

**COMPARISON OF ANALYTICAL RESULTS FOR TRACE ORGANICS IN THE
SANTA ANA RIVER AT THE IMPERIAL HIGHWAY
TO HEALTH RISK-BASED SCREENING LEVELS**

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June 25, 2009

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1.0 INTRODUCTION

A study underway by the National Water Research Institute—Metropolitan Water District—Orange County Water District (NWRI–MWD–OCWD) is assessing the presence of contaminants of emerging concern in Santa Ana River (SAR), Colorado River, and California State Water Project water. Intertox was asked by OCWD to review and statistically summarize the data from the trace organics analytical program collected on the SAR at the Imperial Highway, and to determine the potential significance of detected concentrations to human health by comparing concentrations to health risk-based screening levels. Specifically, we compared detected concentrations to acceptable daily intakes (ADIs) and drinking water equivalent levels (DWELs) developed by Intertox as part of the Water Research Foundation 3085/WateReuse Foundation (WRF)-04-003 “Toxicological Relevance of Endocrine Disruptors and Pharmaceuticals in Drinking Water” study, the WRF-06-018 “Development and Application of Tools to Assess and Understand the Relative Risks of Drugs and Other Chemicals in Indirect Potable Reuse Water” study and other work we have conducted, and to health risk-based screening levels published by other agencies.

We presented the findings summarized in this report at a meeting on May 28, 2009, in Orange County, organized by NWRI and attended by the NWRI SAR Science Advisory Panel, NWRI Groundwater Replenishment System (GWRS) Independent Advisory Subcommittee Panel, and other agencies, including OCWD and MWD.

The methods and results of the analysis are summarized below.

2.0 DATA ANALYSIS AND STATISTICAL SUMMARY

The OCWD provided Intertox with a summary of analytical data for quarterly water samples collected at 13 locations within the SAR watershed and analyzed by the OCWD and MWD laboratories. Samples were collected on May 22, 2008; August 19, 2008; November 5, 2008; and February 25, 2009, and analyzed for a total of 49 compounds. Intertox was asked to compare concentrations measured at the Imperial Highway location to health risk-based screening levels. For each analyte, a total of four sample measurements were available at the Imperial Highway location. Intertox was not requested to review or verify the laboratory QA/QC data for the analytical program, and we assumed the analytical results we were presented with were valid.

Intertox examined the data to determine whether any seasonal pattern in minimum or maximum concentrations of the various compounds was apparent. No clear trend was evident. Of the 16 detected compounds, the maximum detected concentration was detected on May 22, 2008 for five compounds; August 19, 2008 for four compounds; November 5, 2008 for six compounds; and February 25, 2009 for two compounds (for one compound, the same maximum concentration was detected in two different quarters).

In general, per U.S. EPA guidance, the exposure point concentration (EPC) used in risk assessments should represent “a reasonable estimate of the concentration likely to be contacted over time”—in other words, an average concentration (U.S. EPA, 1989; U.S. EPA, 2002). However, since only four data points were available for each analyte at the Imperial Highway location, we compared the maximum detected concentrations to health risk-based screening levels. Using the maximum

detected concentration is consistent with U.S. EPA recommendations when sample sizes are small (e.g., <5 samples) (U.S. EPA, 2002). However, U.S. EPA cautions that “defaulting to the maximum observed concentration may not be protective when sample sizes are very small because the observed maximum may be smaller than the population mean” (U.S. EPA, 2002). In other words, collected samples may not reflect the true mean for the exposure area if sampling episodes were not representative of typical conditions.

Per U.S. EPA (2007), for datasets where most (e.g., > %95) of the observations for a contaminant lie below the detection limit(s), the sample median (rather than a sample average which cannot be computed accurately) should be used as an estimate for the EPC term. In the current evaluation, since only four data points were available for a given compound, when all samples were nondetect, the minimum reporting limit (MRL) for a given compound was compared to the DWEL associated with a health risk-based screening level.

For each compound at the Imperial Highway location, Table 1 summarizes the MRL, frequency of detection, and range of detected concentrations.

3.0 COMPARISON OF SAMPLING RESULTS TO HEALTH RISK-BASED SCREENING LEVELS

In order to assess the potential human health risks associated with exposure to the trace organics detected in SAR water, the maximum detected concentrations at the Imperial Highway location were compared to health risk-based screening levels. These included ADIs developed by Intertox as part of past work addressing the potential human health risks of pharmaceuticals and personal care products (PPCPs) or endocrine disrupting compounds (EDCs) in drinking water or water intended for indirect nonpotable reuse, or various types of health risk-based screening levels developed and published by other agencies.

Health risk-based screening levels, known by such names as ADIs, tolerable daily intakes (TDIs), or reference doses (RfDs), are commonly defined as 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, 1993a). Appendix A describes the methods Intertox applied to develop ADIs for PPCPs and EDCs. The various screening levels are typically presented in terms of dose per unit of body weight per day (e.g., micrograms per kilogram body weight per day, or $\mu\text{g}/\text{kg}\text{-d}$), or as equivalent water concentrations calculated based on assumptions about the amount of water a person consumes per day and their body weight.

