

Toxicological Significance of EDCs in Drinking Water

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State of Knowledge of Endocrine Disruptors and Pharmaceuticals in Drinking Water

Subject Area:
High-Quality Water

State of Knowledge of Endocrine Disruptors and Pharmaceuticals in Drinking Water

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Tailored Collaboration

Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water

Subject Area:
Environmental Leadership

Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water

Prepared by:

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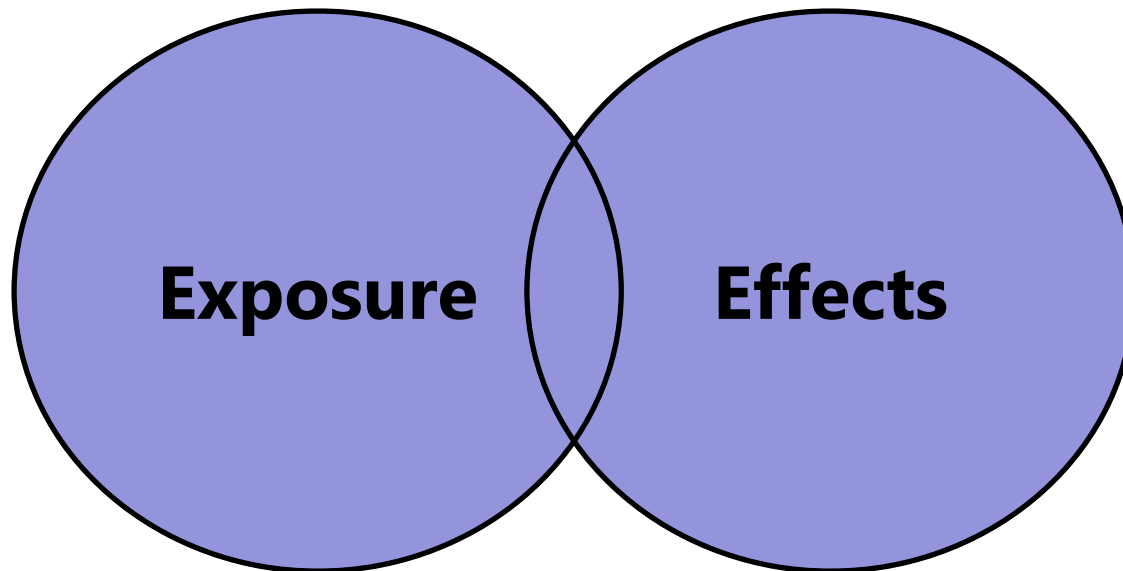
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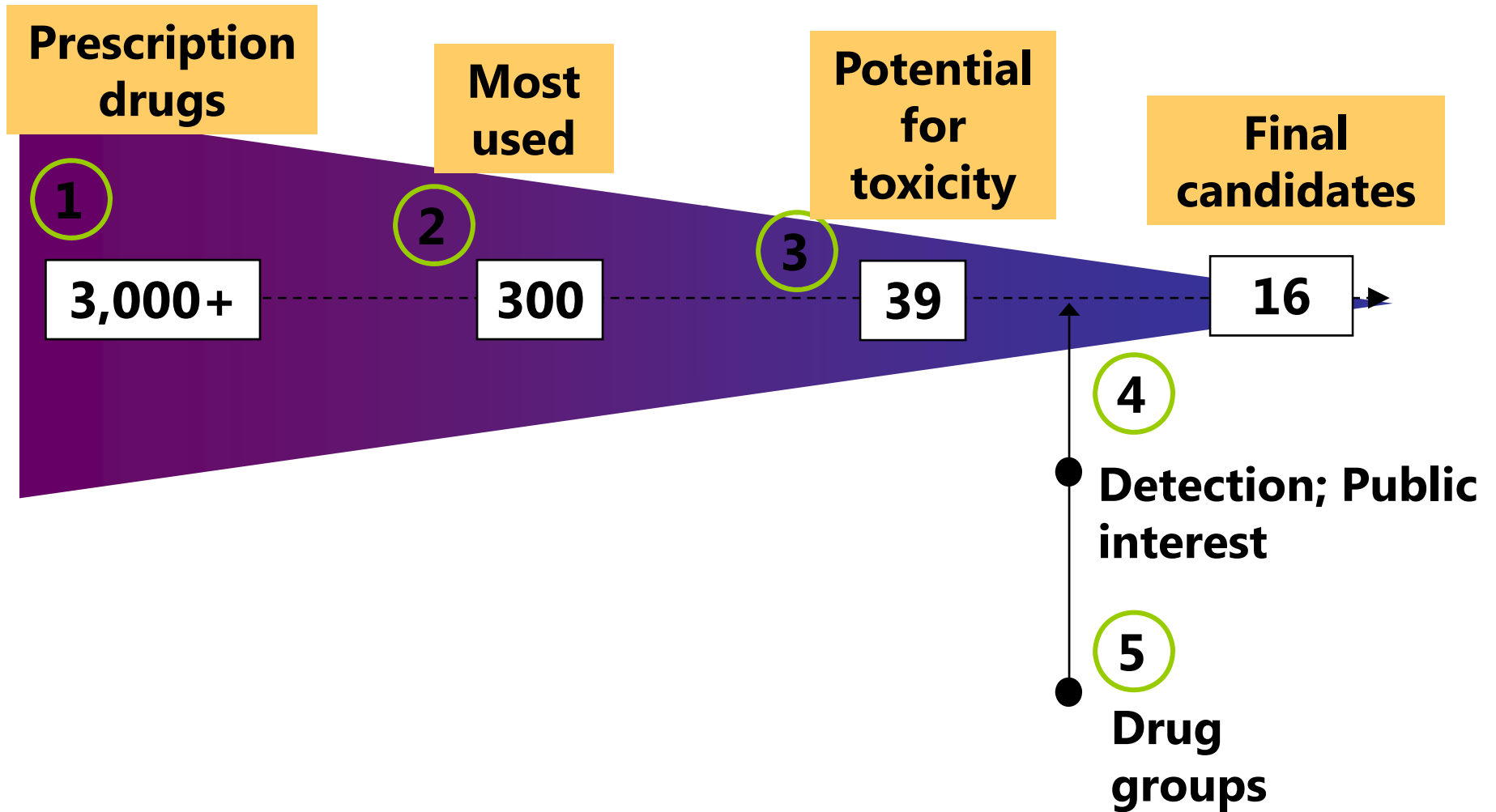
Potential for Human Health Risk

Risk is the probability of adverse effects resulting from exposure to an environmental agent or mixture of agents.

