THE CUMULATIVE RISK OF PHARMACEUTICALS IN NEW JERSEY SURFACE WATER TO HUMAN HEALTH

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ABSTRACT OF THE DISSERTATION

The Cumulative Risk of Pharmaceuticals in NJ Surface Water to Human Health

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Surface water in New Jersey is used to supply many residential drinking water facilities. In the surface water, there are contaminants from industrial and residential sources, one set of these contaminants being pharmaceuticals. This research looks at the concentrations of 18 pharmaceuticals in 30 locations in New Jersey, their acceptable daily exposures, and potential drug-drug interactions. The surface water sampling and analytical concentration determination was done by United States Geological survey (USGS) personnel according to their protocols and analyzed in a USGS laboratory. Acceptable daily exposures (ADE) for human health were set for each pharmaceutical in the study. Each pair of pharmaceuticals was researched for known adverse health interactions and their potential impact on human health was quantified. This interaction factor ranged from 0.4 times to 5.0 times the adverse effect, as measured in some cases by plasma levels in man. These factors were brought together using a cumulative hazard index risk assessment calculation to assess the overall risk of pharmaceuticals in surface water to human health. The cumulative risk was assessed

for each of the 30 sample locations, and none reached the level of human health concern. When including the potential from drug-drug interactions in the assessment, the risk did increase but not an appreciable amount. The Hazard Index (HI) for the sample locations ranged from <0.00001 to 0.01 with the drug-drug interaction (DDI) only adding less than 1.2 times increase to the overall risk. When the simulation of these mixtures was extended to an extreme for drug-drug interactions, 7 times a noticeable increase in the calculated risk was seen, but in no cases did the risk in any of the sample locations reach a level of concern.

Acknowledgement and Dedication

This work is dedicated to my wife Janis and my kids Allison and Timothy who tolerated the years of late nights and missed events.

I would also like to thank my committee chair Dr. Mark Robson and committee members Dr. Edward Sargent, Dr. Jun-Yan Hong, and Dr. George DiFerdinando for support and guidance. I would like to thank the USGS-NJ Water Science Center and Water Quality Assessment Studies Chief Jeff Fischer for make the stream sampling data available. My thanks also go out to Dr. David Dolan, of Amgen, for reviewing my Excel® spreadsheet calculations and Kathy Longo for editorial review and comments.

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Introduction

Our health is something we often take for granted. Even as we eat well and exercise, we are exposed to chemicals in all aspects of our daily lives. The risk from these many chemicals coming from many routes all add up over time. We breathe and there are particulates and volatiles in air from engine exhaust and solvents. We eat and preservatives, antibiotics, and pesticides are in our food. We drink and we do not think about what is there as we get it from a bottle, tap from a treated source, or an isolated well, all that we presume are clean. The source water for what we drink has many contaminants which it gained after passing through sewage treatment plants before being recycled back into the environment. In the surface water, there is run-off from agriculture and farm animals, as well as industrial waste and bi-products of our industrialized society.

All of the quantities measured in recent history are small. The Clean Water Act has helped remove the immediate acute hazards. More recently, people realize that we drink small amounts of many chemicals every day. This chronic exposure has caused concern. One set of these contaminants in our water is pharmaceuticals. In addition to their presence in our water sources, we see them on a daily basis in print, on-line, and on television the many benefits and all the very many possible adverse effects of these pharmaceuticals. The question is: do they present a risk to our health?

In exploring this question, the focus is on New Jersey surface water as it is one of the sources of drinking water in the state (American Water 2011). Pharmaceuticals are

not the only contaminants in NJ surface waters. The contaminants in addition to pharmaceuticals include fecal waste products, pesticides, detergents, flame retardants, and other anthropogenic as well as natural chemicals (Richardson 2009, Barber et al. 2005, Kolpin et al. 2002, Halling-Sørensen et al. 1998, Heberer 2002). The question being researched here is: what is the human health risk from the pharmaceuticals occurring in NJ surface water?

Many of these contaminants enter surface water via sewage treatment plants (STP) including pharmaceuticals which enter after patients use them and then excrete the waste. Most human fecal waste is treated in STPs before being discharged to surface water, but municipal STPs are designed to remove only biological contaminants rather than pharmaceuticals and other chemicals. The discharge of these pollutants impacts the water quality downstream at drinking water intakes (Waiser, Tumber & Holm 2011, WHO 2011). These pharmaceuticals that contaminate water sources come under different acronyms such as Pharmaceuticals in the Environment (PIE), Pharmaceuticals and Personal Care Products (PPCP), etc. and have come under increased regulatory and public attention (Kolpin et al. 2002, Williams 2005, Carlsson et al. 2006, Fick et al. 2009, Larsson, de Pedro & Paxeus 2007, Daughton, Jones-Lepp 2001, Daughton, Ruhoy 2009, USGAO 2011, Jones, Graves 2010, Post 2010).

Most risk assessments of pharmaceuticals have focused primarily on single contaminants found in the environment (Williams 2005, Webb 2001, Webb et al. 2003). These assessments have examined the risk to human health posed by individual

contaminants (Schwab et al. 2005, Blanset 2006, Cunningham, Binks & Olson 2009, Cunningham et al. 2010, Bound, Voulvoulis 2004, USEPA 2000b, Bercu et al. 2008, Blanset, Zhang & Robson 2007). Unfortunately, contaminants do not occur in isolation. Rather, our society uses and disposes of a wide variety of chemicals on a daily basis. This research is an assessment of the risk to human health from a set of mixtures of pharmaceuticals in surface water. Some assessments of pre-set mixtures of pharmaceuticals and whole effluents have been conducts for aquatic species but only one of surface water mixtures of pharmaceuticals looking at human health (Ferrari et al. 2003, Faust et al. 2003, Cleuvers 2003, Sanderson et al. 2004, Arrhenius et al. 2004, Crane, Watts & Boucard 2006, Johnson et al. 2007, Sun, Zha & Wang 2009, Pomati et al. 2008, Pomati et al. 2007, de Jongh et al. 2012). There are examples in the environmental health literature for mixtures of other chemicals including pesticides (WHO 2011, Webb 2001, USEPA 2003, Price, Chaisson 2005, Price, Hollnagel & Zabik 2009, Bogen et al. 2009). The United States Environmental Protection Agency (USEPA or EPA) has conducted cumulative risk assessments at Super Fund hazardous waste sites. Articles in the media and presentations by regulators show that this is a concern of the public and regulators, and has been commented on by the World Health Organization as an area of needed research (WHO 2011, Post 2010, Cunningham, Binks & Olson 2009, Brooks, Huggett & Boxall 2009, Lissemore et al. 2006, Renner 2009).

This research has four principal components: determining the environmental concentrations of exposure, the determination of acceptable daily exposure (ADE) for each pharmaceutical being analyzed, and determining the drug-drug interaction (DDI)

between individual pharmaceuticals, all which will be included in the risk equations used in this assessment. These components are brought together in the fourth part to calculate the hazard index values with and without interactions. The summary of these hazard index values becomes a cumulative risk assessment of the individual mixtures.

