA	0.63	25 months	Rat (F)	Cancer (mammary gland adenocarcinomas)	NA, 3.8x	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.026 mg/kg-d (schizophrenia in adults).

Table D-24. Summary of Toxicity Data for Simvastatin

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Manson et al., 1996	0.6	NA	Gestation	Human (F)	Developmental (no effect)	3x, NA	30 (1,3,1,3,3)= 0.020
Plotkin et al., 2002	0.6	NA	NA	Human (F)	Reproductive (no effect)	3x, NA	30 (1,3,1,3,3)= 0.020
de Jongh et al., 2002	NA	0.2	48 weeks	Human, children (M&F)	Developmental/ Systemic (decreased adrenal hormones)	NA, 1x	30 (1,3,3,1,3)= 0.0067
Drugs.com, 2007b	NA	25	34 weeks	Rat (M)	Reproductive (decreased fertility)	NA, 20x	1,000 (10,3,10,1,3)= 0.025
Drugs.com, 2007b	25	NA	11 weeks	Rat (M)	Reproductive (no effect)	20x, NA	300 (10,3,1,3,3)= 0.083
Gerson et al., 1989	3	10	6 weeks	Dog (M)	Reproductive (testicular atrophy, decreased spermatogenesis, spermatocytic degeneration)	8.5x, 28x	300 (10,3,1,3,3)= 0.010
Manson et al., 1996	6.25	12.5	GD 6–17	Rat (F)	Developmental (decreased fetal body weight)	5x, 10x	300 (10,3,1,3,3)= 0.021
Manson et al., 1996	10	20	GD 6–17	Rat (F)	Developmental (decreased pup birth weight)	8x, 16x	300 (10,3,1,3,3)= 0.033
Manson et al., 1996	NA	60**	GD 6–17	Rat (F)	Developmental (increased resorptions and skeletal malformations)	NA, 49x	3,000 (10,3,10,3,3)= 0.020
Manson et al., 1996	10	NA	GD 6–18	Rabbit (F)	Developmental (no effect)	16x, NA	300 (10,3,1,3,3)=

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
							0.033
Gerson et al., 1989	10	50	2 years	Dog	Eyes (cataracts)	28x, 140x	300 (10,10,1,1,3)= 0.033
Gerson et al., 1989	30	90	6 days	Rabbit	Liver (necrosis)	49x, 150x	3,000 (10,10,1,10,3)= 0.010
Horsmans et al., 1990	30	125	18 days	Guinea-pig	Liver (lesions, increased enzymes)	30x, 125x	3,000 (10,10,1,10,3)= 0.010
Drugs.com, 2007b	NA	360	NA	Dog	Neurological (CNS vascular lesions)	NA, 1000x	30,000 (10,10,10,10,3)= 0.012
Drugs.com, 2007b	NA	180	14 weeks	Dog	Eyes (optic nerve degeneration)	NA, 500x	10,000 (10,10,10,3,3)= 0.018
Smith et al., 1991	150	180	4 weeks	Rat (F)	Muscle (skeletal muscle degeneration)	120x, 145x	3,000 (10,10,1,10,3)= 0.050
Drugs.com, 2007b	NA	50	2 years	Rat (M&F)	Cancer (liver carcinomas and adenomas, thyroid follicular adenomas)	NA, 41x	NA
Drugs.com, 2007b	NA	25	2 years	Rat (F)	Cancer (thyroid follicular adenomas)	NA, 20x	NA

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Drugs.com, 2007b	25	100	72 weeks	Mouse	Cancer (liver carcinomas and adenomas, lung adenomas)	10x, 41x	NA
Drugs.com, 2007b	25	NA	92 weeks	Mouse	Cancer (no effect)	10x, NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.20 mg/kg-d (hypercholesterolemia in children).
**Based on administration of the active hydroxyacid metabolite of simvastatin.

Table D-25. Summary of Toxicity Data for Sulfamethoxazole

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Monarch Pharmaceuticals, 2006	350	NA	NA	Rat	Reproductive (no effect)	3.1x, NA	1,000 (10,3,1,3,10)= 0.35
Monarch Pharmaceuticals, 2006	512	533	Gestation	Rat	Developmental (primarily cleft palate)	6.4x, 6.6x	1,000 (10,3,1,3,10)= 0.51

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 13 mg/kg-d (urinary tract infection in children).

Table D-26. Summary of Toxicity Data for Tamoxifen

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Gill-Sharma et al., 1993**	NA	0.040	60–90 days prior to mating	Rat (M)	Reproductive (reduced testosterone, potency, fecundity, number of implantation sites, fertility index, and litter size)	NA, 0.022x	3,000 (10,3,10,3,3)= 0.000013
Drugs.com, 2007d	NA	0.04	Two weeks prior to mating until GD 7	Rat (F)	Reproductive/developmental (fertility and reproductive indices markedly reduced; fetal mortality increased)	NA, 0.022x	3,000 (10,3,10,3,3)= 0.000013
Drugs.com, 2007d	NA	0.16	GD 7–17	Rat (F)	Developmental (fetal mortality increased)	NA, 0.090x	3,000 (10,3,10,3,3)= 0.000053
Poulet et al., 1997	NA	1.4***	PND 1–5	Rat (F)	Developmental (epithelial hypertrophy and myometrial thickening)	NA, 0.79x	3,000 (10,3,10,3,3)= 0.00047
Yamasaki et al., 2005	0.00012	0.0006	GD 6 – PND 21	Rat (M&F)	Developmental (day of preputial separation prolonged in male offspring and cleft phallus detected in female offspring)	0.000066x, 0.00033x	300 (10,3,1,3,3)= 0.00000040
Drugs.com, 2007d	NA	5	13–15 months	Mouse (M&F)	Cancer (increased granulose cell ovarian tumors and interstitial cell testicular tumors)	NA, 1.4x	NA
Carthew et al., 1995	NA	21	86 weeks	Rat (F)	Cancer (increased hepatocellular carcinoma)	NA, 12x	NA
Halakivi-Clarke et al.,	NA	0.28****	GD 15–20	Rat (F)	Developmental/cancer (increased incidence of mammary tumors in	NA, 0.16x	NA

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
2000					female offspring)		
Hard et al., 1993	NA	11.3	Up to 1 year	Rat (F)	Cancer (increased hepatocellular carcinoma)	NA, 6.2x	NA
Hirsimaki et al., 1993	11.3	45	1 year	Rat (F)	Cancer (increased hepatocellular carcinoma)	6.2x, 25x	NA
Karki et al., 2000	NA	45	1 year	Rat (F)	Cancer (increased hepatocellular carcinoma)	NA, 25x	NA
Williams et al., 1993	2.8	11.3	1 year	Rat (F)	Cancer (increased hepatocellular carcinoma)	1.6x, 6.2x	NA
Drugs.com, 2007d	NA	5	2 years	Rat (M&F)	Cancer (increased hepatocellular carcinoma)	NA, 26x	NA

Note. NOAEL= no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993), and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 0.29 mg/kg-d (breast cancer in adults).

**Other studies by these authors at the same and higher doses showed similar effects on male fertility.

***Based on a subcutaneous dose of 0.1 mg/d; assumes a rat body weight of 0.3 kg and a relative oral bioavailability of 24% (Shin, Choi, and Li, 2006).

****Based on a subcutaneous dose of 0.020 mg/d; assumes a rat body weight of 0.3 kg and a relative oral bioavailability of 24% (Shin et al., 2006).