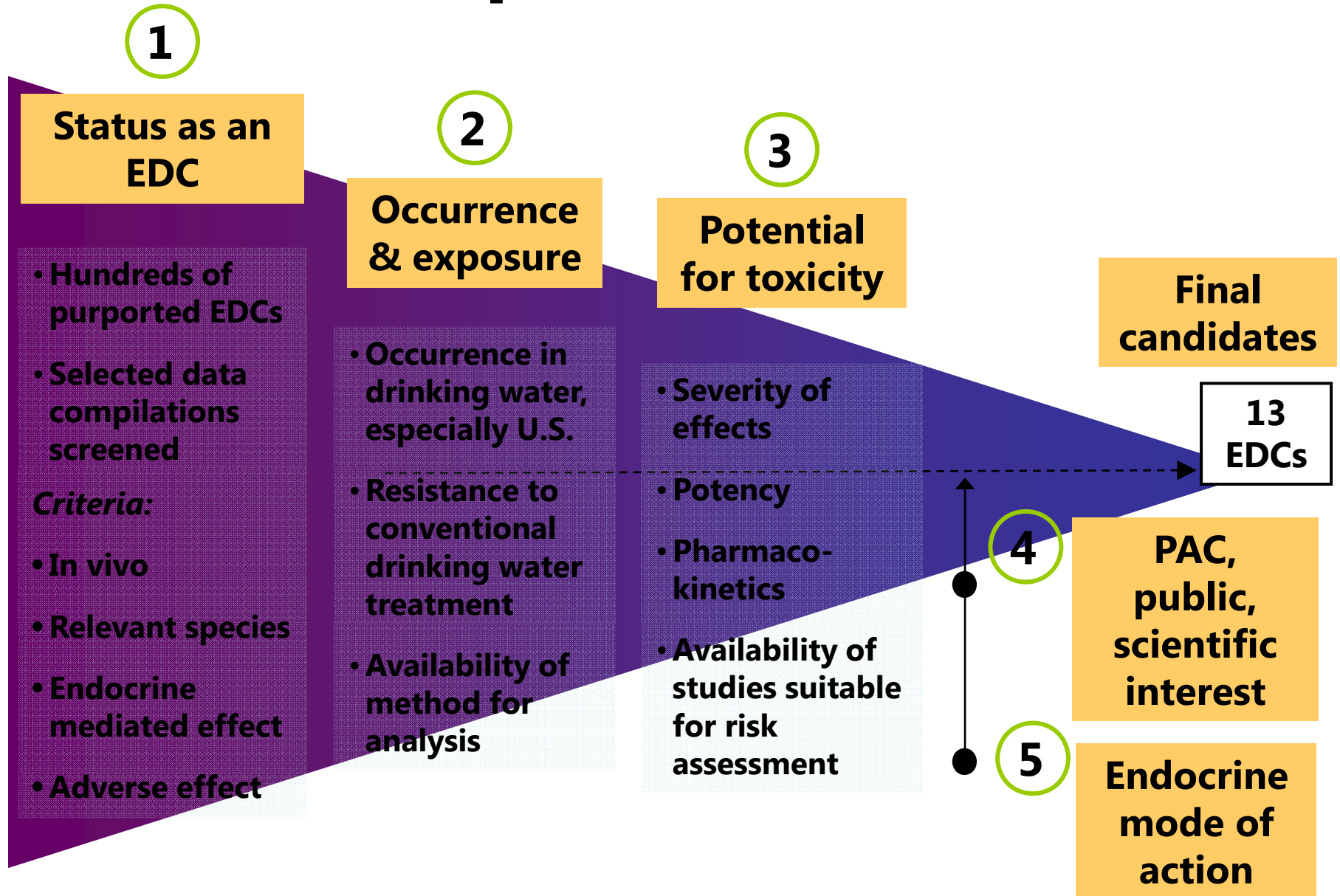
Risk results from the interaction of exposure and effects.