To keep the scope of this research to a manageable proportion, this work is limited to samples of New Jersey (NJ) surface water and the components assessed in a United States Geological Survey (USGS) NJ-wide sampling survey in 2001. The watersheds covered by the sampling sites do extend beyond the state boundaries into New York and Pennsylvania. Companies supplying water to NJ residential customers use surface water, ground water, or a mixture of both (American Water 2011). Based on this, surface waters can serve as a realistic measure of human exposure for a large part of publicly supplied drinking water in NJ. Ground water concentrations would be needed for a more complete picture of exposures from drinking water, but they are not going to be assessed in this research. The surface water samples used were collected and analyzed by the USGS (Barnes et al. 2008, Fischer 2011). The scientific literature was reviewed to determine acceptable daily exposure (ADE) values for individual pharmaceuticals, as well as the degree of interaction between the pharmaceuticals that were assessed.

The surface water samples were collected by the USGS in the fall during low-flow river conditions. These are grab samples from one point in time and location. Higher concentrations could possibly be measured in the environment, but these incidences

would be limited in their duration and therefore have limited exposure time and impact. The concentrations measured are unlikely to exist for much of the year as rain events and higher seasonal flows will dilute the concentrations detected. The USGS did collect other samples at various times during the year at several of the sampling locations. The seasonal variation that could be expected at individual sites was not part of this work. The acceptable daily exposure values are for the lowest animal toxicity or human health effect endpoints. For the antibiotics on the list, antibiotic resistance was not addressed; neither was any carcinogenic potential the pharmaceuticals may possess. The pharmaceutical components were the only components of the mixtures analyzed; other chemicals were present and have the potential to add to the overall risk but are not addressed in this work. It has been noted by several authors that mixture effects observed at therapeutic doses do not translate into mixture effects at levels well below the therapeutic doses (Kortenkamp, Backhaus & Faust 2009). The assumption for this risk assessment is that the health effects can occur even at low-level exposures.

This risk assessment is designed as a screening tool with several assumptions which potentially overemphasize the risk potential to human health. The underlying EPA risk calculations have assumptions that are conservative. The ADE calculations used in this research assume a standard weight for adults to be 70 kilograms per person and they consume 2 liters of water daily from the water sources in question (USEPA 1997). Neither value is completely correct for most people in the study area, but they do provide standardized values around which risk assessment screenings such as this can be framed and compared to other analyses. With an understanding of the potential

risks associated with this research, further investigations will lead to a more complete understanding of the risk to human health from mixtures of pharmaceuticals in surface water.

Hypothesis

The research hypothesis for this dissertation is that mixtures of pharmaceuticals (drugs) found in NJ surface water sources will not impact human health either as simple mixtures or including drug-drug interactions (DDI). This could be possible because their simultaneous presence in the mixtures may not be a significant factor in a cumulative human health risk assessment.

Research Questions

There are three areas of focus in this dissertation:

1) Which cumulative risk assessment calculation method is the most relevant to human health when examining a mixture of pharmaceuticals in surface waters?

2) What is the cumulative risk to human health from a mixture of pharmaceuticals found in New Jersey surface waters?

3) Will drug-drug interactions impact a cumulative risk assessment calculation enough to require risk assessment calculations and management practices to account for this additional interaction?

Material and Methods

Concentration in Surface Water

The concentrations of pharmaceuticals in water sources have been measured for a number of years at sites around the world (Kolpin et al. 2002, Halling-Sørensen et al. 1998, Heberer 2002, Kümmerer 2001, Zuccato et al. 2006, Zuccato et al. 2006, Kim et al. 2007, Stasinakis et al. 2008, Sui et al. , Schultz et al. 2010, Bound, Voulvoulis 2006, Kim, Carlson 2006, Kinney et al. 2006, Liebig, Moltmann & Knacker 2006, MacLeod, Wong). State environmental agencies and international government agencies have also collected data on pharmaceuticals in their local waters. Universities, both domestic and international, have collected and analyzed water sources from Canadian, European, and Asian countries (WHO 2011, Williams 2005, Fick et al. 2009, Larsson, de Pedro & Paxeus 2007, Liebig, Moltmann & Knacker 2006, Straub 2002). These water sources all have some contamination from human activities. These contaminants include industrial contaminants, human waste products, as well as pharmaceutical contaminants (Fick et al. 2009, Larsson, de Pedro & Paxeus 2007). Based on measured concentrations, various authors have modeled or created models to predict in-stream concentrations because sampling is an expensive and labor-intensive task (Webb 2001, Webb et al. 2003, Schwab et al. 2005, Bound, Voulvoulis 2006, Liebig, Moltmann & Knacker 2006, Liebig, Moltmann & Knacker 2006, Altenburger, Greco 2009, Fick et al. 2010, Simeonov, Hassanien & Arnot 2009, Anderson et al. 2003).

The USGS has published data on the concentrations of pharmaceuticals and other contaminants from locations in 30 states and 139 streams including NJ sources

(Kolpin et al. 2002). The USGS has other publications quantifying pharmaceuticals in other United States water sources. The 2002 Kolpin paper is only one of the first looking at United States surface water. The USGS website has publications and data on other environmental compartments where pharmaceuticals and other contaminants are found and could be part of a fuller exposure scenario for man (Barnes et al. 2008, Focazio et al. 2008). These other areas, such as ground water, sediment, sewage sludge, and septic systems are not covered in this work. The exposure data available for NJ in a large enough data set was only from surface water sources (Fischer 2011).

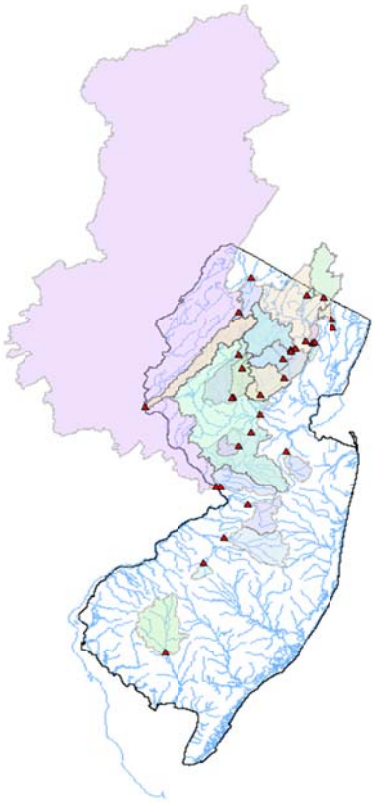
Not including these other sources also simplifies the exposure scenario in the model used. If any of these compartments do contribute to human exposure, part of the contribution would be via surface water. It is understood that ground water sources, which are also used for drinking water, will not be accounted for in this risk assessment. This is a limitation of this analysis. Environmental Agencies from other states have also collected data on the concentrations of pharmaceuticals in their local surface waters. New Jersey has several state-specific studies that collected data on concentrations, of contaminants (Kolpin et al. 2002, Blanset 2006, Alvarez et al. 2005, Post et al. 2009). Unpublished contaminant concentration data from the USGS was used for this research. In this NJ analysis, 107 chemicals were analyzed from 30 sample sites and the concentrations of chemicals measured (Fischer 2011).