Screening levels in $\mu\text{g}/\text{kg}\text{-d}$ were converted to drinking water equivalent level (DWELs) in $\mu\text{g}/\text{L}$ by multiplying the screening level by an assumed body weight (e.g., 70 kg, the U.S. EPA default adult body weight) and dividing by an average daily drinking water ingestion rate (e.g., 2 liters per day, the U.S. EPA default adult drinking water ingestion rate) (U.S. EPA, 2006):

$$\text{DWEL } (\mu\text{g} / \text{L}) = \frac{\text{Health risk – based screening level } (\mu\text{g} / \text{kg} - \text{d}) \times 70 \text{ kg}}{2 \text{ L} / \text{d}}$$

A body weight of 70 kg, or about 150 pounds, is approximately equal to the mean body weight for adults (U.S. EPA, 1997), while a daily drinking water consumption rate of 2 L/day corresponds to

about the 84th percentile of the average daily intake distribution for adults; the mean is about 1.4 L/day (U.S. EPA, 1997).

Often, when setting toxicity-based standards for contaminants in surface water systems, regulatory agencies incorporate additional factors into the above equations. One factor, known as a relative source contribution or RSC, accounts for the possibility that, on any given day, a person could be exposed to the substance through some other source than drinking water ingestion (e.g., consumption in food, exposure through other environmental media). RSCs typically range in value from 20 to 80% based on knowledge about likely alternative sources of exposure to the chemical (U.S. EPA, 2000; CDPH, 2007; U.S. EPA, 2006). Thus, if this approach is used, the resulting DWEL would correspond to a dose that is 20 to 80% of the ADI. In addition, in deriving Maximum Contaminant Levels (MCLs), U.S. EPA typically considers best available treatment technologies and costs. Thus, DWELs calculated from ADIs based on assumptions about the average body weight and drinking water consumption rate should not be interpreted as regulatory limits—rather, they represent a concentration below which adverse health effects over a lifetime of exposure are considered unlikely (for noncarcinogens) or are within a *de minimis* risk level (for carcinogens).

For the 49 analytes in SAR water, we determined the availability of health risk-based screening levels from the following sources:

- *ADIs and DWELs developed by Intertox in Water Research Foundation 3085/ WRF-04-003: “Toxicological Relevance of Endocrine Disruptors and Pharmaceuticals in Drinking Water” (Snyder et al., 2008).* This project developed ADIs for 16 PPCPs and 13 EDCs and applied them to assess the potential risk associated with drinking water exposure concentrations measured in water samples submitted by utilities across the United States. The final report has been published.
- *ADIs and DWELs developed by Intertox in WRF-06-018 “Development and Application of Tools to Assess and Understand the Relative Risks of Drugs and Other Chemicals in Indirect Potable Reuse Water” (Bruce et al., 2009).* This project developed ADIs for a total of 43 PPCPs, EDCs, and other emerging compounds of interest potentially present in water intended for indirect potable reuse. The project report is in final draft and will be published by the WateReuse Foundation this year.
- *ADIs and DWELs developed by Intertox in WRF-05-005 “Identifying Pharmaceuticals / Personal Care Products of Most Health Concern and Persistence through Water Treatments Used for Potable Reuse.”* This project focused on developing and conducting a workshop attended by an expert panel of regulators and scientists to discuss alternative methods to efficiently develop human health risk-based screening levels for PPCPs and EDCs in potable water. Screening levels were identified for a total of 42 PPCPs, EDCs, and other emerging compounds of interest in water. The workshop was held in November 2008, and a final draft consensus report from the workshop has been developed. Although the objective of this project was not to develop final ADIs, but rather to explore the utility of various approaches for developing ADIs, the methods used are consistent with other programs (see those above); for purposes of the current project, we selected the lowest (most conservative) screening values developed in WRF-05-005 as ADIs. Because the report has not been finalized, ADIs and DWELs from that report are listed herein as *draft* values.