Table D-27. Summary of Toxicity Data for Triclosan

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Barbolt, 2002	50	NA	90 days	Rat	Systemic (no effect)	NA	3,000 (10,10,1,3,10)= 0.01
Barbolt, 2002	12.5	NA	13 weeks	Dog	Systemic (no effect)	NA	3,000 (10,10,1,3,10)= 0.0042
Barbolt, 2002	3	NA	13 weeks	Rabbit	Systemic (no effect)	NA	3,000 (10,10,1,3,10)= 0.0010
Barbolt, 2002	75	NA	13 weeks	Hamster	Systemic (no effect)	NA	3,000 (10,10,1,3,10)= 0.025
Barbolt, 2002	52–67	NA	2 years	Rat (M&F)	Liver (non-neoplastic changes)	NA	1,000 (10,10,1,1,10)= 0.067
Barbolt, 2002	75	NA	2 years	Hamster	Systemic (no effect)	NA	1,000 (10,10,1,1,10)= 0.075
Barbolt, 2002	168	NA	2 years	Rat (M)	Cancer (no effect)	NA	NA
Barbolt, 2002	218	NA	2 years	Rat (F)	Cancer (no effect)	NA	NA

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = NA.

Table D-28. Summary of Toxicity Data for Trimethoprim

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect	Relative to Lowest Therapeutic Dose*	Composite UF and Associated Dose (mg/kg-d)
Monarch Pharmaceuticals, 2006	70	NA	NA	Rat	Reproductive (no effect)	1.4x, NA	1,000 (10,3,1,3,10)= 0.070
Monarch Pharmaceuticals, 2006	192	200	Gestation	Rat	Developmental (primarily cleft palate)	3.9x, 4.0x	1,000 (10,3,1,3,10)= 0.19

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female. The last column lists study-specific UFs identified using the U.S. EPA, 2002 approach, for the following categories: interspecies differences, intra-individual susceptibility, LOAEL to NOAEL, study duration, and database (Table 3.1).

*Derived by converting the NOAEL/LOAEL to a human equivalent dose based on the body surface area of the animal species relative to an adult human (FDA, 1993) and comparing to the lowest therapeutic dose. Lowest therapeutic dose = 8.0 mg/kg-d (urinary tract infection in children).

Table D-29. Summary of Toxicity Data for Atrazine

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Most recent noncancer criterion: U.S. EPA-OPPTS RfD: 0.018 mg/kg-d (U.S. EPA, 2006a)	1.8	3.65	6 months	Rat	Attenuation of pre-ovulatory lutenizing hormone (LH) surge, as a biomarker indicative ofhypothalamic function disruption UF: 100
Other noncancer criterion: U.S. EPA RfD: 0.035 mg/kg-d (Ciba-Geigy Corp.,1986 as cited in U.S. EPA, 1993a)	3.5	25	2 year feeding study	Rat (M&F)	Decreased body weight gain UF: 100
Other noncancer criterion: U.S. EPA MCL: 3 µg/L (U.S. EPA, 2006a)	NA	NA	NA	NA	NA
U.S. EPA, 1993a	3.5 (M) 3.78 (F)	34.97 (M) 37.45 (F)	Multi-generation reproduction study (oral)	Rat	Decreased body weight in pups
Other noncancer criterion: Cal OEHHA non-cancer health protective level: 30 µg/L (CalEPA, 1999a)	0.48	4.97	1 year (oral)	Dog	Cardiomyopathy UF: 100; RSC: 20%
Other noncancer criterion: ATSDR MRL: 0.003 mg/kg-day (Gojmerac et al., 1999 as cited in ATSDR, 2003)	NA	1	19 days repro study (oral)	Pig (F)	Delay in estrus was accompanied by significant alterations in estradiol levels UF: 300
Cancer criterion: Cal OEHHA PHG: 0.15 µg/L; slope factor = 0.23 (mg/kg-d)-1 (CalEPA, 1999a)	NA	NA	2 years (oral)	Rat (F)	Mammary tumors (adenocarcinomas and fibroadenoma)
Lower NO(A)EL/LO(A)ELs Reported in More Recent Studies					
Gojmerac et al., 1999 as cited in ATSDR, 2003	NA	1	19 days (oral)	Pig (F)	Reproductive (delayed estrus)

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Ćurić et al., 1999 as cited in ATSDR, 2003	NA	1	19 days (oral)	Pig (F)	Reproductive (disruption of estrus cyclicity)
Rodriguez et al., 2005	NA	5	6 month, evaluating brain monoamine systems (oral)	Rat (M)	Developmental (persistent hyperactivity and altered behavioral responses; effects on dopaminergic systems)
Coban and Filipov, 2007	NA	5	14 days, evaluating dopaminergic effects (oral)	Mouse, juvenile (M)	Developmental (persistent loss of tyrosine hydroxylase-positive (TH+) neurons, possibly confined to basal ganglia 64 days after cessation of 14-day dosing)
Rayner et al., 2007	NA	100	Cross-fostering repro/devel study (dosing on GD15-19) (oral)	Rat (M)	Developmental ("gestational ATR exposure delays PPS when male offspring suckle an ATR dam, but leads to increased lateral prostate weight via transplacental exposure alone")

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestational day; PND = postnatal day; M = male; F = female.

Table D-30. Summary of Toxicity Data for Bisphenol A (oral route only)

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Most recent RfD: U.S. EPA RfD: 0.05 mg/kg-d (NTP, 1982 as cited in U.S. EPA, 1993b)	none	50	Oral (diet); 103 weeks	Rat; adult	Systemic (reduced mean body weight)
EFSA, 2007: TDI = 0.05 mg/kg-d (Tyl et al., 2002) UF = 100	5	50	Oral (diet); 3-generation	Rat	Developmental (reduced body weight and body weight gains, reduced absolute and increased relative weanling and adult organ weight [liver, kidneys, adrenals, spleen, pituitary, and brain], in all generations)
Nakanishi, 2007: Calculated ADIs based on selected NOAELs and UFs:					
0.05 mg/kg-d (systemic effects—UF = 100; Tyl et al., 2002)	5	50	Oral (diet); 3-generation	Rat	Developmental (reduced body weight and body weight gains, reduced absolute and increased relative weanling and adult organ weights [liver, kidneys, adrenals, spleen, pituitary, and brain], in all generations)
0.046 mg/kg-d (liver effects—UF = 500; NTP-CERHR, 2007)	23		Oral (103 weeks)	Mice	Systemic (increased multinucleated giant hepatocytes in male mice)
0.5 mg/kg-d (reproductive effects—UF = 100; Tyl et al., 2002)	50	500	Oral (diet); 3-generation	Rat	Reproductive/developmental (decreased the average number of live pups per litter at birth in all generations at 500 mg/kg-d, but no maternal or fetal effects at 50 mg/kg-d)

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Health Canada, 2008 NOAEL = 5 mg/kg-d (systemic effects; Tyl et al., 2002)	5	50	Oral (diet); 3-generation	Rat	Developmental (reduced body weights and body weight gains, reduced absolute and increased relative weanling and adult organ weights (liver, kidneys, adrenals, spleen, pituitary, and brain), in all generations)
NOAEL = 50 mg/kg-d (reproductive and developmental toxicity; Tyl et al., 2002)	50	500	Oral (diet); 3-generation	Rat	Reproductive/developmental (decreased average number of live pups per litter at birth in all generations at 500 mg/kg-d, but no maternal or fetal effects at 50 mg/kg-d)
ECB, 2003: NOAEL = 50 mg/kg-d (Tyl et al., 2002)	50	500	Oral (diet); 3-generation	Rat	Reproductive/developmental (decreased average number of live pups per litter at birth in all generations at 500 mg/kg-d, but no maternal or fetal effects at 50 mg/kg-d)
EU SCF, 2002: TDI = 0.01 mg/kg-d (Tyl et al., 2002) UF = 500	5	50	Oral (diet); 3-generation	Rat	Developmental (reduced body weight and body weight gains, reduced absolute and increased relative weanling and adult organ weight [liver, kidneys, adrenals, spleen, pituitary, and brain], in all generations)
Lowest NO(A)EL/LO(A)EL Reported in More Recent Studies					
Endocrine-Estrogenic Effects					
Yamasaki et al., 2000 as cited in NTP-CERHR, 2007 (#125)	NA	160	Oral (gavage); 3 days	Rat; immature (F)	**Lowest effect level for rat/oral study** (uterine measures): Increased uterine wet weight (measure of estrogenicity)
Strohecker et al., 2003 as cited in NTP-CERHR, 2007 (#247)	200	NA	Oral (gavage); 4 days	Rat; immature and adult (F)	**Highest no effect level for rat/oral study** (uterine measures): No effect on uterine wet or dry weight (measure of estrogenicity)