The data available from the USGS for NJ was surface water concentrations (Fischer 2011). Drinking water measurements for NJ residents would provide greater accuracy to the risk assessment by virtue of being a better measure of what people

drink but this was not available (Snyder et al. 2008). Drinking water treatment facilities are not designed specifically to remove pharmaceuticals but to remove particulates, biologicals, and items that would reduce the palatability of the water supplied to customers (Kim et al. 2007, Focazio et al. 2008, Black & Veatch 2007a, Stackelberg et al. 2004). In NJ, the treatment of ground water supplied as drinking water has also been examined (Stackelberg et al. 2004, Stackelberg et al. 2007, Black & Veatch 2007b). In the case of water treatment technology in general, the removal of organic chemicals through typical techniques of coagulation and filtration is modest at best. The studies of NJ waters do not have specific removal rates by chemical, but generalize that up to 50% of some organic chemicals could be removed by existing drinking water treatment technology (Black & Veatch 2007a). In research supported by the American Water Works Association Research Foundation (AWWARF) removal of some pharmaceuticals was measured. In the AWWRF work, acetaminophen removal was >80% in drinking water treatment facilities, but sulfamethoxazole removal ranged from <20% removal to >80% removal (Snyder et al. 2007). This variability in removal percentages complicates the calculation of a risk assessment. The removal percentage is based on multiple factors that would have to be matched to facilities in NJ to provide relative and meaningful results. As a screening risk assessment, this was not done. In locations where the risk approaches a human health concern, removal efficiencies and drinking water concentration measurements should be considered to refine the risk of pharmaceuticals and other chemicals to human health.

In the data used for this analysis, the USGS analyzed surface water sources for a variety of chemicals associated with human presence. These included fragrances, pesticides, flame retardants, combustion products and byproducts, steroids, detergents, and prescription and OTC pharmaceuticals. There are many chemicals that were not analyzed for in this data set, such as hormones and other estrogenic compounds that have been shown to exist in surface waters else were. The data used here was collected in 2001 from surface waters that are sources for drinking water supplies and have a sewage treatment plant upstream of a drinking water supply intake. Figure 1 below illustrates geographically where the samples were taken and which river watershed areas the samples represent in NJ and the surrounding area (Fischer 2011). In Figure 1, the areas of NJ with little coverage by surface water supply location, namely much of South Jersey, is supplied primarily by ground water wells and were not sampled in this data set. Of the 107 chemicals analyzed, 55 chemicals were detected while 52 chemicals were not detected. The list of chemicals that were analyzed by the USGS in this sample set is presented in Appendix 1.

Figure 1 NJ Sampling Locations and Associated Water Sheds



The water samples for this study were taken in the fall during low-flow conditions, sampled according to USGS protocol, and quantified by USGS analytical methods appropriate to the chemical being analyzed by the USGS laboratories (Fischer 2011). These are one-point-in-time grab samples. Higher seasonal concentrations are possible, but they would be limited in duration and therefore have limited impact on the overall exposure. The concentrations measured are unlikely to exist for much of the year as rain events and higher seasonal flows will dilute the concentrations detected. The USGS did collect other samples at various times during the year at several of the sampling locations. That data was not available for this study. The seasonal variation that could be expected at individual sites was not part of this work, but would be

expected to be lower due to dilution. Several publications have used data collected in NJ and looked primarily at occurrence of pharmaceuticals and other anthropogenic chemicals but not the human health risk (Kolpin et al. 2002, Blanset 2006, Alvarez et al. 2005, Post et al. 2009).

The source and route of the pharmaceuticals in the USGS data have been well described by other authors. The pharmaceuticals come primarily from patient use and in some cases only metabolites remain before entering the environment via STPs. Pharmaceuticals can enter surface water after veterinary use in herd animals from farms, aquaculture, improper disposal via the sewage systems, and manufacturing discharges. The data available for this research is from surface water with no regard to the original source. This creates an inclusive sample capturing many, if not all, of the potential sources within New Jersey. The sample locations were selected by the USGS with the expectation that some would be contaminated and also upstream of drinking water intakes. The sources of the individual pharmaceutical in individual samples were not examined in this research. Not all of the sources listed above are relevant to the New Jersey surface water sampled in this analysis.

Acceptable Daily Exposures

To calculate the risk of a chemical, a no-effect concentration needs to be compared to the environmental concentration. In the case of this research, human and animal data will be used to set no-effect-concentrations for individual pharmaceuticals or their metabolites that can be consumed daily with no expected health consequences. This is referred to as an acceptable daily exposures (ADE) or acceptable daily intakes

(ADI), the term ADE will be used primarily in the work (Webb 2001, Webb et al. 2003, Dolan et al. 2005, Naumann, Sargent 1997, Schulman et al. 2002, Kroes, Kleiner & Renwick 2005, Renwick 2005, Layton et al. 1987, ISPE 2009). With pharmaceuticals, large data sets of human data are typically available. This allows for a good estimate of an ADE for many pharmaceuticals. The intent of an ADE is to establish an estimated concentration that would not be expected to cause harm even from chronic (long-term) exposure. Human health is the focus in this dissertation; environmental toxicity endpoints in species such as lethality or adverse effects in fish, algae, or other aquatic and terrestrial wildlife are not examined in this research. An ADE is calculated by establishing a value (a low/no-effect value) and divided by a sum of uncertainty factors. The common calculation is presented in Equation 1.

Equation: 1

$$ADI = \frac{POD}{UFtotal}$$

Point of Departure

In establishing a no-effect concentration, the available literature was reviewed for each of the pharmaceuticals in this study. No toxicity testing was performed for this research to establish these data points. The lowest relevant human health end-point was selected as the point of departure (POD) in these calculations when possible. When human data was not available, animal data from pharmaceutical filing data and the

general literature was used (USEPA 2000b, Bull et al. 2011, USEPA 2000a, USEPA 2007). The specific data are discussed for individual pharmaceuticals in Appendix 2.

Uncertainty Factors

To extrapolate from the available data (POD) to a human chronic equivalent uncertainty factors (UF) are used. The use of uncertainty factors is a well-established method of calculating predicted-no-effect levels from biological end-points no-observed-effect concentrations. The EPA has published how to use uncertainty factors for chemical exposure assessments, as have other organizations for purposes of setting occupational exposure limits during chemical manufacturing such as the American Conference of Governmental Industrial Hygienists (ACGIH) (USEPA 2000b, USEPA 2000a, USEPA 2007). Others have done so for pharmaceuticals to provide employee protection limits (Naumann, Sargent 1997, Naumann et al. 2009, Naumann, Weideman 1995). The no-observed-effects levels (NOELs) with the associated uncertainty factors will be referred to as acceptable daily exposures (ADE) in this research but have often been referred to as ADIs in other risk assessment literature (Webb et al. 2003, Dolan et al. 2005, Schulman et al. 2002, ISPE 2009).