- *Schwab et al. (2005) ADIs for pharmaceuticals.* Schwab et al. (2005) developed screening levels for 16 pharmaceuticals by dividing the lowest therapeutic dose by uncertainty factors ranging from 10.2 to 150.
- *California Environmental Protection Agency Public Health Goals (PHGs) for contaminants in drinking water.* A PHG is a level of contaminant in drinking water (in units of $\mu\text{g/L}$) that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime (CA EPA, 2009). PHGs typically incorporate a RSC of 20 to 80% based on knowledge about likely alternative sources of exposure to the chemical (CDPH, 2007).
- *U.S. EPA Reference Doses (RfDs) (in units of $\mu\text{g/kg-d}$) and Maximum Contaminant Limits (MCLs, in units of $\mu\text{g/L}$) for various compounds, including pesticides.* A reference dose is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (U.S. EPA, 2009b). An MCL is the maximum permissible level of a contaminant in water which is delivered to any user of a public water system, and takes into account best available treatment technologies and costs. The MCL is set as close to the Maximum Contaminant Level Goal (MCLG) as feasible. For noncarcinogens, the MCLG is the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, allowing for an adequate margin of safety (U.S. EPA, 2006), and is typically calculated from the DWEL (computed by multiplying an RfD by a body weight of 70 kg and dividing by an average water ingestion rate of 2 L/day) multiplied by an RSC (often 20%) (U.S. EPA, 2006). For carcinogens, the MCLG is set as zero.
- *U.S. EPA slope factors for carcinogenic compounds, in units of $(\text{mg/kg-d})^{-1}$.* A slope factor is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a dose of 1 mg/kg-d (U.S. EPA, 2009b). The slope factor is converted to an ADI by dividing an assumed *de minimis* lifetime acceptable cancer risk rate of one in one million (10^{-6}) by the slope factor. The ADI is in turn converted to a DWEL by multiplying it by an average adult body weight of 70 kg and dividing by a drinking water ingestion rate of 2 L/d.

The ADIs and DWELs identified for the 49 compounds are listed in Table 1.

The sections below compare concentrations of trace analytes detected at the Imperial Highway location to health risk-based screening levels presented as DWELs, estimate the amount of water with the maximum-detected concentration of each detected compound that a person would have to consume per day to reach a dose equal to the screening level, and summarize the findings.

3.1 Comparison of Water Concentrations at the Imperial Highway to Health Risk-Based DWELs

Table 2 compares maximum detected concentrations at the Imperial Highway location to health risk-based DWELs, if available, for each of the 16 detected compounds. The potential significance of the 33 nondetected compounds is also assessed by comparing MRLs to DWELs, if available.

3.1.1 Comparison of Maximum Detected Concentrations to Health Risk-Based DWELs

Health risk-based screening levels were identified for all of the detected compounds (Table 2). As shown, maximum detected concentrations of all compounds are below the respective health risk-based DWELs.

3.1.2 Comparison of MRLs for Nondetected Compounds to Health Risk-Based DWELs

Thirty three of the 49 compounds were not detected in any samples at the Imperial Highway location at concentrations above their MRLs. For these compounds, we compared the MRLs to health risk-based DWELs, if available. Health risk-based DWELs were identified for 18 of the nondetected compounds. The MRLs for all of these compounds were below their DWELs with the exception of two, benzo(a)pyrene and pentachlorophenol.

The MRL for benzo(a)pyrene, a polycyclic aromatic hydrocarbon (PAH) that can form when organic materials (e.g., gasoline, garbage, or any animal or plant materials) burn incompletely, was 0.025 µg/L. This concentration is above the California EPA PHG for benzo(a)pyrene of 0.004 µg/L (CA EPA, 1997). The PHG is based on evidence of gastric tumors in mice administered benzo(a)pyrene in the diet, and an assumed acceptable lifetime excess cancer incidence due to exposure to benzo(a)pyrene of 1 in 1,000,000 (i.e., 10⁻⁶). The U.S. EPA MCL for benzo(a)pyrene in drinking water is 0.2 µg/L.

The MRL for pentachlorophenol, a pesticide and wood preservative, was 1.0 µg/L. This concentration is above the California EPA PHG for pentachlorophenol of 0.3 µg/L (CA EPA, 2009). The PHG is based on evidence of carcinogenicity (primarily liver tumors) in mice administered pentachlorophenol in the diet, and an assumed acceptable lifetime excess cancer incidence due to exposure to pentachlorophenol of 1 in 1,000,000 (i.e., 10⁻⁶). The U.S. EPA MCL for pentachlorophenol in drinking water is 1.0 µg/L.

3.2 Daily Water Consumption Required to Equal Health Risk-Based Screening Levels

To put the health risk-based screening levels into understandable terms to support risk communication, the amount of water with the maximum-detected concentration that a person would have to consume, in liters per day, to reach a dose equal to the health risk-based screening level was calculated. The calculation used to compute these values is as follows:

$$\text{Required water consumption (L/day)} = \frac{\text{Health Risk-Based DWEL } (\mu\text{g/L}) \times 2 \text{ L/d}}{\text{Maximum water concentration } (\mu\text{g/L})}$$

The equivalent amount of water in eight ounce glasses of water per day was computed by multiplying the amount in L/day by 4.23. These calculations assume exposure only through drinking water; if a person is likely to be exposed to the compound through other sources, the required water consumption volume would be lower. However, it is unlikely that a person would directly consume water from this source, day after day, and average concentrations in finished drinking water would likely be much lower than the maximum concentrations assumed here. Therefore, these computations are expected to be reasonably to very conservative, and result in required water consumption estimates to equal health risk-based screening levels that are much lower than would be expected for

drinking water. The results of the water consumption calculations are presented in Table 3.