Pharmaceuticals

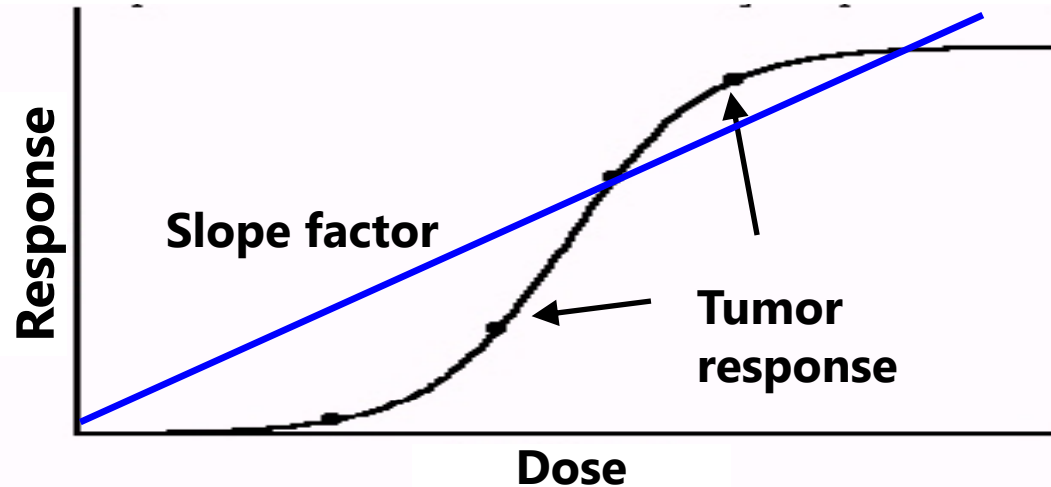


Suspected EDCs



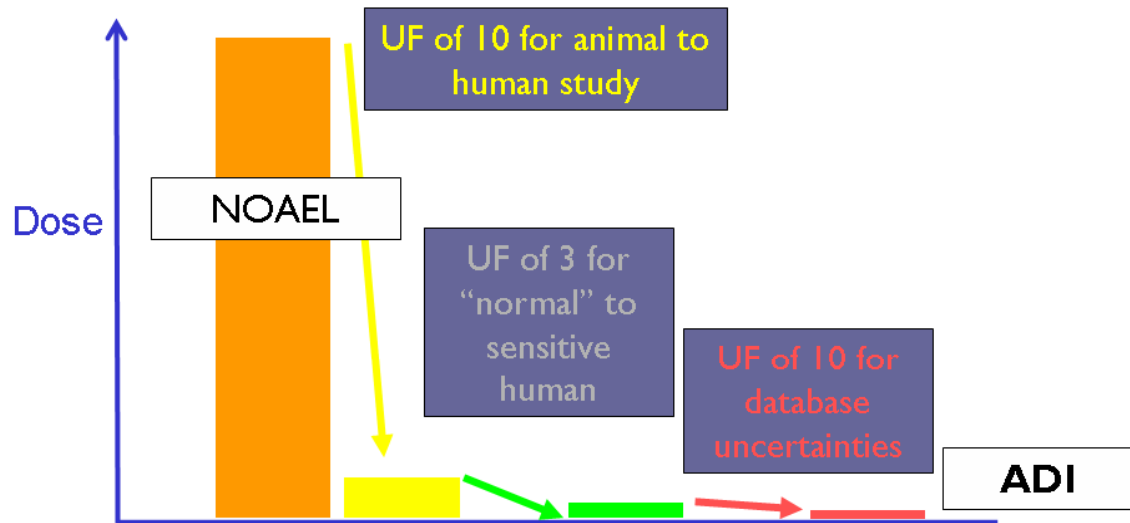
Deriving ADIs / Screening Values

Carcinogens



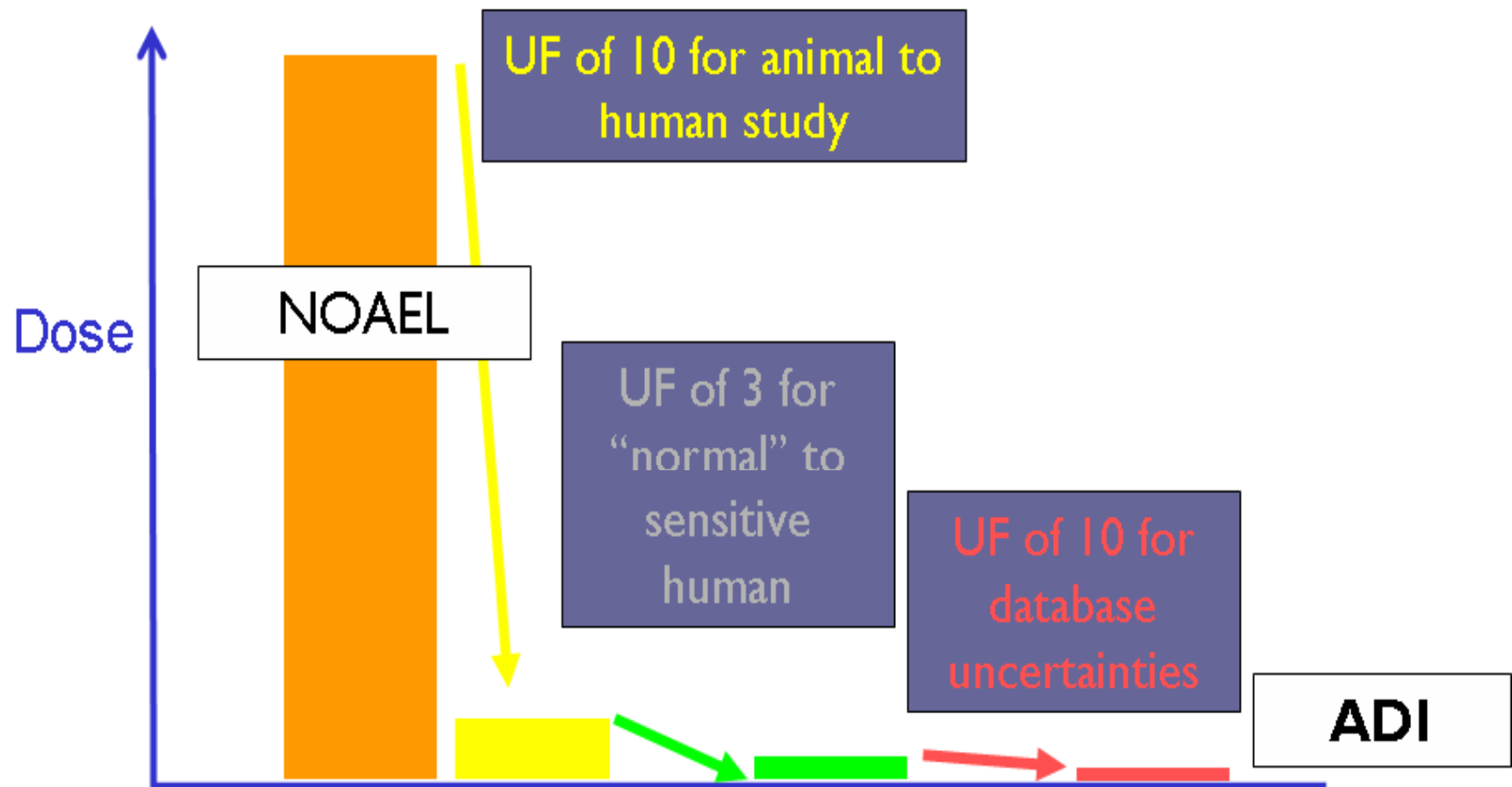
$$\text{ADI} = \frac{\text{Highest NOAEL or lowest LOAEL}}{\text{Uncertainty factors}}$$