The five uncertainty factors typically discussed in the relevant literature are presented in Table 1, along with the definitions and ranges; these are the USEPA definitions (USEPA 2000a). The list is typical, including a factor between a no-observed-effect level and a lowest-observed-effect level, extrapolating from animal data to human data, variability within individuals, acute data versus long-term (chronic) data, and data quality. The extrapolation between LOEL values to a NOEL value depends on

the data that is available. If dosing data are available the effects at reduced doses can be compared to the change in dose (1.5x, 2x, 3x, or 5x) which are common steps in between doses. These steps can be used as the uncertainty between a LOEL and a NOEL if the effects warrant it. When using animal data to start from extrapolating to human data is often a 3 or by allometric scaling which depends on the species. The rat to human scaling factor is 4, while the monkey to human scaling factor is 2. There are other scaling factors that are used as animal species to human uncertainty factors (Price, Hollnagel & Zabik 2009).

To extrapolate from short term to long term studies a similar range of 1-10 is used. The shorter the duration of the point of departure study, the larger the UF. If multiple long term animal studies (90 days or more) are available in multiple species a UF of 1-3 may be appropriate as an example. The uncertainty for inter-individual variability addresses the range of doses that different individuals exhibit the same effect. If little or no human data are available, an UF of 10 is often used for inter-individual variability. When less variation exists a 3-5 is used. The last UF typically used is a data quality or miscellaneous uncertainty factor. This allows for a limited data set, were only a few animal or human data points are available to the author. This also can be used to account for old or poorly summarized data with uncertain relativity, to poor described or uncertain study design. Another example is when a chemical family with known reproductive hazards is being assessed but no reproductive data is available for the specific chemical being assessed. This is a case where additional uncertainty would be added to an ADE assessment.

The pharmaceuticals that were identified in the USGS survey and used in this research are a mixture of antibiotics, analgesics, over-the-counter medicines and metabolites of various drugs, among other materials. ADEs were established for each of the pharmaceuticals in this research (Dolan et al. 2005, Naumann et al. 2009, Naumann, Weideman 1995).

Table 1: Uncertainty Factors

Extrapolation Uncertainties		**Considerations for uncertainty factor selection**
LOAEL to NOAEL	UF_L	• 10 when a NOAEL is not available • 3 when the LOAEL is a therapeutic response and is operative only in a disease state • 1 when the LOEL is associated with a homeostatic response or an equivocal effect
Duration of Exposure	UF_D	• 10 when no chronic data available • 3 no chronic data are available, but pharmacokinetic or pharmacodynamic analyses suggest little persistence of either the compound or the effect. • 1 when no chronic data available, but pharmacokinetic and pharmacodynamic analysis suggest little persistence (compound and effect). • 1 when adequate chronic data are available.
Interspecies	UF_A	• 10 is recommended when no human data are available • 3 is recommended when ADME data are similar for multiple species, including humans or non-human primates. • 1 is used when derivation is based on human data.
Intra-individual susceptibility	UF_H	• 10 as a default, if NOAEL is from adult population and/or animal study, and no multigenerational study in any species. • 3 when the effect is therapeutic and there is little difference between the median effective dose and the minimally effective dose (e.g., the ratio of a quantal ED50 to ED05 is less than 3). • 3 when using an adjusted LOEL, NOEL or therapeutic dose specific to a subpopulation generally thought to be sensitive (e.g., i.e., the elderly, children, etc.). • 1 is recommended when using a LOEL or NOEL for a specifically-identified sensitive human population
Data Quality	UF_M	• Factors of 10, 3 or 1, or a number smaller than 1, to reflect professional judgment on the quality of data: • Critical studies used small number of animals or groups (UF >1). • Results are poorly described or analyzed (UF >1). • Require route-to-route extrapolation to be relevant to exposure condition (UF < or >one depending on the relevance) • Important specialized studies not conducted (e.g., reproductive toxicology, teratogenicity, carcinogenicity in compounds • NOEL is the highest dose tested (possibly a UF <1)

The ADEs established for this dissertation are detailed in Appendix 2 and summarized in Table 2. The POD and the uncertainty factors (UF) used to calculate the

ADEs are described in detail, along with associated toxicology data establishing the POD relative to the other therapeutic or toxic effects for each pharmaceutical in this research. In Table 2 below, the substances are listed in alphabetical order next to their individual points of departure values. Also listed are the individual uncertainty factors used for each substance. The five UFs are listed in order presented in Table 1, with the individual values explained in Appendix 2. The ADE to be used for this research is under the column titled "Roden ADE", which is the POD value (mg/kg/day) divided by the five uncertainty factors multiplied together (UF_L * UF_A * UF_H * UF_D * UF_M). The Roden ADE values have been converted to (micro-grams) μg/kg/day for comparison to the surface water concentrations. Other researchers have published human health ADEs for the substances in Table 2, and these are listed under "ADE from Literature" (Schwab et al. 2005, Cunningham et al. 2010, Snyder et al. 2008, Kumar, Xagoraraki 2010, Renwick, Lazarus 1998, Dourson, Felter & Robinson 1996). Why there are differences between the values in the Roden ADE column and the values from literature vary. In the case of acetaminophen, a lower therapeutic dose was selected. Schwab et.al., used 650 mg, the lowest therapeutic dose, as a standalone dose, while the Roden ADE is based on one-half that therapeutic value, 325 mg, the lowest therapeutic dose used in a combination pharmaceutical (Schwab et al. 2005). The differences between Roden ADEs and others in cases such as Ciprofloxacin and Fluoxetine are rounding differences. There are no differences between values for diltiazem and codeine, for example.