Based on the data shown in Table 3 and the assumptions described above, estimated amounts of water that must be consumed to equal the health risk-based screening level for all detected compounds range from 19 L/day for primidone (about 82 8-oz. glasses per day) to 580,000 L/day for triclosan (about 2,400,000 8-oz. glasses per day). All of the compounds had an estimated water consumption value that significantly exceeded the assumed default daily water consumption rate of 2 L/day.

4.0 SUMMARY AND CONCLUSIONS

As discussed above, maximum detected concentrations of all 16 compounds detected in the SAR at the Imperial Highway location were below their health risk-based DWELs. Exceedance of a health risk-based screening level does not mean that adverse health effects are likely or will occur. Health risk-based screening levels incorporate numerous sources of conservatism, and do not represent thresholds at or above which adverse health effects are likely; rather, they represent levels below which adverse health effects are extremely unlikely to occur. Exceedance of a health risk-based screening level suggests that further examination of detected concentrations and their significance relative to exposure levels associated with adverse health effects is warranted.

For 15 of the 33 analytes that were not detected at the Imperial Highway location, health risk-based screening levels were not identified. Of the 18 nondetected compounds with DWELs, two had MRLs that were slightly above their DWELs. These were benzo(a)pyrene, which had an MRL of 0.025 µg/L and a California EPA PHG of 0.004 µg/L, and pentachlorophenol, which had an MRL of 1.0 µg/L and a California EPA PHG of 0.3 µg/L. While these compounds could theoretically be present at concentrations slightly above the PHG but below the MRL, they were detected very infrequently in the SAR watershed (benzo(a)pyrene was detected in only four of 52 samples at the 13 sample locations, and pentachlorophenol was not detected in any of the 52 samples) suggesting low potential for either of these compounds to be present in water at the Imperial Highway location at levels that present a human health concern.

It is unlikely that a person would drink untreated water from the Santa Ana River. However, based on our review of the water data collected at the Imperial Highway on May 22, 2008, August 19, 2008, November 5, 2008, and February 25, 2009, even if someone routinely consumed untreated drinking water from this source, no adverse health effects would be expected for any of the 49 analyzed compounds.

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TABLE 1. Basis of Health Risk-Based Screening Levels

Compound	Group	ADI (µg/kg-d)	DWEL (µg/L)	Source of ADI	Basis of ADI
Acetaminophen	Drug (antibiotic)	340	12,000	Schwab et al. (2005) ADI ^a	Therapeutic dose & 27 UF
Anthracene	Polycyclic aromatic hydrocarbon	300	11,000	U.S. EPA (1993b) RfD	Noncancer toxicity data (no effect level for systemic effects in mice)
Atrazine	Triazine herbicide	ND ^b	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG	Systemic effects in rats (reduced body weight); mammary tumors in rats
Atrazine-Desethyl	Metabolite and degradate of triazine herbicides	ND ^b	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG ^c	Atrazine MCL and PHG
Atrazine-Desisopropyl	Metabolite and degradate of triazine herbicides	ND ^b	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG ^c	Atrazine MCL and PHG
Azithromycin	Drug (antibiotic) (Zithromax®)	NA	NA	NA	NA
Benzo(a)pyrene	Polycyclic aromatic hydrocarbon	ND ^b	0.004	CA EPA (1997) PHG	Gastric tumors in mice
Bisphenol A	Intermediate in production of resins	50	1,800	U.S. EPA (1993c) RfD; Snyder et al. (2008) ADI	Systemic effects in mice (reduced body weight)
Butylparaben	Preservative in personal care products	NA	NA	NA	NA
Caffeine	Food additive/natural ingredient	2,500	87,500	Health Canada (2007)	Recommended maximum consumption for children ≤ 12 years based on potential for increased anxiety
Carbamazepine	Drug (anticonvulsant) (Tegretol®)	0.34	12	Snyder et al. (2008) ADI	Liver tumors in rats
Ciprofloxacin	Drug (antibiotic)	0.60	21	WRF-06-018 ADI (Draft value)	Minimum inhibitory concentration for GI flora
Cyanazine	Triazine herbicide	ND ^b	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG ^c	Atrazine MCL and PHG
Cyprazine	Triazine herbicide	ND ^b	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG ^c	Atrazine MCL and PHG
o,p-DDD	Drug (treatment of Cushings disease) (Mitotaine®)	0.0042	0.15	U.S. EPA (1988b) cancer slope factor for p,p-DDD (0.24 (mg/kg-d) ⁻¹)	Liver tumors in mice
DEET	Insect repellent	2.3	81	WRF-06-018 ADI	Neurological effects in rats
Diclofenac	Drug (NSAID analgesic)	67	2,300	Snyder et al. (2008) ADI	Developmental effects in mice
Diethylstilbestrol	Drug (synthetic estrogen for miscarriage prevention); no longer approved	NA	NA	NA	NA
Dilantin (Phenytoin)	Drug (anticonvulsant)	0.19	6.7	Snyder et al. (2008) ADI	Liver tumors in mice