Non-cancer



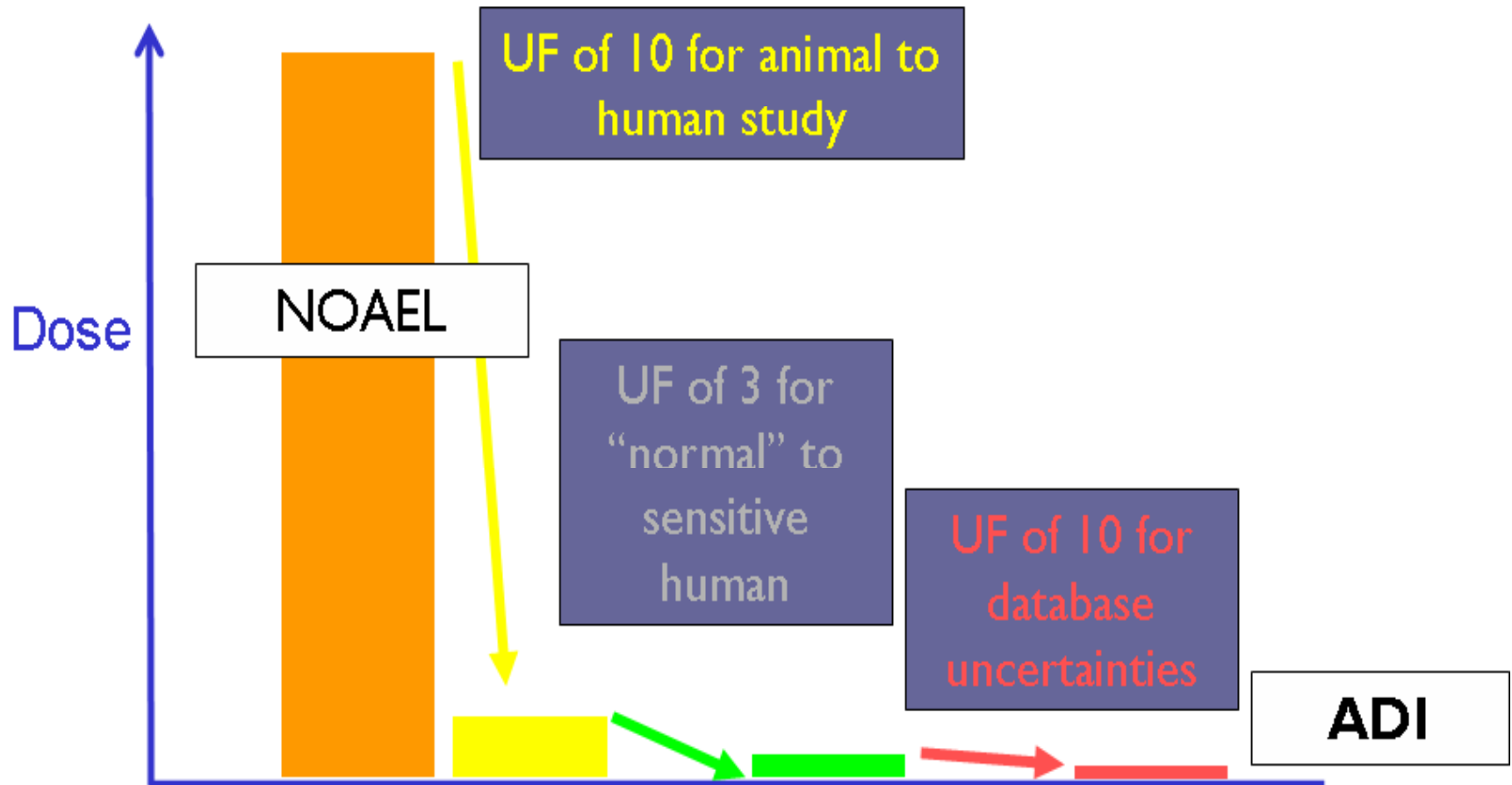
Acceptable Daily Intake (ADI)

$$\text{ADI} = \frac{\text{Highest NOAEL or lowest LOAEL}}{\text{Uncertainty factors}}$$

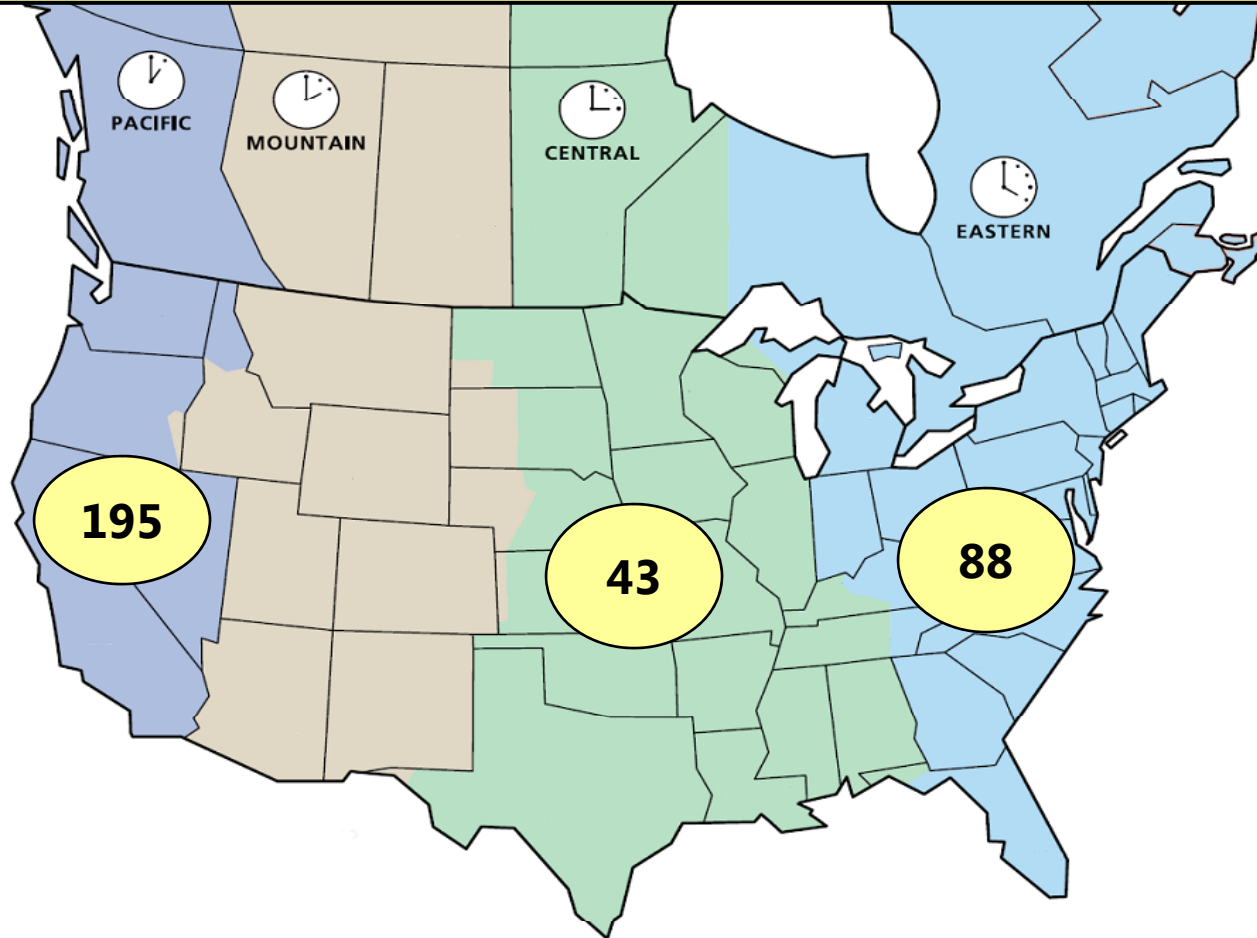


DWEL ≈ MCLG

$$\text{Drinking Water Equivalent Level (DWEL)} = \frac{\text{ADI} * 70 \text{ kg}}{2 \text{ L}}$$