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Laws et al., 2000 as cited in NTP-CERHR, 2007 (#237)	400	NA	Oral (gavage); PND 21–35	Rat; immature (F)	**Highest no effect level for rat/oral study** (vaginal measures): No effect on vaginal opening (measure of estrogenicity)
Tinwall and Joiner, 2000 as cited in NTP-CERHR, 2007 (#261)	300	NA	Oral (gavage); 3 days	Mouse; immature (F)	**Highest no effect level for mouse/oral study** (uterine or vaginal measures): No effect on blotted uterine weight (measure of estrogenicity)
Endocrine- Androgenic Effects					
Kim et al., 2002 as cited in NTP-CERHR, 2007 (#296)	1000	none	Oral (gavage); 7 days	Rat; immature (M)	**Highest no effect level for rat oral study** (no mouse study available): No effect on weights of ventral prostate, seminal vesicles, glans penis, or levator ani plus bulbocavernosus muscle, or serum concentrations of LH or testosterone (measure of androgenic/ antiandrogenic effects)
Developmental					
Della Seta et al., 2006 as cited in NTP-CERHR, 2007 (#369)	NA	0.040	Oral (pipette)	Rat; PND23-30 (M)	**Lowest effect level for rat/single dose study:** decreased serum testosterone, behavioral effects (decreased investigation of new object and decreased intromission latency)
Palanza et al., 2002, Laviola et al., 2005, and Timms et al., 2005 as cited in NTP-CERHR, 2007 (#403, 413, 402)	NA	0.010	Oral (pipette); GD 11–18 or 14–18	Mouse; adult (F)	**Lowest effect level for mouse/single dose study**: effects in offspring including behavioral effects (e.g., decreased place preference, decreased time nursing, increased time grooming and resting alone; Palanza et al., 2002, Laviola et al., 2005) and increased number of prostate ducts and proliferating cell nuclear antigen staining in prostate, increased prostate volume (Timms et al., 2005)
Schonfelder et al., 2004 as cited in NTP-CERHR, 2007 (#322)	none	0.1	Oral (gavage); GD 6– PND 21	Rat; adult (F)	**Lowest effect level for rat/multiple dose study:** increased epithelial cell nuclei, increased epithelial cells with cavities, decreased ERβ-positive cells in uterine tissue

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Nagel et al., 1997; Nagao et al., 2002 as cited in NTP-CERHR, 2007 (#275, 428)	none	0.002	Oral (gavage); GD 11–17	Mouse; adult (F)	**Lowest effect level for mouse/multiple dose study:** effects in male offspring—increased prostate weight (Nagel et al., 1997), decreased absolute seminal vesicle weight (Nagao et al., 2002)
Reproductive					
Yamasaki et al., 2002 as cited in NTP-CERHR, 2007 (#158)	200	600/1000	Oral (gavage); 28 days	Rat; adult (F)	**Lowest effect level for female/reproductive toxicity study:** altered estrous cycle
Yamasaki et al., 2002 as cited in NTP-CERHR, 2007 (#158)	200	600/1000	Oral (gavage); 28 days	Rat; adult (M)	**Lowest effect level for male/reproductive toxicity study:** decreased relative ventral prostate weight, increased relative testes weight
Tyl et al., 2002 as cited in NTP-CERHR, 2007 (#527)	4.75	47.5	Oral (diet); 2 generation	Mouse; multi-generation (M & F)	**Lowest effect level for multigeneration/ reproductive toxicity study:** Advanced F1 preputial separation

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; NA = not applicable; M = male; F = female.

Table D-31. Summary of Toxicity Data for Butylbenzyl Phthalate

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Most recent noncancer criterion: U.S. EPA RfD: 0.2 mg/kg-d (NTP, 1985 as cited in U.S. EPA, 1993c)	159	470	6 months; oral (diet)	Rat (M)	Systemic (significantly increased liver-to-body weight and liver-to-brain weight ratios (testicular atrophy at 1417 mg/kg-d))
					UF: 1000
Lower NO(A)EL/LO(A)ELs Reported in More Recent Studies					
NTP, 1997a	NA	120 (M); 300 (F)	2 years; oral (diet)	Rat (M&F)	Systemic (increased kidney weight in males and nephrotoxicity in females)
TNO NaFRI, 1998 as cited in NTP-CERHR, 2003	0.14	0.385	Premating, gestation, and lactation; oral (water)	Rat	Reproductive/developmental (increased pup mortality; NTP reviewers have low confidence in results)
Ashby et al., 1997	0.18	NA	Gestation and lactation; oral (water)	Rat (F)	Developmental (no significant differences in sexual development in pups of treated dams at PND60)
Aso et al., 2005	NA	100	Two generation; oral (gavage)	Rat (M)	Reproductive/developmental (softening of testes, diffuse atrophy of testicular seminiferous tubules, decreased spermatozoa and/or residual germ cells in epididymal lumina observed in F1 generation)
Nagao et al., 2000	20	100	Two generation; oral	Rat	Developmental (decreased neonate body weight)
Tyl et al., 2004	50	250	Multigeneration; oral (diet)	Rat (M&F)	Reproductive/developmental (reduced F1 and F2 generational male anal-genital distance)
Ema and Miyawaki, 2002	250	500	GD 15–17; oral (gavage)	Rat (M&F)	Reproductive/developmental (increased undescended testes and anal-genital distance in male offspring)

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F = female; NA = not applicable.

Table D-32. Summary of Toxicity Data for Diethylhexylphthalate*

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Most recent noncancer criterion: U.S. EPA RfD: 0.02 mg/kg-d (Carpenter et al., 1953 as cited in U.S. EPA, 1997)	NA	19	1 year, oral (diet)	Guinea pig	Systemic (increased relative liver weight—consideration of endocrine effects not indicated) UF: 1000
Most recent cancer criterion: CA OEHHA PHG: 12 µg/L (equiv to 3.4E-4 mg/kg-d*) (Hazleton, 1996 as cited in CalEPA, 1997)	NA	146.6	2 year, oral (diet)	Rat (M)	Cancer (liver carcinoma or neoplastic nodule—consideration of endocrine effects not indicated) OEHHA reports that in other studies, higher doses of DEHP result in testicular atrophy, impaired male reproductive performance, and various cellular and endocrine changes.
Other cancer criterion: U.S. EPA cancer SF: 0.014 $(mg/kg\text{-}d)^{-1}$ (equiv. to 7.1 E-5 mg/kg-d) (NTP, 1982 as cited in U.S. EPA, 1997)	NA	32	103 weeks, oral (diet)	Mouse (M)	Cancer (hepatocellular carcinoma and adenoma—consideration of endocrine effects not indicated)
Lower NO(A)EL/LO(A)ELs reported in more recent studies					
NTP 2004 as cited in NTP-CERHR, 2006	3-5	14-23	Multigeneration, oral (diet)	Rat	Reproductive/developmental (revised NOAEL/LOAEL from expert panel recommendations; small reproductive organ size in F1 and F2 generation)
Akingbemi et al., 2001 as cited in NTP-CERHR, 2006	1	10	28-day repro study, oral (gavage)	Rat (M)	Reproductive (decreased 17alpha-hydroxolase in testis, ex vivo Leydig cell testosterone synthesis)
Arcadi et al., 1998	NA	3.0-3.5	GD 1 to PND 21; oral (drinking water)	Rat	Developmental (decreased absolute kidney and testes weights)
Kobayashi et al., 2006	400	NA	GD 6 to PND 20; oral (gavage)	Rat	Developmental (no significant changes in physical development parameters or in somatic hormone profiles)
Grande et al., 2006	5	15	GD 6 to PND 22; oral (gavage)	Rat	Reproductive/developmental (delay in the age of vaginal opening [about 2 days])
Ge et al., 2007	NA	10	Pups dosed from PND 21–48; oral (gavage)	Rat (M)	Reproductive/developmental (effect on time of preputial separation, serum testosterone, and seminal vesicle

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
					weights)
Andre and Markowski, 2006; Andrade et al., 2006	1.215	5	GD 6– PND 21; oral (gavage)	Rat (M)	Reproductive/developmental (higher incidence of cryptorchidism and higher testes weights in offspring)

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F = female; NA = not applicable.