Table 2: Acceptable Daily Exposures

Substance	**POD** (mg/kg/day)	**UF_L**	**UF_A**	**UF_H**	**UF_D**	**UF_M**	**Roden ADE** (µg/kg/day)	**ADEs from Literature**			
								A	**B**	**C**	**D**
Acetaminophen	4.6	3	1	3	1	1	**516**	340			
Caffeine	0.03	1	1	1	1	3	**10**				
Carbamazepine	3	10	1	3	3	3	**11**		15.9	10.6	100
Ciprofloxacin	N/A	-	-	-	-	-	**2**	1.6			
Codeine	0.21	10	1	1	10	1	**2**	2			
Cotinine: metabolite of nicotine	0.5	3	1	3	10	1	**6**				
Dehydronefedipine: metabolite of nifedipine	100	1	10	10	10	1	**100**	100			
Diltiazem	0.43	3	1	1	10	1	**14**	14			
1,7-Dimethylxanthine: metabolite of caffeine	0.03	1	1	1	1	3	**10**				
Diphenhydramine	0.36	3	1	10	1	1	**12**				
Enroflaxacin	N/A	-	-	-	-	-	**2**				
Erythromycin-H_2O: metabolite of erythromycin	3.6	3	1	3	10	1	**40**	40			
Fluoxetine	0.29	10	1	1	10	1	**3**	2.9			
Ibuprofen	2.9	3	1	3	1	3	**107**	110			
Minocycline	0.64	3	1	3	1	5	**14**				
Sulfamethizole	N/A	-	-	-	-	-	**10**				
Sulfamethoxazole	2.2	1	3	3	1	10	**24**	130			
Trimethoprim	N/A	-	-	-	-	-	**4**	4.2		190	

Table summary of Appendix 2 data A: (Schwab et al. 2005), B: (Cunningham et al. 2010), C: (Snyder et al. 2008), D: (Kumar, Xagoraraki 2010)

Interactions

A key part of this analysis is the determination and use of interaction values that are incorporated into the EPA cumulative risk assessment calculation presented later in this paper. Interactions are a well-known factor in the medical community when prescribing drugs. Drugs interact with other prescription drugs, OTC medicines and some foods and drinks (caffeine, grapefruit juice). Chemicals in the general environment from solvents to pesticides can, on occasion, interact as well. This is the reason why risk assessors, when analyzing the entire exposure scenario of public health, look at all exposures from all routes and their cumulative and interactive effects. The problem is the more vectors of exposure and the more layers of effect from multiple sources, the more difficult it is to accurately assess the impact and predict an outcome (USEPA 2007).

To screen for those documented drug-drug interactions (DDI), the drug interaction database at www.drugs.com was used (Drug.com 2011). This database includes interactions that are included in drug filings with agencies such as the USFDA. This database is not all inclusive, as it may not be up to date and all interactions may not have been reported to either the responsible company or an agency monitoring this type of data. Interactions described in the database and in the literature are described as one-way or two-way. When two drugs are present in the body simultaneously, drug A can affect drug B; drug B may or may not affect drug A. Based on the literature reviewed and the DDI database, most interactions are one-way.

In this research there are 18 pharmaceuticals, four being metabolites of parent compounds being studied. The drug combinations were investigated in the interaction database, but several were not present as they are no longer or never were prescribed to man, such as veterinary antibiotics (Drug.com 2011). The metabolites of these pharmaceuticals are not in the database; only the parent compounds. The parent materials for 1, 7-dimethylxanthine is caffeine, for example, and caffeine and the metabolite were measured in some to the NJ surface water samples (Fischer 2011). Caffeine was researched here to look for known interactions with the other components of the surface water samples. Since many metabolites are less pharmacologically active than their parent compound, this will overestimate the interaction and increase the calculated risk in this screening analysis for these few cases. The metabolites are assumed to be as active as the parent for purposed of this risk assessment as the activity difference between the parent and metabolites are not well documented. A matrix of the potential 153 one-way interactions or potentially 306 two-way reactions is presented in Figure 2.

In Figure 2, the substances in this research are listed to the left of the matrix and across the top. The grayed boxes running diagonally across the matrix are where the same substance intersects. No interaction occurs here. The rest of the boxes represent the 306 potential interactions. The www.drug.com interaction database categorizes interactions into the three qualitative categories of “Major”, “Moderate”, and “Minor”. These are not quantifiable for purposes of calculating a risk assessment. Most interactions are described as one-way. This corresponds to what has been noted by the

EPA in their guidance on interactions (USEPA 2000b, USEPA 2007, Drug.com 2011, Teuschler 2007).

Only two of the interactions are considered major by the drug website interaction-database and highlighted in red on Figure 2. The major interactions are those with more serious potentially adverse effects. Nineteen interactions are considered moderate, with less severe interactions and have been labeled in orange on the matrix in Figure 2. Four are marked in yellow in Figure 2 are minor interactions. Typically minor interactions are a category of "could potentially have an effect", but reported clinical signs are sporadic in occurrence or have a potential effect because of similar mechanisms of action.

Figure 2 Interaction Matrix (One-Way)

	Acetaminophen	Caffeine	Carbamazepine	Ciprofloxacin	Codeine	Cotinine	Dehydronifedipine	Diltiazem	1,7-Dimethylxanthine	Diphenhydramine	Enrofloxacin	Erythromycin–H_2O	Fluoxetine	Ibuprofen	Minocycline	Sulfamethizole	Sulfamethoxazole	Trimethoprim
Acetaminophen	---																	
Caffeine		---																
Carbamazepine	Mod		---															
Ciprofloxacin		Mod		---														
Codeine			Mod		---													
Cotinine		Minor				---												
Dehydronifedipine			Mod		Mod		---											
Diltiazem			Mod		Mod		Mod	---										
1,7-Dimethylxanthine									---									
Diphenhydramine			Mod		Mod					---								
Enrofloxacin											---							
Erythromycin–H_2O			**Major**	Mod			Mod	**Major**				---						
Fluoxetine			Mod		Mod					Mod		Mod	---					
Ibuprofen							Mod	Mod					Mod	---				
Minocycline															---			
Sulfamethizole																---		
Sulfamethoxazole				Minor								Minor					---	
Trimethoprim																	Minor	---

The interaction equation assumes that only two components are needed to be present to create an interaction. Based on the EPA research, only in rare cases are three components needed to cause an interactive effect (USEPA 2000b). The documented health effects caused by the interactions are typically increases or decreases in known primary or secondary pharmacological effects. The increases or decreases can be caused by changes to the normal absorption, distribution, metabolism, or elimination of a pharmaceutical (Delafuente 2003). These mechanisms are changed impacting the expected effects of the drug. A delayed elimination or increased absorption can lead to an increased bodily exposure to a pharmaceutical. This would be equivalent to taking an increased dose. Interference can also reduce the efficacy of a drug. A given dosage of pain medication, for example, if interfered with would not take away the amount of pain expected. As in the case of codeine and fluoxetine, codeine conversion to morphine is regulated by CYP450-2D6. Fluoxetine and methadone can inhibit the conversion and reduce the analgesic effects of morphine (Ferrari et al. 2004). In the case of metabolism pathways, the enzymes CYP450-3A4, 2D6 and 1A2 commonly regulate drug metabolism. The available mechanisms of interactions have been summarized in Appendix 3.

There are other drug mechanism pathways such as calcium channel blockers and serotonin reuptake inhibitors (SRI) that can be impacted by interaction. All of the interactive effects that have been observed have not had their mechanisms agreed upon or proven. Changes in the metabolism of a pharmaceutical by increasing the rate of or slowing the rate of metabolism can impact the patient's internal exposure to a

drug or any other toxin (Delafuente 2003, Shapiro, Shear 2001, Virani et al. 1997). As individuals take greater quantities of drugs, more interactions can be expected, as in the case with the elderly or at times the chronically ill (Delafuente 2003).