Samples Collected per Time Zone



17 participating utilities

Selected Pharmaceuticals: Cancer and Non-cancer Endpoints

Drug	Effect Dose (mg/kg-d)	Effect	Cancer*	UF
Atenolol	0.80 (LOAEL)	Developmental, human	R	300
Atorvastatin (o-hydroxy atorvastatin)	20 (LOAEL)	Developmental, rat	R/M	3,000
Carbamazepine	3.0 (LOAEL)	Developmental, human	R	300
Diazepam	1.0 (LOAEL)	Developmental, rat		1,000
Diclofenac	20 (NOAEL)	Developmental, mouse		300
Enalapril	0.070 (LOAEL)	Developmental, human		300
Fluoxetine (norfluoxetine)	0.30 (LOAEL)	Developmental, human		300
Gemfibrozil	92 (LOAEL)	Developmental, rat	R	3,000
Meprobamate	75 (NOAEL)	Systemic, mouse		10,000
Naproxen	170 (NOAEL)	Reproductive/developmental, mouse		300
Phenytoin	17.5 (NOAEL)	Developmental, mouse	R/M	300
Risperidone	0.16 (LOAEL)	Reproductive, rat	R/M	3,000
Simvastatin (simvastatin hydroxy acid)	0.2 (LOAEL)	Developmental, human	R	300
Sulfamethoxazole	512 (NOAEL)	Developmental, rat		1,000
Triclosan	75 (NOAEL)	Systemic, hamster		1,000
Trimethoprim	192 (NOAEL)	Developmental, rat		1,000

*Evidence of cancer in rat (R) or mouse (M)

Pharmaceutical Evaluation

Drug	Class	ADI-DWEL (µg/L)	Max. conc. (µg/L)	Sites with Detection (n=18)	Liters per Day to Exceed DWEL
Risperidone	Antipsychotic	0.49	0.0029	1	340
Phenytoin	Anticonvulsant	6.8	0.019	10	700
Carbamazepine	Anticonvulsant	12	0.018	8	1,300
Atenolol	Beta-blocker	70	0.018	8	7,800
Meprobamate	Antianxiety agent	260	0.042	14	13,000
Gemfibrozil	Antilipidemic	45	0.0021	7	43,000
Fluoxetine	SSRI antidepressant	34	0.00082	2	82,000
Norfluoxetine	Metabolite	34	0.00077	1	88,000
Diazepam	Benzodiazepine tranquilizer	35	0.00033	1	210,000
Sulfamethoxazole	Anti-infective	18,000	0.003	4	12,000,000

Endocrine Toxicology

EDC	Effect Dose (mg/kg-d)	Effect	UF
Atrazine	5.0 (LOAEL)	Neurologic/behavioral, mouse	1,000
Bisphenol A	0.002 (LOAEL)	Developmental (endocrine), mouse	1,000
Butylbenzyl phthalate	100 (LOAEL)	Developmental/reproductive (endocrine), rat	1,000
DEHP	1.215 (NOAEL)	Developmental (endocrine), rat	100
17 β -Estradiol	0.005 (NOAEL)	Endocrine-mediated effects, human	300
Estrone	0.004 (NOAEL)	Endocrine-mediated effects, human	300
Ethinylestradiol	0.0001 (NOAEL)	Endocrine-mediated effects, human	1,000
Lindane	0.056 (LOAEL)	Reproductive, rat	1,000
Linuron	<i>-- No new relevant studies --</i>		
Methoxychlor	0.020 (LOAEL)	Developmental/behavioral (endocrine), mouse	1,000
4-Nonylphenol	1.5 (NOAEL)	Renal toxicity, rat (3-generation reproductive study)	30
4-tert-Octylphenol	12.5 (LOAEL)*	Developmental, rat	1,000
Vinclozolin	<i>-- No new relevant studies--</i>		

* LOAEL observed at lower dose (0.020 mg/kg-d), but not replicated in other studies

EDC Evaluation

Drug	Class	ADI-DWEL (µg/L)	Max. conc. (µg/L)	Sites with Detection (n=18)	Liters per Day to Exceed DWEL
Atrazine	Herbicide	3	0.870	15	8
Linuron	Herbicide	70	0.0062	2	23,000
p-Nonylphenol	Industrial chemical	1,800	0.10	2	35,000
Bisphenol A	Industrial chemical	1,800	0.025	1	140,000
Triclosan	Antibacterial	2,600	0.0012	1	4,400,000
17β-Estradiol	Hormone	1.8	<0.00050	0	>7,000
Bis(2-ethylhexyl) phthalate	Industrial chemical	420	<0.10	0	>8,400
Butylbenzyl phthalate	Industrial chemical	3,500	<0.050	0	>140,000

Other Efforts to Develop Screening Levels or ADIs

- **Others have developed screening levels or ADIs for pharmaceuticals or EDCs in drinking water**
- **Early efforts for pharmaceuticals were based on therapeutic dose as the starting point, but pharmaceuticals can have adverse effects at doses less than the therapeutic dose**
- **Australian drinking water guidelines including guidelines for certain pharmaceuticals and EDCs were also released in 2008 - *Australian Guidelines for Water Recycling: Managing Health and Environmental Risks (Phase 2): Augmentation of Drinking Water Supplies.***

Pharmaceuticals

	ADIs (µg/kg-d)		
	Snyder et al. 2008 ¹	EPHC AUS ADIs ²	Schwab et al. 2005 ADIs ³
Atenolol	2.0		
Carbamazepine	0.34	2.8	
Diazepam	1	0.071	
Fluoxetine	0.97	0.28	2.9
Gemfibrozil	1.3	17	55
Meprobamate	7.5		
Phenytoin	0.19		
Risperidone	0.14		
Sulfamethoxazole	510	10	130
Triclosan	75		
Atorvastatin	0.54	0.14	
Diclofenac	67	0.5	
Enalapril	0.23		
Naproxen	570	6.3	
Simvastatin	0.54		
Trimethoprim	190	20	4.2