*Other recent studies of DEHP were identified, but with NOAELs/LOAELs at least an order of magnitude higher than those from studies already found in the table. Thus, there are not included here.

Table D-33. Summary of Toxicity Data for Ethynylestradiol

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Kerr and Benitez, 1997	NA	0.00014	Reported lowest oral therapeutic dose	Human (F)	Used therapeutically to treat menopausal and postmenopausal symptoms, to treat female hypogonadism, and in oral contraceptive formulations (in combination with progestagens).
Australia EPHC, 2008	NA	0.0004	Reported lowest oral therapeutic dose	Human (F)	Lowest therapeutic dose identified in a search of selected sources.
Mashchak et al., 1982	NA	0.0001	2-week treatment in postmenopausal women (therapeutic dose), oral	Human (F)	Significant increase in serum corticosteroid-binding globulin binding capacity and significant suppression of serum leutenizing hormone at both tested doses (no dose-response relationship observed).

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F = female; NA = not applicable.

Table D-34. Summary of Toxicity Data for Lindane

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Most recent noncancer criterion: U.S. EPA-OPP FQPA for chronic dietary: 0.0016 mg/kg-d (U.S. EPA-OPPTS, 2002)	0.47	4.81	Chronic carcinogenicity study	Rat	Systemic (periacinar hepatocyte hypertrophy, increased liver/spleen weight, decreased platelets) (consideration of endocrine effects not indicated) UF: 100 FQPA SF: 3
Other noncancer criterion: U.S. EPA RfD: 0.0003 mg/kg-d (Zoecon Corp., 1983 as cited in U.S. EPA, 1991)	0.33	1.55	12–18 weeks, oral (diet)	Rat	Systemic (liver and kidney toxicity in males) (consideration of endocrine effects not indicated) UF: 1000
Cancer criterion: CA OEHHA PHG: 0.032 µg/L (equiv to 9.1E-7 mg/kg-d assuming 2 L/d and 70 kg BW) (Thorpe and Walker, 1973 as cited in CalEPA, 1999b; CalEPA, 2005)	NA	48	110 weeks, oral (diet)	Mouse	Cancer (liver tumors) Slope factor = 1.1 $(mg/kg\text{-}d)^{-1}$
Lower NO(A)EL/LO(A)ELs reported in more recent studies					
Matsuura et al., 2005	NA	0.56	Two generation, oral (diet)	Rat (M&F)	Systemic (increased liver weights, centrilobular hepatocellular hypertrophy; Reproductive effects were observed at doses higher than this LOAEL)
Johri et al., 2008	0.0625	0.125	GD 5–21, oral	Rat	Developmental (increased expression of CYP450 mRNA in liver and brain persisting up to 90 days of age)
Maranghi et al., 2007	NA	15	GD 9–16	Rat	Reproductive/developmental (increased absolute and relative uterus weight on postnatal day 22, earlier vaginal patency and reduced diameters of primary oocytes at full sexual maturity)
Scascitelli and Pacchierotti,	15	25	Immediately prior to or immediately after	Rat	Reproductive/developmental (increased degenerating

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
2003			mating		two-cell embryos)
Traina et al., 2003	NA	15	GD 9–16	Mouse	Reproductive/developmental (effects on sperm and testes parameters at PND60)
Ananya et al., 2005	NA	1.5	21-day cardio	Rat (M&F)	Cardiological (changes in heart oxidative stress parameters)

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F= female; NA = not applicable.

Table D-35. Summary of Toxicity Data for Linuron*

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Most recent noncancer criterion: U.S. EPA OPP RfD: 0.008 mg/kg-d (Malley, 1988 as cited in U.S. EPA, 1995)	0.77 (F), 0.79 (M)	3.49 (F), 4.17 (M)	1 year; oral (diet)	Dog	Hematological changes (consideration of endocrine effects not indicated) UF: 100
Other noncancer criterion: U.S. EPA RfD: 0.002 mg/kg-d (du Pont, 1962 as cited in U.S. EPA, 1993)	NA	0.625	2 years; oral (diet)	Dog	Abnormal blood pigment (consideration of endocrine effects not indicated) UF: 300
CA OEHHA Prop 65 MADL: 460 µg/d (0.0066 mg/kg-d) (Haskell Laboratory, 1985 as cited in CalEPA, 2002)	8	50	2-generation; oral	Rat	Developmental (decreased pup weights at birth in F1 and F2 generations)

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F= female; NA = not applicable.

*Several more recent studies of linuron were identified, but with NOAELs/LOAELs at least an order of magnitude higher than those from studies already found in the table. Thus, there are not included here.

Table D-36. Summary of Toxicity Data for Methoxychlor

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Most recent noncancer criterion: ATSDR Intermediate Duration MRL: 0.005 mg/kg-d (Chapin et al., 1997 as cited in ATSDR, 2002)	NA	5	GD 7–PND 7 (dams), PND 7–42 (pups); oral (gavage)	Rat; adult (F) and pups	Developmental effects on the female reproductive system in offspring (delayed vaginal opening, decreased ovary weight, decreased weight of the pregnant uterus, lowered serum FSH during estrus) UF: 1000
Other noncancer criterion: CA OEHHA PHG: 30 µg/L (equiv to 0.00085 mg/kg-d*) (Chapin et al., 1997 as cited in CalEPA, 1999c)	NA	5	GD 7–PND 7 (dams), PND 7–42 (pups); oral (gavage)	Rat; adult (F) and pups	Developmental effects on the female reproductive system in offspring (delayed vaginal opening, decreased ovary weight, decreased weight of the pregnant uterus, lowered serum FSH during estrus) UF: 1000 RSC: 0.2
Other noncancer criterion: U.S. EPA RfD: 0.005 mg/kg-d (Kincaid Enterprises, Inc., 1986 as cited in U.S. EPA, 1993e)	5.01	35.5	GD 7–19; oral	Rabbit (F)	Excessive loss of litters UF: 1000
Lower NO(A)EL/LO(A)ELs Reported in More Recent Studies					
Guo et al., 2005	NA	0.8	GD 7–PND 64; oral (diet)	Rat (F, dams; M&F, offspring)	Developmental (decreased bone marrow cells and colony-forming units in femur [which induce formation of non-lymphoid blood cells] of offspring [hypothesized as due to endocrine effect])
Suzuki et al., 2004	NA	4.8	GD 15–PND 10; pups examined at 8–15 weeks; oral (diet)	Rat (F)	Reproductive/developmental (decreased serum FSH in males, decreased lordosis behavior [vertebral dorsiflexion by the female permitting fertilization] and increased serum LH in females)
Latchoumycandane and Mathur, 2002	NA	1	45 days; oral	Rat (M)	Reproductive/developmental (decreased activities of antioxidant enzymes in testes, specifically catalase,

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
					glutathione reductase and glutathione peroxidase, and increased hydrogen peroxide generation and lipid peroxidation in fractions of testes)
Palanza et al., 2002	NA	0.020	GD 11–17; oral (corn oil)	Mouse (F)	Developmental/behavorial: Dams— decreased time spent nursing and increase in time spent resting, eating, and self-grooming. Pups—decreased latency to perform righting reflex on PND2 and self-avoidance reflex on PND2 and PND5; decreased aggression of young male mice toward male siblings at PND39, but not at PND54; increased novelty preference; increased exploratory behavior (F only). ATSDR noted some effects were transient and there was no dose-response (in general no effect was seen at 0.2 or 2 mg/kg/day)
Palanza et al., 2001	0.020	0.20	GD 11–17; oral (corn oil)	Mouse (F)	Developmental (increased number of live pups, decreased anogenital distance)
Staub et al., 2002	NA	5	GD 14–PND 17 (dams), PND 7–42 (pups); oral (gavage)	Rat (F, dams; M, offspring)	Reproductive/developmental (decreased spermatogonial nuclei per gram of testicular parenchyma and per teste, increased round spermatids per spermatogonium)

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F= female; NA = not applicable.