TABLE 1 (cont). Basis of Health Risk-Based Screening Levels

Compound	Group	ADI (µg/kg-d)	DWEL (µg/L)	Source of ADI	Basis of ADI
Diuron	Herbicide	2.0	70	U.S. EPA (1988a) RfD	Hematological effects in dogs
Epitestosterone	Endogenous hormone	NA	NA	NA	NA
17a-Estradiol	Endogenous hormone	NA	NA	NA	NA
17b-Estradiol	Endogenous hormone	0.017	1.8	Snyder et al. (2008) ADI	Minimum dose for therapeutic effect in human & 100 UF
Estriol	Endogenous hormone	NA	NA	NA	NA
Estrone	Endogenous hormone	0.050	0.46	Snyder et al. (2008) ADI	No effect on endocrine measurements in humans
Ethylparaben	Preservative in personal care products	NA	NA	NA	NA
Ethinylestradiol	Drug (oral contraception)	NA	NA	NA	NA
Gemfibrozil	Drug (antilipidemic) (Lopid®)	1.3	46	Snyder et al. (2008) ADI	Testicular tumors in rats
Ibuprofen	Drug (NSAID analgesic)	0.97	34	WRF-06-018 ADI (Draft value)	Therapeutic dose & 3000 UF
Lindane	Organochlorine insecticide	ND ^b	0.032	CA EPA (2005) PHG	Liver tumors in mice
Linuron	Substituted urea herbicide	2.0	70	U.S. EPA (1990) RfD; Snyder et al. (2008) ADI	Hematological effects in dogs
Methoxychlor	Organochlorine insecticide	0.020	0.70	Snyder et al. (2008) ADI	Developmental effects in mice (EPA MCL = 40 µg/L; CA EPA PHG = 30 µg/L)
Methylparaben	Preservative in personal care products	NA	NA	NA	NA
4-n- and 4-t-Octylphenol	Surfactant	0.50	18	WRF-05-005 ADI (Draft value)	Noncancer toxicity data (developmental, rat)
4-n-Nonylphenol	Surfactant	50	1,800	Snyder et al. (2008) ADI	Developmental effects in rats
Nonylphenol ethoxylates (total)	Surfactant	NA	NA	NA	NA
Pentachlorophenol	Pesticide, wood preservative	ND ^b	0.3	CA EPA (2009) PHG	Liver tumors in mice
4-Phenylphenol	Chemical intermediate	NA	NA	NA	NA
Primidone	Drug (anticonvulsant) (Mysoline®)	0.024	0.84	WRF-06-018 ADI	Liver tumors in mice
Progesterone	Endogenous hormone	NA	NA	NA	NA
Propazine	Triazine herbicide	ND ^b	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG ^c	Atrazine MCL and PHG
Propylparaben	Preservative in personal care products	NA	NA	NA	NA

TABLE 1 (cont). Basis of Health Risk-Based Screening Levels

Compound	Group	ADI (µg/kg-d)	DWEL (µg/L)	Source of ADI	Basis of ADI
Simazine	Triazine herbicide	ND ^b	4	U.S. EPA (2009a) MCL; CA EPA (2001) PHG	Reduced body weight in rats
Sulfamethoxazole	Drug (antibiotic) (Generic)	510	18,000	Snyder et al. (2008) ADI	Developmental effects in rats
TCEP	Reducing agent	0.12	4.2	WRF-06-018 ADI	Virtually safe dose for nongenotoxic carcinogenicity
Testosterone	Endogenous hormone	NA	NA	NA	NA
Tetrabromobisphenol A	Brominated flame retardant	NA	NA	NA	NA
2,4,6-Trichlorophenol	Pesticide, preservative	0.091	3.2	U.S. EPA (1994) slope factor (0.011 (mg/kg-d) ⁻¹)	Leukemia in mice
Triclosan	Drug (antibacterial/antimicrobial) (Generic)	75	2,600	Snyder et al. (2008) ADI	No effect on systemic endpoints in hamsters

ADI– Acceptable daily intake; DEET– N,N-Diethyl-meta-toluamide; PHG– Public Health Goal; NA–Value not available; RfD– Reference dose; TCEP– tris(2-carboxyethyl)phosphine

a. Schwab et al. (2005) calculated an ADI for acetaminophen from a therapeutic dose of 650 mg/day, or 9.3 mg/kg-d assuming exposure to a 70 kg adult. However, Schwab et al. applied a combined UF of 27, whereas more recent work by Intertox, including the results of the expert panel convened in WRF-05-005, concluded that application of a default UF of 3,000 to minimum therapeutic doses is appropriate. Application of a UF of 3,000 to 9.3 mg/kg-d would yield an ADI of 3.1 µg/kg-d.