Potential EDCs

	ADIs (µg/kg-d)			
	Snyder et al 2008 ¹	EPHC AUS ADIs ²	Schwab et al. 2005 ADIs ³	U.S. EPA IRIS RfD ⁴
Atrazine	5.0			35
Bisphenol A	50	50		50
Linuron	2.0			2
4-Nonylphenol	50	150		
Butylbenzyl phthalate	100			200
Diethylhexyl phthalate	12			20
17β-Estradiol	0.050	0.05		
Estrone	0.013	0.00086		
Ethinylestradiol	0.00010	0.000043		
Lindane	0.56			0.3
Methoxychlor	0.20			5
Octylphenol	150	15		
Vinclozolin	12			25

References

1. Snyder, S.A., R.A. Trenholm, E.M. Snyder, G.M. Bruce, R.C. Pleus, and J.D.C. Hemming. (2008). *Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water*. Denver, Colorado: American Water Works Association Research Foundation (AwwaRF).
2. EPHC. (2008). *Australian Guidelines for Water Recycling: Managing Health and Environmental Risks (Phase 2): Augmentation of Drinking Water Supplies*. Draft for Public Comment. July 2007. Adelaide, South Australia: Australian Health Ministers' Conference, Natural Resource Management Ministerial Council, Environment Protection and Heritage Council (EPHC).
3. Schwab, B.W., E.P. Hayes, J.M. Fiori, F.J. Mastrocco, N.M. Roden, D. Cragin, R.D. Meyerhoff, V.J. D'Aco, and P.D. Anderson. (2005). Human pharmaceuticals in US surface waters: a human health risk assessment. *Regulatory Toxicology and Pharmacology* 42(3): 296-312.
4. U.S. EPA IRIS (Reference doses (RfDs) and cancer slope factors (CSFs)): <http://www.epa.gov/iriswebp/iris/subst/index.html>

Comparison of Pharmaceutical DWELs with Maximum Drinking Water Concentrations

Drug	Class	DWEL (µg/L)	Maximum finished water conc. (µg/L)	Minimum margin of safety
Risperidone	Antipsychotic	0.49	0.0029	170
Phenytoin	Anticonvulsant	6.8	0.032	210
Enalapril	ACE inhibitor	8.1	<0.00025	>32,000
Carbamazepine	Anticonvulsant	12	0.018	670
Atorvastatin	Antilipidemic	19	<0.00025	>76,000
Simvastatin	Antilipidemic	19	<0.00025	>76,000
Simvastatin hydroxy acid	Metabolite	19	<0.00025	>76,000
o-Hydroxy atorvastatin	Metabolite	19	<0.00050	>38,000
p-Hydroxy atorvastatin	Metabolite	19	<0.00050	>38,000
Fluoxetine	SSRI antidepressant	34	0.00082	41,000
Norfluoxetine	Metabolite	34	0.00077	44,000
Diazepam	Benzodiazepine tranquilizer	35	0.00033	110,000
Gemfibrozil	Antilipidemic	45	0.0021	21,000
Atenolol	Beta-blocker	70	0.026	2,700
Meprobamate	Antianxiety agent	260	0.043	6,000
Diclofenac	NSAID	2,300	<0.00025	>9,200,000
Triclosan	Antibacterial	2,600	0.0012	2,200,000
Trimethoprim	Antibacterial	6,700	<0.00025	>27,000,000
Sulfamethoxazole	Anti-infective	18,000	0.003	6,000,000
Naproxen	NSAID	20,000	<0.00050	>40,000,000

Comparison of EDC DWELs with Maximum Drinking Water Concentrations

Chemical	Class	DWEL (µg/L)	Maximum finished water conc. (µg/L)	Minimum margin of safety
Estrone	Endogenous estrogenic steroid hormone, drug	0.46	<0.00020	>2,300
Methoxychlor	Organochlorine pesticide	0.7	<0.010	>70
17β-Estradiol	Endogenous estrogenic steroid hormone, drug	1.8	<0.00050	>3,600
Lindane	Organochlorine pesticide	20	<0.010	>2,000
Linuron	Herbicide	70	0.0083	8,400
Atrazine	Herbicide	180	1.0	180
Vinclozolin	Agricultural fungicide	420	<0.010	>42,000
Diethylhexyl phthalate	Phthalate	420	<0.10	>4,200
Bisphenol A	Industrial chemical	1,800	0.025	72,000
4-Nonylphenol	Surfactant, synthesis intermediate, nonylphenol ethoxylate degradate	1,800	0.11	16,000
Butylbenzyl phthalate	Phthalate plasticizer	3,500	<0.050	>70,000
Octylphenol	Surfactant, chemical synthesis intermediate, degradate of octylphenol ethoxylates	5,300	<0.025	>210,000

Comparison of Pharmaceutical DWELs with Maximum Drinking Water Concentrations

Drug	Class	DWEL (µg/L)	Maximum finished water conc. (µg/L)	Minimum margin of safety	Number of glasses of water per day to exceed ADI-DWEL (8-oz glass/d)
Risperidone	Antipsychotic	0.49	0.0029	170	1,400
Phenytoin	Anticonvulsant	6.8	0.032	210	1,800
Enalapril	ACE inhibitor	8.1	<0.00025	>32,000	>270,000
Carbamazepine	Anticonvulsant	12	0.018	670	5,600
Atorvastatin	Antilipidemic	19	<0.00025	>76,000	>640,000
Simvastatin	Antilipidemic	19	<0.00025	>76,000	>640,000
Simvastatin hydroxy acid	Metabolite	19	<0.00025	>76,000	>640,000
o-hydroxy atorvastatin	Metabolite	19	<0.00050	>38,000	>320,000
p-hydroxy atorvastatin	Metabolite	19	<0.00050	>38,000	>320,000
Fluoxetine	SSRI antidepressant	34	0.00082	41,000	350,000
Norfluoxetine	Metabolite	34	0.00077	44,000	370,000
Diazepam	Benzodiazepine tranquilizer	35	0.00033	110,000	900,000
Gemfibrozil	Antilipidemic	45	0.0021	21,000	180,000
Atenolol	Beta-blocker	70	0.026	2,700	23,000
Meprobamate	Anti-anxiety agent	260	0.043	6,000	51,000
Diclofenac	NSAID	2,300	<0.00025	>9,200,000	>78,000,000
Triclosan	Antibacterial	2,600	0.0012	2,200,000	18,000,000
Trimethoprim	Antibacterial	6,700	<0.00025	>27,000,000	>230,000,000
Sulfamethoxazole	Anti-infective	18,000	0.003	6,000,000	51,000,000
Naproxen	NSAID	20,000	<0.00050	>40,000,000	>340,000,000