Table D-37. Summary of Toxicity Data for 4-Nonylphenol*

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Test Description	Species (Gender)	Effect
Lower NO(A)EL / LO(A)ELs Reported in More Recent Studies					
Tyl et al. 2006	1.5	15	3 generation; oral (diet)	Rat	Developmental (most sensitive effect was increases in kidney weights in male rats)
Chapin et al., 1999	NA	9-35	3.5 generation; oral (diet)	Rat	Developmental (decreased weight gain, histopathological changes in the kidneys in males)
Laws et al., 2000	25	50	Estrogenic activity assay, 3 days dosing in preputeral rats; oral (gavage)	Rat	Reproductive/developmental (increased uterine weights)
NTP, 1997b	15 (200 ppm)	50 (650 ppm)	3 generation; oral (diet)	Rat	Developmental (reduced terminal body weight in F2 males. F1 females, and F3 females at some time points; accelerated vaginal opening; decreased epididymal sperm density in F2 males; increased relative kidney weights and tubule degeneration/ dilatation in F1, F2, and F3 males; decreased ovarian weights in F2 females)
Nagao et al., 2001a	10	50	2 generation; ral (gavage)	Rat	Reproductive/developmental (decreased numbers of implantation sites and live pups, decreased ovary weights, increased male kidney weights and changes in weights of other organs in males)
de Jager et al., 2001	NA	50	70 days; oral (gavage)	Rat	Reproductive (smaller litter size and lack of conception in treated animals)
Odum et al., 1997	37.5	75	Estrogenic activity assay, 3 days dosing in preputeral rats; oral (gavage)	Rat (F)	Reproductive/developmental (increased uterine weight)
Moon et al., 2007	10	100	GD 15–19; oral (gavage)	Rat	Reproductive/developmental (effects on progesterone receptor expression and TSH levels in female

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Test Description	Species (Gender)	Effect
					offspring at PND41)
McClusky et al., 2007	NA	100	GD 7–lactation (dams); pups dosed directly; oral (gavage)	Rat	Reproductive/developmental (difference in male offspring spermatogenesis cycle parameters [e.g., increased capase index, reduction in duration of spermatogenesis stages])

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F= female; NA = not applicable.

*Studies summarized are from the literature in the last 10 years only.

Table D-38. Summary of Toxicity Data for 4-Tert-octylphenol

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Lower NO(A)EL/LO(A)ELs reported in more recent studies					
Blake et al., 2004	NA	0.020	4 months; oral (drinking water)	Rat (M)	Reproductive (increased epididymal sperm with tail abnormalities)
Nagao et al., 2001b	12.5	50	PND 1–5; oral (gavage)	Rat	Developmental (decreased body weight gain)
Tyl et al., 1999	15	150	Two generation; oral (diet)	Rat	Developmental (body weight gain reductions, organ weight changes); no treatment-related reproductive parameter changes observed
Bian et al., 2006	50	150	30 days; oral (gavage)	Rat (M)	Reproductive (reduced sperm motility)
Pocock et al., 2002	NA	95–250 (low dose)	Prior to mating thru PND 21; oral (diet)	Rat	Reproductive/developmental (decreased body weight in adults of both sexes, disrupted vaginal cyclicity and decreases in seminiferous tubule diameter and testis, kidney, spleen, and ovary weights; behavioral effects)
Diel et al., 2004	50	200	3 days; oral (gavage)	Rat (F)	Reproductive (changes in uterine wet weight, thickness, and thickness of the vaginal epithelium)

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F= female; NA = not applicable.

Table D-39. Summary of Toxicity Data for Vinclozolin*

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Most recent noncancer criterion: U.S. EPA-OPP FQPA RfD for chronic dietary: 0.012 mg/kg-d (U.S. EPA, 2000)	1.2	2.3	Chronic; oral	Rat	Systemic/ reproductive (histopathological lesions in the lungs (males), liver (males), ovaries (females) and eyes (both sexes)) UF: 100 States: "The chronic NOAEL with an UF of 1,000 is protective of the developmental, reproductive, and carcinogenic effects of vinclozolin's antiandrogenicity."
Other noncancer criterion: U.S. EPA RfD: 0.025 mg/kg-d (BASF Corp. 1982 as cited in U.S. EPA, 1992)	2.5	7.5	6 months; oral (diet)	Dog	Systemic (organ weight changes, esp. adrenal glands and kidney) (consideration of endocrine effects not indicated) UF: 100
Lower NO(A)EL/LO(A)ELs Reported in More Recent Studies					
Colbert et al., 2005	NA	1.5	GD 14–PND 3; oral	Rat (M)	Reproductive (decreased erectile function on PND22 and PND34)
Buckley et al., 2006	10	50	GD 13–17; oral	Rat (M&F)	Reproductive/developmental (feminization of male embryos of exposed dams [hypospadias], masculinization of female embryos [longer urethras])
Veeramachaneni et al., 2006	NA	7.2	GD 15–postnatal week 4; oral	Rat (M)	Reproductive/developmental (effects on sperm morphology parameters in offspring)
Matsuura et al., 2005	~2.3-5.9	~11–29	Two generation; oral (diet)	Rat (M)	Reproductive/developmental (differences in anal-genital distance, sexual maturation, nipple development, sex organ weights, and blood sex hormone concentrations in parental and offspring males)

Reference	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration	Species (Gender)	Effect
Bisenius et al., 2006	NA	10	Mid-gestation–postpartum week 4; oral	Rabbit (M&F)	Developmental (differences in gene expression and cell size in brain of offspring at postpartum week 6)
Hass et al., 2007	NA	5	GD 7–day prior to expected birth; oral	Rat (M)	Reproductive/developmental (differences in nipple retention in male offspring)
Shin et al., 2006	NA	3.125	28 days; oral	Rat (M)	Systemic (effects on liver and Cowper's gland weights)
Vilela et al., 2007	NA	10	GD 13–17; oral	Mouse (M)	Reproductive/developmental (increased hypospadias in pups)
Metzdorff et al., 2007	5	10	GD 7–PND 16; oral	Rat (M)	Reproductive/developmental (effects on sex organ weight)
Veeramachaneni, 2008	NA	25 umol	GD 14 to postpartum week 4; oral	Rat (M)	Reproductive/developmental (effects on sperm morphological parameters)
Andre and Markowski, 2006	NA	1.5	GD 14–PND 3; oral	Rat (M)	Developmental (effects on conditioned running response)

Note. NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; M = male; F= female; NA = not applicable.

*There are many toxicological studies that evaluated doses of vinclozolin of 200 mg/kg-day in publication range of interest; this dose is significantly higher than the NOAELs and LOAELs of interest, so these studies are generally not summarized in the table.