b. The DWELs for these compounds were set equivalent to published U.S. EPA MCLs or California EPA PHGs. Because MCLs and PHGs incorporate additional factors into calculation of acceptable water concentrations from ADIs (e.g., relative source contributions for both MCLs and PHGs, and best available technologies and costs for MCLs), ADIs were not backcalculated from these values.

c. The DWELs for atrazine-desethyl, atrazine-desisopropyl, cyanazine, cyprazine, and propazine are assumed to be the same as the DWEL for atrazine-desisopropyl atrazine proposed in WRF-06-018, which is equivalent to the U.S. EPA MCL for atrazine. Per U.S. EPA, the chlorotriazine herbicides and their metabolites are assumed to share the same neuroendocrine mechanism of toxicity and to be “toxicologically equivalent (equipotent) to atrazine” (U.S. EPA-OPPTS, 2006).

TABLE 2. Statistical Summary of Sampling Data for Trace Organics in the Santa Ana River at the Imperial Highway and Comparison to Health Risk-Based DWELs

Compound	Lab	MRL (µg/L)	Freq. of Detect	Concentration (µg/L)			Source of DWEL	Max (or MRL) > DWEL? ^a
				Min. Detect	Max.	Health Risk-Based DWEL		
Detected Compounds								
Acetaminophen	OCWD	0.001-0.020	3/4	0.0037	0.430	12,000	Schwab et al. (2005) ADI	No
Atrazine	MWD	0.001	3/4	0.0022	0.0029	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG	No
Caffeine	MWD & OCWD	0.005	4/4	0.035	1.255	87,500	Health Canada (2007)	No
Carbamazepine	MWD & OCWD	0.001	4/4	0.052	0.120	12	Snyder et al. (2008) ADI	No
Ciprofloxacin	OCWD	0.010-0.1	1/4	0.022	0.022	21	WRF-06-018 ADI (Draft value)	No
DEET	MWD & OCWD	0.020	4/4	0.020	0.156	81	WRF-06-018 ADI (Draft value)	No
Diclofenac	MWD	0.005	1/4	0.015	0.015	2,300	Snyder et al. (2008) ADI	No
Dilantin (Phenytoin)	MWD	0.005	4/4	0.035	0.143	6.7	Snyder et al. (2008) ADI	No
Diuron	MWD	0.005	4/4	0.053	0.954	70	U.S. EPA (1988a) RfD	No
Gemfibrozil	MWD & OCWD	0.005	4/4	0.0069	0.023	46	Snyder et al. (2008) ADI	No
Ibuprofen	MWD & OCWD	0.010	3/4	0.042	0.309	34	WRF-06-018 ADI (Draft value)	No
Primidone	MWD & OCWD	0.002	4/4	0.041	0.087	0.84	WRF-06-018 ADI (Draft value)	No
Simazine	MWD	0.020	3/4	0.024	0.060	4	U.S. EPA (2009a) MCL; CA EPA (2001) PHG	No
Sulfamethoxazole	MWD & OCWD	0.001	4/4	0.041	0.084	18,000	Snyder et al. (2008) ADI	No
TCEP	MWD	0.005	4/4	0.111	0.217	4.2	WRF-06-018 ADI (Draft value)	No
Triclosan	MWD & OCWD	0.005	1/4	0.009	0.009	2,600	Snyder et al. (2008) ADI	No
Non-Detected Compounds								
Anthracene	MWD	0.010	0/4	ND	ND	11,000	U.S. EPA (1993b) RfD	No
Atrazine-Desethyl	MWD	0.020	0/4	ND	ND	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG	No
Atrazine-Desisopropyl	MWD	0.020	0/4	ND	ND	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG	No
Azithromycin	OCWD	0.001-0.005	0/4	ND	ND	NA	NA	NA

TABLE 2 (cont). Statistical Summary of Sampling Data for Trace Organics in the Santa Ana River at the Imperial Highway and Comparison to Health Risk-Based DWELs