Range of Interaction Values

In the EPA calculation for cumulative risk with interactions, the factor for quantifying interactions has a range of values from 0.2 to 5. To determine this, the EPA tested a series of 27 chemicals for all possible pairs in equivalent volumes and 53 pairs of equatoxic amounts. The difference observed between the predicted LD_{50} values when added together and the test results of the mixtures resulted in the interaction values from 0.2-5 for factor M (USEPA 2000b, USEPA 2003). This was considered the default range where most values fell. Based on the literature and investigations by the EPA higher values for M are possible. The EPA referenced Mehendale in its risk assessment guidance documents and briefly described a case where the M factor is much higher than 5. No cases were presented that were below 0.2 (Mehendale 1989, Mehendale 1994).

In the EPA guidelines, there is reference to the case of carbon tetrachloride where its 48 hour LD_{50} mL/kg was compared in rats pre-dosed with chlordecone and rats not pre-dosed with chlordecone. In male rats pre-dosed with chlordecone, the rat 48-hour LD_{50} mL/kg for carbon tetrachloride was 67 times higher than that of the control, which was not pre-treated with chlordecone. In female rats, the difference was 26 times. Pre-dosing with phenobarbital, a similarly structured chemical, before carbon tetrachloride exposure only resulted in a 1.6 times increase in LD_{50}. When substituting

another halomethane, bromotrichloromethane, resulted in an increase in LD_{50} of 4.5 times. When tested in mice, the original chlordecone and carbon tetrachloride combination only induced a 4.2 times increase in LD_{50} toxicity (Mehendale 1989, Mehendale 1994).

In the case above, Mehendale shows that two different effects occurring together induce this highly increased interaction of 67 in male rats. The combination of liver toxicity and the shutting down of the cellular repair mechanism in the liver in rats are causes for these effects (Mehendale 1994). The double pathways of interference with a specific chemical combination in one species and sex need to be in place to create an interaction factor greater than 5 according to Mehendale's work.

The United States Food and Drug Agency (USFDA or FDA) has set up draft guidelines for running interaction studies between pharmaceuticals, and authors have examined in-vitro and in-vivo comparisons based on enzyme induction potentials and clinical pharmacokinetics (USFDA 2012, Mao et al. 2012, Mao et al. 2011). This research was done to model the potential interactions so investigators can anticipate and study potential problems in the clinic while conducting clinical trials for patient safety (Ohno, Hisaka & Suzuki 2007, Ohno et al. 2008, Hisaka et al. 2010). In the 2012 draft, the FDA categorizes interactions as no interaction, weak, moderate, and strong interactions as described in Table 3 below under the Mao column (Mao et al. 2012, Mao et al. 2011).

The primary difference between the FDA and EPA ranges is that the FDA range is based on measured internal exposure as measured by AUC (area under the curve),

whereas the EPA range is based on observed effect such as LD_{50} (Lethal Dose of a chemical where 50% of animals, rats typically, die). This may also be because of the different chemical families examined by the two agencies, known biologically as active pharmaceuticals versus all chemicals except pharmaceuticals. General chemicals often do not have detailed animal internal exposure data, AUC, while pharmaceuticals do. Interactions measurements are purposely determined between two pharmaceuticals, when the two pharmaceuticals are expected to be co-prescribed with or expected to be present together because of age or other existing disease state. Regardless, interaction levels above a factor of 5 are possible and considered in this analysis. The EPA analysis considered the number of interactions "M" occurring at values greater than 5 to be infrequent.

The interactions summarized by Mao, who analyzed only drug-drug interactions observed in the clinic, are compared to modeling attempts of CYP450 3A4 mediated interactions, which is more relevant to this research. The range of the interaction for the drug summarized by Mao is from 0.82 to a 16 times increase in the AUC of the drugs measured. The highest interaction was observed between ketoconazole, a triazole anti-fungal, and midazolam, a benzodiazepine, at the high end of normal therapeutic doses and showed dose-dependent correlations. In this analysis, these high interactions averaged a 9.6 times increase in AUC, with a median value of 7.7 across seven direct comparisons. The next highest group in Mao's research is the interaction between voriconazole, another triazole antifungal, and midazolam with average and median increases of 6.7 times voriconazole AUC (Mao et al. 2012, Mao et al. 2011).

In Table 3 below, the FDA categories are listed in the left-hand column followed by the group AUC range as set by the FDA draft guidance. A summary of Mao's data is in the next set of columns. For example, the average of all of Mao's interactions measuring greater than 5 is 7.12 and the median is 6.94. The average interaction values grouped by AUC values available by this research are listed in the columns under Roden as a comparison to Mao. The interactions are CYP450 3A4 and other enzyme-mediated drugs, so it is reasonable to compare the two sets and set the value of 7 as a reasonable worst-case scenario in addition to the EPA upper range of 5 for interactions (USEPA 2000b, USEPA 2003, Mao et al. 2012, Mao et al. 2011). With the exception of the FDAs category "Strong" in Table 3, where there is only one point of data in this research data set, the two groups, Roden and Mao, are comparable and reinforce the ranges used for the interaction factor "M" in the cumulative risk determination as presented later in Calculation 6.

Table 3 Interaction Range/Group Estimate

FDA	AUC	Mao				Roden		
Multiplier	Range	#	Average	Median		#	Average	Median
None	<1.25	6	1.03	1.03		7	0.93	1.1
Weak	≥1.25 <2	18	1.56	1.54		17	1.51	1.5
Moderate	≥2 <5	19	3.23	3.07		3	3.10	3.0
Strong	≥5	10	7.12	6.94		1	5.00	5.0

(Mao et al. 2012)

The individual interactions identified by Drugs.com interaction database have been reviewed and for those with data, either pharmacokinetics (AUC) or other effects data are detailed in Appendix 3. The summary of these data are presented in Table 4. The list of chemicals in the first column is the actor on the recipient in the second

column according to the drug.com interaction database (Drug.com 2011). The third column, M factor, lists the interaction multiplier to be used in the calculation to determine the estimated risk for this research. The last column "Comments" has a "Default", where the group default value is used based on the grouping, from Table 3, that match the drug.com database categorized for the interaction and the FDA data (Drug.com 2011, Mao et al. 2012, Mao et al. 2011). If two pharmaceuticals are not documented having interactions based on the data available, the pair is not included in Table 4. Interactions that are potentially two-way, pharmaceutical, for example "A" impacts the concentration/effect of pharmaceutical "B" and then "B" also impacts the concentration/effect of "A", are noted by an "2-Way" in the "Comments" column.