APPENDIX D REFERENCES

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APPENDIX E

IN VITRO GENOTOXICITY DATA FOR CASE STUDY CHEMICALS

Table E-1. In Vitro Genotoxicity Data for Case Study Chemicals

Compound	Ames Test Result	MLA (mouse lymphoma assay) Result	MN (In vitro micronucleus assay) Result	CA (In vitro chromosomal aberration assay) Result	Overall Screening-level Genotoxicity Assumption[a]
PPCPs					
Alendronate	Negative (Merck, 1997)	NA	Negative (Merck, 1997)	Weakly pos in presence of cytotoxicity (Merck, 1997)	Negative
Atenolol	Negative (Astrazeneca, 2007)	NA	NA	NA	Negative
Atorvastatin	Negative (Pfizer, 2003)	NA	NA	Negative (Pfizer, 2003)	Negative
Carbamazepine	Negative (Shire, 2006)	NA	Positive (Celik, 2006)	NA	Positive
Desloratadine	Negative (Schering Corp, 2004)	NA	Negative (Schering Corp, 2004)	NA	Negative
Diazepam	Positive (IPCS, 1997)	NA	Positive (IPCS, 1997)	Negative (IPCS, 1997)	Positive
Diclofenac	Negative (Drugs.com, 2006a)	Negative (Drugs.com, 2006a)	NA	Negative (Drugs.com, 2006a)	Negative
Doxycycline	NA	NA	NA	Weakly positive (CollaGenex, 2006)	Positive
Enalapril	Negative (NLM Daily Med, 2007)	NA	Negative (NLM Daily Med, 2007)	NA	Negative
Fluconazole	Negative (RxList, 2008a)	Negative (RxList, 2008a)	NA	NA	Negative
Fluoxetine	Negative (IPCS, 1998)	NA	NA	NA	Negative
Furosemide	Negative (Drugs.com, 2006b)	"Questionably positive at highest dose tested" (Drugs.com, 2006b)	NA	Positive (Drugs.com, 2006b)	Positive

Compound	Ames Test Result	MLA (mouse lymphoma assay) Result	MN (In vitro micronucleus assay) Result	CA (In vitro chromosomal aberration assay) Result	Overall Screening-level Genotoxicity Assumption[a]
Galaxolide	Negative (Mersch-Sundermanno, 1998)	NA	Negative (Kevekordes et al., 1997)	Negative (Api and San, 1999)	Negative
Gemfibrozil	Negative (Fitzgerald et al., 1981)	NA	NA	NA	Negative
Ifosfamide	Positive (NLM Gene-Tox, 1995)	NA	Positive (NLM Gene-Tox, 1995)	NA	Positive
Iopamidol/ iopromide	Negative (Drugs.com, 2008a)	NA	NA	NA	Negative
Lansoprazole	Negative (TAP, 2004)	NA	NA	NA	Negative
Meprobamate	Negative (Drugs.com, 2008b)	NA	Positive (Drugs.com 2008b)	Positive (Drugs.com, 2008b)	Positive
Methotrexate	Negative (IARC, 1987)	Positive (IARC, 1987)	NA	Positive (IARC, 1987)	Positive
Mirtazapine	Negative (Drugs.com 2007a)	NA	NA	Negative (Drugs.com, 2007a)	Negative
Naproxen	Negative (Philipose et al., 1997)	NA	NA	NA	Negative
Phenytoin	Positive (IARC, 1996)	NA	NA	Negative (Kindig et al., 1992)	Positive
Risperidone	Negative (Drugs.com, 2007b)	Negative (Drugs.com, 2007b)	NA	Negative (Drugs.com, 2007b)	Negative
Simvastatin	Negative (Drugs.com, 2007c)	NA	NA	Negative (Drugs.com, 2007c)	Negative
Sulfamethoxazole	Negative (IARC, 2001)	NA	NA	NA	Negative

Compound	Ames Test Result	MLA (mouse lymphoma assay) Result	MN (In vitro micronucleus assay) Result	CA (In vitro chromosomal aberration assay) Result	Overall Screening-level Genotoxicity Assumption[a]
Tamoxifen	Negative (BC Cancer Agency, 2006)	NA	NA	NA	Negative
Triclosan	Negative (Ho Tan Tai, 2004)	Negative (Ho Tan Tai, 2004)	Negative (Ho Tan Tai, 2004)	Negative (Ho Tan Tai, 2004)	Negative
Trimethoprim	Negative (Monarch Pharmaceuticals, 2006)	NA	NA	Negative (Monarch Pharmaceuticals, 2006)	Negative
EDCs					
Atrazine	Negative (ATSDR, 2003)	NA	NA	Mixed, mostly negative (ATSDR, 2003)	Negative
Bisphenol A	Negative (NTP-CERHR, 2007); Positive (GENETOX)	Negative (NTP-CERHR, 2007)	NA	Negative (NTP-CERHR, 2007)	Negative
Butylbenzyl phthalate	Negative (Zeiger et al., 1982)	NA	NA	NA	Negative
DEHP	Negative (ATSDR, 2002a)	Negative (ATSDR, 2002a)	NA	Negative (ATSDR, 2002a)	Negative
Dibutyl phthalate	Positive (ATSDR, 2001)	Negative (ATSDR, 2001)	NA	Positive (ATSDR, 2001)	Positive
17ß-Estradiol	Negative (Lang and Reimann, 1993)	NA	NA	NA	Negative
Estrone	2- & 4-hydroxy estrone Negative (Rossi et al., 2007)	NA	NA	NA	Negative
Ethynylestradiol	Negative (NLM Gene Tox, 1991)	NA	NA	NA	Negative

Compound	Ames Test Result	MLA (mouse lymphoma assay) Result	MN (In vitro micronucleus assay) Result	CA (In vitro chromosomal aberration assay) Result	Overall Screening-level Genotoxicity Assumption[a]
Lindane (BHC-gamma)	Negative (ATSDR, 2005)	NA	NA	Negative (ATSDR, 2005)	Negative
Linuron	Negative (U.S. EPA, 1995)	NA	NA	Negative (Extoxnet, 1996)	Negative
Methoxychlor	Negative (ATSDR, 2002b)	Positive (ATSDR, 2000b)	NA	NA	Positive
Nonylphenol	Negative (Isidori et al., 2007)	NA	NA	Negative (Tayama et al., 2008)	Negative
Octylphenol (OP)	Positive (Isidori et al., 2007)	NA	NA	Negative (Tayama et al., 2008)	Positive
Vinclozolin	Negative (U.S. EPA, 1985)	Negative (Kevekordes et al., 1996)	NA	Negative (Kevekordes et al., 1996)	Negative

[a]A positive genotoxic compound was defined as one that is positive in at least one standard genotoxicity test.

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APPENDIX F

SUMMARY OF DATA USED TO SELECT UNCERTAINTY FACTORS TO APPLY TO THERAPEUTIC DOSES FOR CASE STUDY COMPOUNDS

Table F-1. Summary of Toxicity Data for Pharmaceutical Case Study Compounds and Comparison to Therapeutic Doses

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Alendronate (Fosamex®)	Drug: Bisphonate inhibitor of bone resorption	*Genotoxicity:* Negative *Carcinogenicity:* Thyroid parafollicular cell carcinomas in male rats *Reproductive:* Protracted parturition due to maternal hypocalcemia in rats (NOAEL = NA; LOAEL = 0.081 mg/kg-d [HED]) (1.1x TD) *Developmental:* Decreased body weight gain in rat pups (NOAEL = NA; LOAEL = 0.16 mg/kg-d [HED]) (2.3x TD) *FDA Pregnancy Category*: C	0.071 mg/kg-d (glucocorticoid-induced osteoporosis)
Atenolol (Tenormin®)	Drug: Beta-blocker, blocks $beta_1$– receptors located primarily in the heart, preventing epinephrine and norepinephrine from acting on beta adrenergic receptors in cardiac tissue, peripheral blood vessels, bronchi, pancreas, and liver; lowering heart rate and blood pressure.	*Genotoxicity:* Negative *Carcinogenicity:* Thyroid parafollicular cell carcinomas in male rats *Reproductive:* Decreased testosterone and sperm motility in rats (NOAEL = NA; LOAEL = 1.5 mg/kg-d [HED]) (4.2x TD) *Developmental:* Increased embryo/ fetal resorptions in rats (NOAEL = 4.0, LOAEL = 8.1 mg/kg-d [HED]) (23x TD) *FDA Pregnancy Category*: D	0.36 mg/kg-d (hypertension in adults) Developmental effects (low birth weight) Immune responses (including appearance of antinuclear antibodies in blood)
Atorvastatin (Lipitor®)	Drug: Antilipidemic	*Genotoxicity:* Negative *Carcinogenicity:* Liver adenomas and carcinomas in mice, and rhabdomyosarcomas and fibrosarcomas in rats *Reproductive:* Reduced testes weights in rats (NOAEL = NA; LOAEL = 4.8 mg/kg-d [HED]) (16x TD) *Developmental:* Behavioral effects in rats (NOAEL = NA; LOAEL = 3.2 mg/kg-d [HED]) (11x TD) *FDA Pregnancy Category:* X	0.3 mg/kg-d (hypercholesterolemia in children) Developmental effects (case report of severe congenital deformity in the child of a woman who took another statin during pregnancy) Biochemical abnormalities of liver function