Compound	Lab	MRL (µg/L)	Freq. of Detect	Concentration (µg/L)			Source of DWEL	Max (or MRL) > DWEL? ^a
				Min. Detect	Max.	Health Risk-Based DWEL		
Benzo(a)pyrene	MWD	0.025	0/4	ND	ND	0.004	CA EPA (1997) PHG	Yes
Bisphenol A	MWD & OCWD	1.0	0/4	ND	ND	1,800	U.S. EPA (1993c) RfD; Snyder et al. (2008) ADI	No
Butylparaben	MWD	0.020	0/4	ND	ND	NA	NA	NA
Cyanazine	MWD	0.020	0/4	ND	ND	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG	No
Cyprazine	MWD	0.020	0/4	ND	ND	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG	No
o,p-DDD	MWD	0.020	0/4	ND	ND	0.15	U.S. EPA (1988b) cancer slope factor for p,p-DDD	No
Diethylstilbestrol	OCWD	0.010	0/4	ND	ND	NA	NA	NA
Epitestosterone	OCWD	0.010	0/4	ND	ND	NA	NA	NA
17a-Estradiol	OCWD	0.010	0/4	ND	ND	NA	NA	NA
17b-Estradiol	OCWD	0.010	0/4	ND	ND	1.8	Snyder et al. (2008) ADI	No
Estriol	OCWD	0.010	0/4	ND	ND	NA	NA	NA
Estrone	OCWD	0.010	0/4	ND	ND	0.46	Snyder et al. (2008) ADI	No
Ethylparaben	MWD	0.020	0/4	ND	ND	NA	NA	NA
Ethinylestradiol	MWD & OCWD	0.010	0/4	ND	ND	NA	NA	NA
Lindane	MWD	0.010	0/4	ND	ND	0.032	CA EPA (2005) PHG	No
Linuron	MWD	0.005	0/4	ND	ND	70	U.S. EPA (1990) RfD; Snyder et al. (2008) ADI	No
Methoxychlor	MWD	0.020	0/4	ND	ND	0.70	Snyder et al. (2008) ADI	No
Methylparaben	MWD	0.020	0/4	ND	ND	NA	NA	NA
4-n-Nonylphenol	MWD & OCWD	1.0	0/4	ND	ND	1,800	Snyder et al. (2008) ADI	No
Nonylphenol ethoxylates (total)	OCWD	10	0/4	ND	ND	NA	NA	NA
4-n- and 4-t-Octylphenol	MWD & OCWD	1.0	0/4	ND	ND	18	WRF-05-005 ADI (Draft value)	No
Penta-chlorophenol	OCWD	1.0	0/4	ND	ND	0.3	CA EPA (2009) PHG	Yes
4-Phenylphenol	OCWD	1.0	0/4	ND	ND	NA	NA	NA

TABLE 2 (cont). Statistical Summary of Sampling Data for Trace Organics in the Santa Ana River at the Imperial Highway and Comparison to Health Risk-Based DWELs

Compound	Lab	MRL (µg/L)	Freq. of Detect	Concentration (µg/L)			Source of DWEL	Max (or MRL) > DWEL? ^a
				Min. Detect	Max.	Health Risk-Based DWEL		
Progesterone	OCWD	0.010	0/4	ND	ND	NA	NA	NA
Propazine	MWD	0.020	0/4	ND	ND	3; 0.15	U.S. EPA MCL (U.S. EPA-OPPT, 2006); CA EPA (1999) PHG	No
Propylparaben	MWD	0.020	0/4	ND	ND	NA	NA	NA
Testosterone	OCWD	0.010	0/4	ND	ND	NA	NA	NA
Tetrabromo-bisphenol A	OCWD	1.0	0/4	ND	ND	NA	NA	NA
2,4,6-Trichloro-phenol	OCWD	1.0	0/4	ND	ND	3.2	U.S. EPA (1994) slope factor	No

ADI– Acceptable daily intake; DEET– N,N-Diethyl-meta-toluamide; MRL–Minimum Reporting Limit; MWD–Metropolitan Water District; OCWD–Orange County Water District; PHG– Public Health Goal; NA–Value not available; ND–Not detected; RfD– Reference dose; TCEP– tris(2-carboxyethyl)phosphine

a. For non-detected compounds, the MRL is compared to the health risk-based DWEL.

TABLE 3. Daily Water Consumption Required to Equal Health Risk-Based Screening Levels.

Required consumption rates are the amount of water with the reported concentration that a person would have to consume each day to ingest a dose equal to the health risk-based screening level. The source of the health risk-based DWEL is indicated in Table 1. The calculation method is summarized in Section 3.2.

Compound	Maximum Conc. (µg/L)	Health Risk-Based DWEL (µg/L)	Consumption Rate Required to Equal Health Risk-Based Screening Level (L/day)	Consumption Rate Required to Equal Health Risk-Based Screening Level (8-oz glasses/day)
Acetaminophen	0.430	12,000	56,000	240,000
Atrazine	0.0029	0.15	100	440
Caffeine	1.255	87,500	140,000	590,000
Carbamazepine	0.120	12	200	850
Ciprofloxacin	0.022	21	1,900	8,100
DEET	0.156	81	1,000	4,400
Diclofenac	0.015	2,300	310,000	1,300,000
Dilantin (Phenytoin)	0.143	6.7	94	400
Diuron	0.954	70	150	620
Gemfibrozil	0.023	46	4,000	17,000
Ibuprofen	0.309	34	220	930
Primidone	0.087	0.84	19	82
Simazine	0.060	4	130	560
Sulfamethoxazole	0.084	18,000	430,000	1,800,000
TCEP	0.217	4.2	39	160
Triclosan	0.009	2,600	580,000	2,400,000

ADI– acceptable daily intake; DEET– N,N-Diethyl-meta-toluamide; DWEL– drinking water equivalent level; NA–Value not available; TCEP– tris(2 carboxyethyl)phosphin