Comparison of Pharmaceutical DWELs with Maximum Drinking Water Concentrations

Drug	Class	DWEL (µg/L)	Maximum finished water conc. (µg/L)	Minimum margin of safety	Number of glasses of water per day to exceed ADI-DWEL (8-oz glass/d)
Risperidone	Antipsychotic	0.49	0.0029	170	1,400
Phenytoin	Anticonvulsant	6.8	0.032	210	1,800
Carbamazepine	Anticonvulsant	12	0.018	670	5,600
Fluoxetine	SSRI antidepressant	34	0.00082	41,000	350,000
Norfluoxetine	Metabolite	34	0.00077	44,000	370,000
Diazepam	Benzodiazepine tranquilizer	35	0.00033	110,000	900,000
Gemfibrozil	Antilipidemic	45	0.0021	21,000	180,000
Atenolol	Beta-blocker	70	0.026	2,700	23,000
Meprobamate	Antianxiety agent	260	0.043	6,000	51,000
Triclosan	Antibacterial	2,600	0.0012	2,200,000	18,000,000
Sulfamethoxazole	Anti-infective	18,000	0.003	6,000,000	51,000,000

Comparison of EDC DWELs with Maximum Drinking Water Concentrations

Chemical	Class	DWEL (µg/L)	Maximum finished water conc. (µg/L)	Minimum margin of safety	Number of glasses of water per day to exceed ADI-DWEL (8-oz glass/d)
Ethinylestradiol	Pharmaceutical estrogen	0.0035	<0.0010	>3.5	>30
Estrone	Endogenous estrogenic steroid hormone, drug	0.46	<0.00020	>2,300	>19,000
Methoxychlor	Organochlorine pesticide	0.7	<0.010	>70	>590
17β-Estradiol	Endogenous estrogenic steroid hormone, drug	1.8	<0.00050	>3,600	>30,000
Lindane	Organochlorine pesticide	20	<0.010	>2,000	>17,000
Linuron	Herbicide	70	0.0083	8,400	71,000
Atrazine	Herbicide	180	1.0	180	1,500
Vinclozolin	Agricultural fungicide	420	<0.010	>42,000	>360,000
Diethylhexyl phthalate	Phthalate	420	<0.10	>4,200	>36,000
Bisphenol A	Industrial chemical	1,800	0.025	72,000	610,000
4-Nonylphenol	Surfactant, synthesis intermediate, nonylphenol ethoxylate degradate	1,800	0.11	16,000	140,000
Butylbenzyl phthalate	Phthalate plasticizer	3,500	<0.050	>70,000	>590,000
Octylphenol	Surfactant, chemical synthesis intermediate, degradate of octylphenol ethoxylates	5,300	<0.025	>210,000	>1,800,000

Comparison of Lifetime Risks Associated with Different Events or Situations

Event or situation	Approximate lifetime risk
<i>Risks of accidental death</i>	
Dying in a motor vehicle accident	1 in 100
Dying in a motor vehicle accident per 100 miles traveled	1 in 1,000,000
Dying while a pedestrian	1 in 1,000
Drowning	1 in 1,000
Dying from a fall at home	3 in 1,000
Dying from a lightening strike	1 in 100,000
Dying while riding a bicycle	5 in 1,000,000
<i>Risks of developing cancer from environmental agents</i>	
Skin cancer, primarily from exposure to the sun	1 in 5
Cigarette smoking (a pack or more per day)	8 in 100
Outside radiation (radon and cosmic rays)	1 in 1,000
Environmental tobacco smoke (death from cancer)	1 in 1,000
Human-made chemicals in indoor air at home	2 in 10,000
Outdoor air in industrialized area	1 in 10,000
Human-made chemicals in drinking water (chlorination)	1 in 100,000
Consumption of 2 oz. of peanut butter per week (naturally occurring aflatoxin)	8 in 100,000
Consumption of one meal per year of small Lake Michigan trout	1 in 100,000