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Carbamazepine (Tegretol®)	Drug: Anticonvulsant and mood stabilizer	*Genotoxicity*: Positive *Carcinogenicity:* Liver carcinomas in rats *Reproductive:* Decreased fertility and increased resorptions in mice (NOAEL = 24, LOAEL = 33 mg/kg-d [HED]) (33x TD) *Developmental:* Decreased body weight in rat pups (NOAEL = 7.7, LOAEL = 31 mg/kg-d [HED]) (31x TD) *FDA Pregnancy Category*: D	1.0 mg/kg-d (epilepsy in children) Severe and sometimes fatal dermatologic reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), esp. in Asian patients Teratogenic effects, including spina bifida, and developmental delays
Desloratadine (Clarinex®)	Drug: Antihistamine	*Genotoxicity:* Negative *Carcinogenicity:* Liver tumors in mice and rats *Reproductive:* Decrease in fertility in male rats (NOAEL = 0.48, LOAEL = 1.9 mg/kg-d [HED])(53x TD) *Developmental:* Reduced pup body weights and slow righting reflux in rats (NOAEL = 0.48, LOAEL = 1.5 mg/kg-d [HED])(42x TD) *FDA Pregnancy Category*: C	0.036 mg/kg-d (allergy treatment in adults)
Diazepam (Valium®)	Drug: Benzodiazapine antianxiety	*Genotoxicity:* Positive *Carcinogenicity*: No data *Reproductive:* Decreased live pups per litter (NOAEL = NA; LOAEL = 4.2 mg/kg-d [HED])(140x TD) *Developmental:* Behavioral changes, decreased viability in rat pups (NOAEL = NA; LOAEL = 0.16 mg/kg-d [HED])(5.5x TD) *FDA Pregnancy Category*: D	0.029 mg/kg-d (anxiety in adults, geriatric) Case reports of congenital malformations and respiratory and feeding difficulties in neonates exposed to benzodiazepines, in general, during pregnancy.

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Diclofenac (Cataflam®, Voltaren®)	Drug: NSAID	*Genotoxicity:* Negative *Carcinogenicity:* No evidence in rats and mice *Reproductive:* No effect up to 0.65 mg/kg-d (HED) in mice and rats *Developmental:* No effect up to 1.6 mg/kg-d (HED) in mice and rats *FDA Pregnancy Category*: C	1.4 mg/kg-d (arthritis in adults) Increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke associated with NSAIDs
Doxycycline (generics)	Drug: Tetracycline antibiotic	*Genotoxicity:* Positive *Carcinogenicity:* Uterine polyps in female rats, but no evidence of increase in tumors *Reproductive:* Decreased sperm velocity in rats (NOAEL = NA; LOAEL = 8.1 mg/kg-d [HED])(5.8x TD) *Developmental:* Delayed skeletal differentiation in rats (NOAEL = NA; LOAEL = 1.3 mg/kg-d [HED])(0.9x TD) *FDA Pregnancy Category:* D	1.4 mg/kg-d (malaria prophylaxis in adults) Weak but marginally statistically significant increase in fetal malformations
Enalapril (Enalaprit®)	Drug: ACE inhibitor (treatment of high blood pressure)	*Genotoxicity:* Negative *Carcinogenicity:* Not carcinogenic in rats and mice *Reproductive:* Increased resorbed fetuses in rabbits (NOAEL = NA; LOAEL = 0.32 mg/kg-d (HED))(8.9x TD) *Developmental:* Growth retardation and developmental delay in rats (NOAEL = NA; LOAEL = 1.6 mg/kg-d (HED))(44x TD) *FDA Pregnancy Category:* C, D	0.036 mg/kg-d (hypertension, in adults with renal impairment) Developmental: Congenital abnormalities

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Fluconazole (Diflucan®)	Drug: Antifungal	*Genotoxicity:* Negative *Carcinogenicity:* Liver adenomas in rats (LOAEL = 0.80 mg/kg-d [HED]) (1.1x TD) *Reproductive:* Delayed onset of and prolonged parturition in rats (NOAEL = 1.6, LOAEL = 3.2 mg/kg-d [HED])(4.5x TD) *Developmental:* Delays in ossification and fetal anatomical variants in rats (NOAEL = 1.6, LOAEL = 4.0 mg/kg-d [HED])(5.6x TD) *FDA Pregnancy Category:* C	0.71 mg/kg-d (urinary tract infection in adults) Case reports of multiple congenital abnormalities, but not confirmed as due to fluconazole
Fluoxetine (Prozac®)	Drug: SSRI (anti-depressant) Class: III	*Genotoxicity:* Negative *Carcinogenicity:* Not carcinogenic in rats and mice *Reproductive/ developmental:* Increase in stillborn pups and pup deaths and decrease in pup weight in rats (NOAEL = 0.81, LOAEL = 1.9 mg/kg-d [HED])(5.8x TD) *FDA Pregnancy Category*: C	0.33 mg/kg-d (depression and obsessive compulsive disorder in children) Reproductive/ Developmental: Shortened gestation, reduced birth weight, poor neonatal adaptation.
Furosemide (Lasix®)	Drug: Loop diuretic	*Genotoxicity:* Positive *Carcinogenicity*: Mammary tumors in mice *Reproductive:* Maternal deaths and abortions in rabbits (NOAEL = NA; LOAEL = 8.1 to 16 mg/kg-d [HED])(28x TD) *Developmental:* Decreased fetal weights and wavy ribs in rats (NOAEL = NA; LOAEL = 48 mg/kg-d [HED])(170x TD) *FDA Pregnancy Category*: C	0.29 mg/kg-d (edema in adults)

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Gemfibrozil (Lopid®)	Drug: Antilipidemic (treatment of high cholesterol)	*Genotoxicity:* Negative *Carcinogenicity:* Liver cancer in rats *Reproductive:* Decreased fertility in male rats (NOAEL = 15, LOAEL = 50 mg/kg-d [HED])(2.9x TD) *Developmental:* Reduced pup body weights in rats (NOAEL = NA; LOAEL = 15 mg/kg-d [HED])(0.9x TD) *FDA Pregnancy Category*: C	17 mg/kg-d (lipid regulation in adults) Gall bladder disease
HHCB (Galaxolide®)	Musk	*Genotoxicity:* Negative *Carcinogenicity:* No data *Reproductive:* No data *Developmental:* Axial skeletal malformations in rats (NOAEL = 24; LOAEL = 81 mg/kg-d [HED]) *FDA Pregnancy Category:* NA	NA
Ifosfamide (NA)	Drug: Chemotherapy agent	*Genotoxicity:* Positive *Carcinogenicity:* Lung tumors and lymphomas of hematopoietic system in mice, and leiomyosarcomas and mammary fibroadenomas in rats *Reproductive:* Transient oligosperma in rabbits (NOAEL = NA; LOAEL = 19 mg/kg-d [HED])(0.6x TD) *Developmental:* NOAEL = NA; Embryotoxic effects in rats (LOAEL = 0.48 mg/kg-d (HED))(0.01x TD) *FDA Pregnancy Category:* D	34 mg/kg-d (germ cell testicular cancer in adults)
Iopamidol/ iopromide (Isovue®)	X-ray contrast media	*Genotoxicity:* Negative *Carcinogenicity:* No data *Reproductive:* No effect up to ~400 mg/kg-d (HED) in rabbits *Developmental:* No effect up to ~400 mg/kg-d (HED) in rabbits *FDA Pregnancy Category:* B	Assume 150 mg/kg-d Higher mean thyrotropin and lower free triiodothyronine and thyroxine levels in infants