APPENDIX A

METHODS USED BY INTERTOX TO DERIVE ACCEPTABLE DAILY INTAKES (ADIS) FOR PHARMACEUTICALS AND PERSONAL CARE PRODUCTS, ENDOCRINE DISRUPTING COMPOUNDS, AND OTHER COMPOUNDS OF EMERGING INTEREST

As part of Water Research Foundation 3085/WRF-04-003, “Toxicological Relevance of Endocrine Disruptors and Pharmaceuticals in Drinking Water” study, the WRF-06-018 “Development and Application of Tools to Assess and Understand the Relative Risks of Drugs and Other Chemicals in Indirect Potable Reuse Water” study, and other work we have conducted, Intertox developed screening level ADIs for pharmaceuticals and personal care products (PPCPs), endocrine disrupting compounds (EDCs), and other compounds of emerging interest in drinking water or source water.

For compounds of interest, Intertox developed screening levels using several different methods that considered the potential for both noncancer and cancer effects, and selected the screening level corresponding to the lowest (most health protective) value as the ADI. For EDCs, ADIs also considered observations of adverse effects assumed to be mediated through alterations of the endocrine system.

Although no specific regulatory guidance exists prescribing how to assess human health risks of exposure to PPCPs or EDCs in drinking water, standard methods exist for determining exposure levels to environmental contaminants that are not likely to be associated with adverse health effects (WHO, 1994; U.S. EPA, 2000a; ATSDR, 2008). To develop ADIs, Intertox reviewed animal toxicology data and data from human clinical studies, for effects other than carcinogenicity, identified a point of departure upon which to base the ADI. This was typically the highest dose at which an effect was not seen (the no observed adverse effect level, or NOAEL) or the lowest dose at which an effect was seen (the lowest observed adverse effect level, or LOAEL). Below this dose, there is no evidence 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 was then divided by uncertainty factors (UFs) to derive an ADI considered protective to broader population groups, including sensitive populations, such as children or people with immune compromised systems, as follows:

$$\text{ADI } (\mu\text{g/kg-d}) = \frac{\text{NOAEL or LOAEL (mg/kg-d)}}{\text{UFs}} \times \frac{1000 \mu\text{g}}{\text{mg}}$$

UFs individually ranged in value from 3 to 10 with each factor representing a specific area of uncertainty in the available data. For example, if the point of departure is based on an animal study, a factor of 10 was applied to account for possible differences in responsiveness between animals and humans. A second factor of 10 was used to account for variation in susceptibility among humans. Other factors account for database deficiencies, such as when no or minimal information exists on reproductive effects or longer-term exposures. When high-quality toxicity data are available, combined UFs typically ranged from 1,000 to 10,000.

For compounds with evidence of carcinogenicity occurring through genotoxic mechanisms and available tumor incidence data, Intertox derived ADIs using an extrapolation model that assumes a linear relationship between tumor incidence and exposure at low doses (U. S. EPA, 2005; U.S. EPA, 2000b), and the generally accepted *de minimis* cancer risk of one additional cancer per one million exposed people. For compounds with evidence of carcinogenicity in animals occurring through genotoxic mechanisms but no available tumor incidence data, a “virtually safe dose” corresponding to a lifetime cancer risk of one in a million was estimated by dividing the chemical’s maximum tolerated dose from 90-day studies in rodents by 740,000 (Gaylor and Gold, 1998). The maximum tolerated dose is the highest dose predicted to produce minimal systemic toxicity over the course of a

study. For compounds with evidence of carcinogenicity in animals occurring through nongenotoxic mechanisms (e.g., assumed to be a threshold response), a virtually safe dose was estimated by dividing the chemical's maximum tolerated dose from 90-day studies in rodents by 7,000 (Gaylor and Gold, 1998).

In addition, Intertox developed ADIs for pharmaceuticals based on the lowest therapeutic dose divided by uncertainty factors to account for uncertainties in the data and to protect sensitive populations, as follows:

$$\text{ADI } (\mu\text{g/kg-d}) = \frac{\text{Lowest therapeutic dose } (\mu\text{g/kg-d})}{\text{UFs}}$$

To apply to the therapeutic dose, a combined uncertainty factor of 3,000 was used, to account for extrapolation from the lowest therapeutic dose to a NOAEL (10), variations in susceptibility between different members of the population (10), extrapolation from subchronic to chronic exposure durations (10), and gaps in the dataset (3).

For ciprofloxacin, Intertox developed an ADI based on the minimum inhibitory concentration (MIC) to 50% of strains of the most sensitive relevant human gastrointestinal flora, that is, the concentration of ciprofloxacin that will inhibit the visible growth of the microorganism by 50% (WHO, 1997; WHO, 2006). While this response is not explicitly toxic to human cells, it should be considered adverse because of the potential adverse impact on human gastrointestinal health.

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