World Health Organization Drinking Water Quality Guidelines

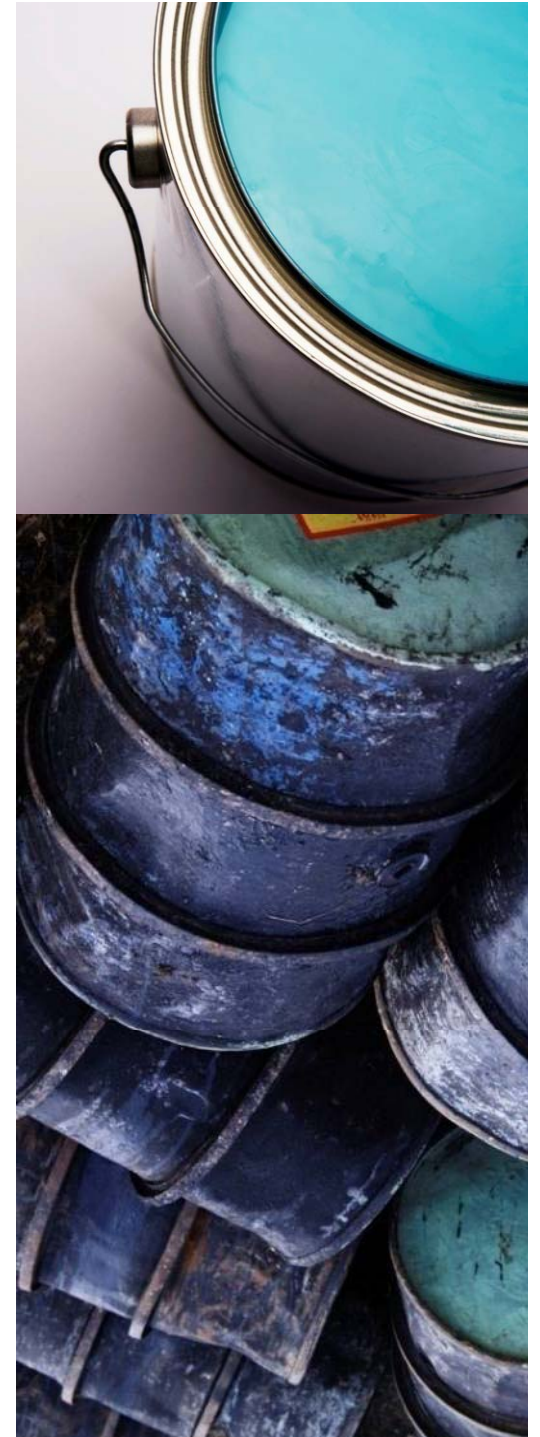
8.2.9 Mixtures

Chemical contaminants of drinking-water supplies are present with numerous other inorganic and/or organic constituents. The guideline values are calculated separately for individual substances, without specific consideration of the potential for interaction of each substance with other compounds present. The large margin of uncertainty incorporated in the majority of the guideline values is considered to be sufficient to account for potential interactions. In addition, the majority of contaminants will not be continuously present at concentrations at or near their guideline value.



Multiple Routes of Exposure to the Same Contaminant

- **Drinking water**
- **Food and beverages**
- **Prescription and non-prescription medications**
- **Environmental pollutants: combustion byproducts, agricultural pesticides**
- **Occupational exposures**
- **Residential activities: cleaning products, personal care products, hobby chemicals, pesticides**



Comparative Exposure

- **Relative importance of various routes of exposure to the same chemical from different sources**
- **Exposure to mixtures of chemicals that might act through the same mode of action or otherwise might collectively produce a different response than would be predicted for a single contaminant**





Summary of Evaluations Performed by the
Joint FAO/WHO Expert Committee on Food Additives
(JECFA 1956-2004)
(First through sixty-third meetings)



Summary of Evaluations Performed by the
Joint FAO/WHO Expert Committee on Food Additives

ESTRADIOL-17BETA

Chemical names:	ESTRA-1,3,5(10)-TRIENE-3,17beta-DIOL
Synonyms:	ESTRADIOL
Functional class:	VETERINARY DRUG (PRODUCTION AID)
Latest evaluation:	1999
ADI:	0-0.00005 mg/kg bw = 50 ng/kg = 3,500 ng/70 kg person
Comments/MRLs:	MRLs: Muscle, liver, kidney and fat (cattle): NOT SPECIFIED
Report:	TRS 893-JECFA 52/57
Residues:	FNP 41/12-JECFA 52/37
Tox monograph:	FAS 43-JECFA 52/43
Previous status:	1987, TRS 763-JECFA 32/17, FNP 41-JECFA 32/7, NOT PREPARED. ADI UNNECESSARY. ACCEPTABLE RESIDUE LEVEL: UNNECESSARY; HORMONE PRODUCED ENDOGENOUSLY AT VARIABLE LEVELS IN HUMAN BEINGS. RESIDUES FROM USE IN ACCORDANCE WITH GOOD ANIMAL HUSBANDRY PRACTICE UNLIKELY TO POSE A HAZARD TO HUMAN HEALTH. AC. MRL 1981, TRS 669-JECFA 25/15. UNLIKELY TO BE ANY CAUSE OF CONCERN WHEN PROPERLY USED

Concentrations of Estrogens in Milk

Milk	Estrogen	Concentration	Reference
Human	Unspecified	15 – 840 µg/L	Borgert et al. 2003, citing Hamosh 2001
Human	Estradiol	0.036 µg/L (mean) 0.045 µg/L (mean)	Messripour et al. 2002
Cow	Unspecified	≤ 0.017 µg/L	Lopez et al. 2002
Cow	17β-Estradiol	0.01 µg/L	Hartmann et al. 1998
Cow	17β-Estradiol	0.01 – 0.09 µg/L (range of means, detected levels)	Fritsche and Steinhart 1999, Hartmann et al. 1998

Concentrations of Estrogens in Milk, Cont'd

Milk	Estrogen	Concentration	Reference
Cow	17β-Estradiol	0.01 - 0.06 μg/L	Hartmann et al. 1998
Cow	17β-Estradiol	3.5-14.4 ng/L (range of means)	Wolford and Argoudelis 1979
Cow	Estrone	0.01 – 0.26 μg/L (range of means for various types)	Fritsche and Steinhart 1999, Hartmann et al. 1998
Cow	Estrone	0.03 – 0.12 μg/L	Hartmann et al. 1998
Cow	Estrone	9.1 – 55.8 ng/L (range of means)	Wolford and Argoudelis 1979

Comparative Exposure: Estrogen and Phytoestrogens in Milk and Infant Formula

Sample	Concentration (µg/L)	
	Estrogens	Phytoestrogens
Human breast milk	15 - 840	6 (mean)
Human breast milk		~60 (max)
Cow milk	≤ 0.017	0.1 - 30
Infant formula		7 - 475
Soy milk		2.5 – 211,600
Soy-based formula		32,000 – 47,000 (means)

Antignac et al. 2003, Ishibashi et al. 2002, Lopez et al. 2002, Borgert et al. 2003.

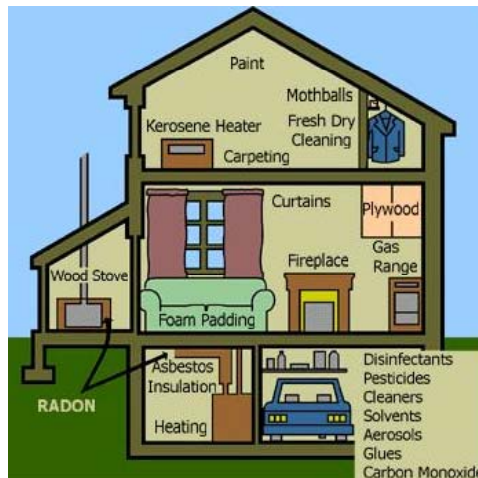
Estrogenicity Comparison



**Teaspoon of soy sauce
(300 ng/L, 15 mL)**

**1 liter of secondary
wastewater
(4.6 ng/L)**

	WATER		INDOOR AIR	
	Conc.	Exposure (2 L/day)	Conc.	Exposure (24 m ³ /day)
	(ng/L)	(μg)	(ng/m ³)	(μg)
BHT	49	0.10	36000	864
TCPP (Fyrol PCF)	530	1	1300	30
Galaxolide	280	0.6	120	3
Butylbenzyl phthalate	55	0.1	18	0.4
Nonylphenol	130	0.3	110	3



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