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Lansoprazole (Prevacid®)	Drug: Antacid/ proton pump inhibitor	*Genotoxicity:* Negative *Carcinogenicity:* Liver tumors in mice and gastric mucosa in rats *Reproductive:* Leydig cell hyperplasia in rat testes (NOAEL = NA; LOAEL = 2.4 mg/kg-d [HED])(11x TD) *Developmental:* No effect at doses up to 11 mg/kg-d (HED) *FDA Pregnancy Category*: B	0.21 mg/kg-d (duodenal ulcer and GERD in adults)
Meprobamate (Equanil®, Miltown®)	Drug: Antianxiety agent	*Genotoxicity:* Positive *Carcinogenicity:* No data *Reproductive:* Increased time in proestrous and estrous, and increased epididymis weight in mice (NOAEL = 61, LOAEL = 98 mg/kg-d [HED])(14x TD) *Developmental:* Less pups born live and decreased pup weight in mice (NOAEL = 61, LOAEL = 98 mg/kg-d [HED]) (14x TD) *FDA Pregnancy Category:* D	7 mg/kg-d (anxiety in children) Possible increased risk of congenital malformations
Methotrexate (Trexall®)	Drug: Treatment of cancer, psoriasis, rheumatic diseases; folic acid antagonist	*Genotoxicity:* Positive *Carcinogenicity:* Not carcinogenic in hamsters, mice, and rats *Reproductive/ developmental:* Embryo lethality and malformation, rabbit (NOAEL = NA; LOAEL = 0.053 mg/kg-d [HED]) (5.3x TD) *FDA Pregnancy Category*: X	0.010 mg/kg-d (cutaneous T cell lymphoma in adults) Potential severe adverse effects on fetus and course of pregnancy: known abortifacient, teratogen Case reports of subsequent neoplasms following treatment.

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Mirtazapine (Remeron®)	Drug: Tetracyclic antidepressant	*Genotoxicity:* Negative *Carcinogenicity:* Liver tumors in mice and rats, and thyroid follicular adenomas and carcinomas in male rats *Reproductive:* Increased post-implantation losses in rats (NOAEL = 2.4; LOAEL = 16 mg/kg-d [HED])(76x TD) *Developmental:* Decreased pup birth weights in rats (NOAEL = 2.4; LOAEL = 16 mg/kg-d [HED])(76x TD) *FDA Pregnancy Category:* C	0.21 mg/kg-d (major depressive disorder in adults) Increase in spontaneous abortions
Naproxen (Aleve®)	Drug: NSAID	*Genotoxicity:* Negative *Carcinogenicity*: Not carcinogenic in rats *Reproductive/ developmental:* No effect up to 14 mg/kg-d (HED) *FDA Pregnancy Category:* B	4 mg/kg-d (juvenile arthritis in children) In pregnancy, may cause premature closure of ductus arteriosus
Phenytoin (Dilantin®)	Drug: Anticonvulsant	*Genotoxicity:* Positive *Carcinogenicity:* Liver neoplasms in rats and mice *Reproductive:* Increased resorptions in rabbits (NOAEL = NA; LOAEL = 24 mg/kg-d (HED))(5.6x TD) *Developmental:* Reduced brain size and weight in mice (NOAEL = 1.4, LOAEL = 2.0 mg/kg-d [HED]) 0.5x TD) *FDA Pregnancy Category:* D	4.3 mg/kg-d (epilepsy in adults) Congenital defects
Risperidone (Risperidal®)	Drug: Antipsychotic	*Genotoxicity:* Negative *Carcinogenicity:* Mammary adenocarcinomas in mice and rats *Reproductive:* Impaired mating in rats (NOAEL = NA; LOAEL = 0.026 mg/kg-d [HED])(1x TD) *Developmental:* Increased pup death in rats (NOAEL = NA; LOAEL = 0.026 mg/kg-d [HED])(1x TD) *FDA Pregnancy Category:* C	0.026 mg/kg-d (schizophrenia in adults) Tardive dyskinesia

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Simvastatin (Zocor®)	Drug: Antilipidemic	*Genotoxicity:* Negative *Carcinogenicity:* Liver tumors in rats and mice, thyroid follicular adenomas in rats, lung adenomas in mice *Reproductive:* Decreased fertility in rats (NOAEL = NA; LOAEL = 4.0 mg/kg-d [HED])(20x TD) *Developmental:* Decreased fetal body weight, rat (NOAEL = 1.0, LOAEL = 2.0 mg/kg-d [HED])(10x TD) *FDA Pregnancy Category:* X *Other:* Skeletal muscle degeneration in rats (NOAEL = 24, LOAEL = 29 mg/kg-d [HED]) (145x TD)	0.20 mg/kg-d (hypercholesterolemia in children) Rare reports of congenital abnormalities in infants exposed to statins in utero Decrease in adrenal hormones Myopathy (muscle pain, tenderness, weakness), acute renal failure
Sulfamethoxazole (Cotrim®)	Drug: Antibacterial	*Genotoxicity:* Negative *Carcinogenicity:* No data *Reproductive:* No effect up to 40 mg/kg-d (HED) *Developmental:* Cleft palate in rats (NOAEL = 83, LOAEL = 86 mg/kg-d [HED])(6.6x TD) *FDA Pregnancy Category:* C	13 mg/kg-d (urinary tract infection in children)
Tamoxifen (NA)	Drug: Chemotherapy agent	*Genotoxicity:* Negative *Carcinogenicity:* Liver carcinoma in rats, granulose cell ovarian tumors an interstitial cell testicular tumors in mice. *Reproductive:* Effects in male and female rats, including reduced testosterone, potency, fecundity, fertility index, litter size (NOAEL = NA; LOAEL = 0.0065 mg/kg-d [HED])(0.02x TD) *Developmental:* Delayed preputial separation in male rats (NOAEL = 0.00002, LOAEL = 0.0001 mg/kg-d [HEC])(0.00034x TD) *FDA Pregnancy Category*: D	0.29 mg/kg-d (breast cancer in adults) Increase in uterine malignancies, endometrial cancers; endometrial changes including hyperplasia; other secondary cancers including liver Deep vein thrombosis, pulmonary embolism Occular disturbances inc corneal changes Expected fetal harm

Compound	Primary Mode of Action	Genotoxicity and Animal Toxicity Data Summary	Lowest Therapeutic Dose and Significant Adverse Effects Seen at Therapeutic Dose in Humans
Triclosan	Antibacterial	*Genotoxicity:* Negative *Carcinogenicity:* Not carcinogenic in rats *Reproductive*: No data *Developmental*: No data *FDA Pregnancy Category*: NA	NA
Trimethoprim (Cotrim®)	Drug: Antiinfective	*Genotoxicity:* Negative *Carcinogenicity*: No data *Reproductive:* No effects in rats up to 11 mg/kg-d (HEC) *Developmental:* Cleft palate in rats (NOAEL = 31, LOAEL = 32 mg/kg-d [HEC])(4x TD) *FDA Pregnancy Category*: C	8.0 mg/kg-d (urinary tract infection in children)

Note. HEC = human equivalent dose; LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; TD = therapeutic dose; NA = not available.

Advancing the Science of Water Reuse and Desalination

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