Table 4: List of DDI values in this Study

Strong Effects ≥5			
Actor	**Recipient**	**M**	**Comments**
Diltiazem	Erythromycin	5.0	
Moderate Effects ≥2, <5			
Erythromycin	Carbamazepine	4.3	
Erythromycin	Fluoxetine	3.1	Default
Fluoxetine	Carbamazepine	3.1	Default
Diphenhydramine	Fluoxetine	3.1	Default
Codeine	Diltiazem	3.1	Default
Ibuprofen	Diltiazem	3.1	Default
Ciprofloxacin*	Erythromycin*	3.1	Default; 2-Way
Codeine	Nifedipine	3.1	Default
Ibuprofen	Nifedipine	3.1	Default
Codeine*	Carbamazepine*	3.1	Default; 2-Way
Carbamazepine	Diltiazem	3.1	Default
Fluoxetine	Ibuprofen	3.1	Default
Carbamazepine	Diphenhydramine	3.1	Default
Diltiazem*	Nifedipine*	3.0	2-Way

Weak Effects ≥1.25, <2			
Ibuprofen	Ciprofloxacin	2.0	
Erythromycin	Nifedipine	1.7	
Ciprofloxacin	Caffeine	1.6	
Sulfamethoxazole	Erythromycin	1.5	Default
Sulfamethoxazole	Ciprofloxacin	1.5	Default
Fluoxetine	Codeine	1.5	
Carbamazepine	Acetaminophen	1.5	
Diphenhydramine	Diltiazem	1.4	
No Effect <1.25			
Nicotine	Caffeine	1.1	
Trimethoprim	Sulfamethoxazole	1.1	
Fluoxetine	Nifedipine	1.0	
Diphenhydramine	Codeine	0.7	Antagonist
Nifedipine	Carbamazepine	0.4	Antagonist

2-Way=Two way interaction potential

Risk Methods

Risk has been calculated in various ways in the literature. The main driver for which method was selected was determined by which data were available. The EPA is the primary regulatory body that publishes methods on calculating health risks of environmental exposure in the USA. There are well documented methods of calculating the risk to human health from environmental chemical exposures (USEPA 2000b, USEPA 2003, USEPA 2007). All methods compare an exposure level to a health impact level. The type of exposure measured or estimated and where the effect is targeted, external exposure, internal consumption or internal body burden, all impact the data that is required and the implications for the risk assessment. An internal body burden is better to understand exposure, but it is hard to get a large enough dataset to evaluate. Even then, are you picking plasma, urine, hair or tissue samples? Depending on the chemical, in this case pharmaceuticals, one target tissue may not be as useful as others to

understand exposure. From a screening perspective, oral consumption, in this case from surface water, is a common level of exposure that has been measured and is available in the literature consistently written widely about the compounds studied in this analysis. There are multiple methods of calculating the risk of a chemical to human health. Various methods, as named by the USEPA, are listed below:

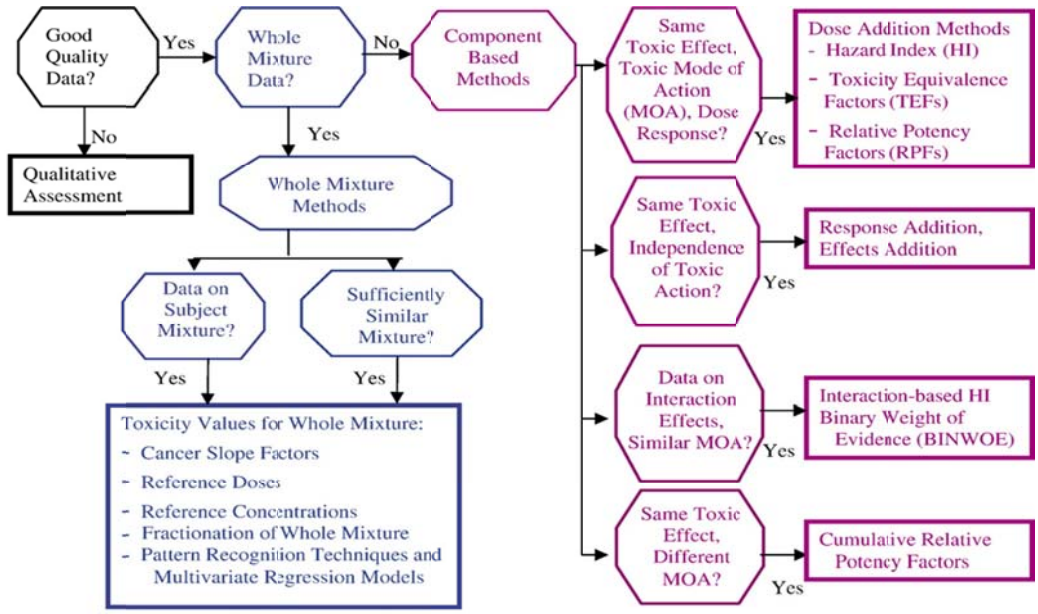
Table 5: Risk Calculation Names USEPA

Relative Potency Factor (RPF)	Point of Departure Index (PODI)
Toxicity Equivalency Factor (TEF)	Margin of Exposure for Mixtures (MOET)
Hazard Index (HI) or HQ for Hazard Quotient	Response Addition (RA)
Interaction Hazard Index (HI_{INT})	Cumulative Risk Index (CRI)

(USEPA 2000b, USEPA 2003)

To pick between the different methods a researcher needs to consider the types of data to be used in an analysis. In the flow chart shown in Figure 3, the author created a decision tree as to which models should be selected based on the type of data that is available (Teuschler 2007). The decision points include having good quality data or not. Because measured data on the environmental concentrations was available and relative human effects data are also available, a qualitative risk assessment was not conducted. The effects data is based on the components of the samples, not the effects of the whole mixture, so component-based calculations were the ones considered.

Figure 3: Risk Calculation Flow-chart



Adapted from Teuschler et al., 2001

Mixtures

When examining mixtures, there are two basic sides to the assumptions made. One is concentration or dose addition (CA or DA); the other is independent action (IA). CA is where the effects of the mixture components are assumed to be additive. This is used when the two chemicals act in the same manner on the same biological endpoint being studied. For example, two statin drugs such as simvastatin and pravastatin, both cholesterol-lowering medications, can be assumed to be additive if combined in a mixture or taken together by a patient. The chemical family "statin" and also the effect "cholesterol lowering" are the same. They are also similar structurally. More stringent models such as the Toxic Equivalent (TEQ) in addition require structural similarities, and dose-response curves which are parallel for the two chemicals being added.

The other side is the assumption of independent action (IA), where the effects of the components are not added. This is assumed where the chemicals operate by different mechanisms of action and with different biological effects. The IA looks at the sum of the individual effects inherent in the individual pharmaceuticals to calculate the mixture effect. The two components overlap but do not impact the effects of the other component. In the case of IA, the additivity is typically less than that calculated by CA models (USEPA 2000b, USEPA 2003, USEPA 2000a, USEPA 2000a, USEPA 2007, Borgert et al. 2012).

As summarized in a "toxicology of mixtures" report, the combination of two chemicals is often described as either CA or IA. The CA method assumes additivity, whereas the IA method assumes that separate mechanisms of action would predict a lower value IA (Kortenkamp, Backhaus & Faust 2009, Teuschler 2007, Borgert et al. 2012, Backhaus, Arrhenius & Blanck 2004). The CA approach here is not expected to be the best-fit model for all the chemicals and paired mixtures in this analysis. The difference can be numerically shown in this example from Borgert. IA would predict a sub-threshold effect of 0+0+0=0 where the CA assumes the same effects represented by 0.5+0.5+0.5=1.5 (Borgert et al. 2012, Mihaich et al. 2005). Therefore, the question posed is whether the risk assessment is trying to be a conservative screen or whether the accuracy of the risk assessment is the most important. CA would work better in this case (Kortenkamp, Backhaus & Faust 2009, Borgert et al. 2012). In this analysis, a screening approach can easily be used in other places with other mixtures including non-pharmaceuticals.

The HI is utilized in this dissertation, and its approach uses a simple environmental concentration over a no-effect concentration. In various older literature and government guidance documents, HI are referred to as Hazard Quotients (HQs). There is no formula difference between HI and HQ, just terminology (USEPA 2000b). The interactive hazard index approach is used for this cumulative risk assessment. Simplified, the HI equation is detailed below in Equation 2. The data used is not necessarily presented in parallel dose response curves or similarly shaped curves. The data are predicted low- or no-observed-effects levels based on low clinical doses of effect adjusted with suitable uncertainty factors.

Equation: 2

$$HI \text{ or } HQ = \frac{exposure}{effect\ concentration}$$

This HI equation can be written as predicted exposure (or environmental) concentration (PEC) over predicted no effect concentration (PNEC), which is typical in environmental risk assessments.

Equation: 3

$$HI = \frac{PEC}{PNEC}$$

The environmental concentrations data used in this research are measured data at low-flow conditions at what is expected to be representative of the highest concentration reasonably available at the sample location (Fischer 2011). In this calculation, the PEC can be replaced with a measured exposure concentration (MEC). The PNEC is derived from the ADI adjusted for daily water consumption. The average

daily water volume used in most risk assessment calculations is 2 liters per day (USEPA 1997).

To calculate a cumulative risk assessment, individual HI values are calculated for each pharmaceutical in a stream mixture and then summed. The calculation used here assumes that the chemicals are additive and the individual toxic effects can be added. This is not necessarily the case with all combined pharmaceuticals, OTC drugs, or chemicals in general. Additivity is appropriate when there is a similar mechanism of action and the same biological end point is measured. It is assumed here because this risk assessment is designed as a worst-case screening tool not dependent on the specific biological effects profile of the individual parts.

In this research, the cumulative additive HI is used, as this is a screening. There are 30 sample sites, 18 pharmaceuticals, and a large number of potential combinations, making it impractical to perform a mixture of individual HI and dose response calculations. The other chemicals present are not added to this risk calculation. In addition, the cumulative risk calculation can incorporate interaction potential, whereas others do not. Overall, this leads to a conservative screening assessment, which can be used to focus on additional research. The calculation from the EPA has at its core a cumulative hazard index, which is a sum of individual hazard indices, or to parallel the EPA format, hazard quotients, as shown in Equation 4 below.

Equation: 4

$$HI: additive = HQ1 + HQ2 + HQ3 + \cdots$$

This is rewritten in Equation 5 in the EPA format with HQ used to differentiate between the inner hazard quotients and the outer or summary hazard index HI.

Equation: 5

$$HI = \sum_{j=1}^{n} \mathrm{HQ_j}$$

The full calculation for a cumulative HI with interactions accounted for is presented in Equation 6. The individual pairs of interactions and hazard quotients are represented by the HQ with the summarized f factor and magnitude modifier. This is then summed across all individual HI calculations to get the Hazard Index with interaction as shown in Equation 6. The individual sections of the equation are further defined below.

Equation: 6

$$HI_{INT} = \sum_{j=1}^{n} (\mathrm{HQ_j} \sum_{\mathrm{j \neq k}}^{\mathrm{n}} \mathrm{f_{jk}}\, \mathrm{M_{jk}^{B_{jk}G_{jk}}})$$

HI_{INT} = Hazard Index for interactions

In this cumulative HI interaction equation, f represents the toxic hazard of one chemical j relative to another chemical k and the total hazard from all chemicals potentially interacting with that chemical. This part is presented in Equation 7 below.

Equation: 7

$$f_{jk} = \frac{HQ_k}{\left[\sum_{j=1}^{n} HQ\right] - HQ_j}$$

The M factor is the interaction magnitude, the influence of chemical j, on the toxicity of chemical k. The M factor has a value with range of 0.2 to 5 for interaction effect. The EPA default value is 5 (USEPA 2000b). The M factor values used in this research are listed in Table 4 and supported by data in Appendix 3.

The weight of evidence factor (B) in the EPA calculation accounts for the quality of the data relative to human health and the direction of effect, synergistic or antagonistic. In this analysis, B_{jk} equals 1, as the data are primarily human data, and the worst-case assumption is that the effects are more than additive (USEPA 2000b). Under different conditions, different B values could be used. In all the cases where the interactions are positive, increasing, the B value is +1. Where the interactions are negative (decreasing or antagonistic), the B value is -1.

Table 6 Weight of Evidence Factors (B)

Default weighting factors for the modified weight of evidence

Category	Description	Direction	
		Greater than additive	Less than additive
I	The interaction has been shown to be relevant to human health effects and the direction of the interaction is unequivocal.	1.0	-1.0
II	The direction of the interaction has been demonstrated in vivo in an appropriate animal model, and the relevance to potential human health effects is likely.	0.75	-0.5
III	An interaction in a particular direction is plausible, but the evidence supporting the	0.50	0.0

	interaction and its relevance to human health effects is weak.		
IV	The assumption of additivity has been demonstrated or must be accepted.	0.0	0.0

Reproduced from (USEPA 2000b, USEPA 2003)

The factor G is the degree with which chemical pairs are in the mixture in equatoxic amounts and is presented in Equation 8 below.

Equation: 8

$$G_{jk} = \frac{\sqrt{HQ_j * HQ_k}}{(HQ_j + HQ_k)/2}$$

Microsoft Excel was the tool used to calculate the hazard index values for the surface water mixtures. The data for each stream with its unique mixture of pharmaceuticals was set up on its own worksheet as part of one workbook. Each worksheet has a set of equations that matches the number of pharmaceuticals and over-the-counter chemicals present and the number of DDI combinations possible in this unique mixture. As shown below in Figure 4, the left side of each sheet calculates the individual HI of each contaminant. This is then summed to calculate the cumulative HI for the set of contaminants in this mixture. The right side of the spreadsheet then calculates the components of the inner summation covering f and M, as well as the exponents B and G, which are described above. These are then summed to get the final column, which lists the interacted HIs. Then these are summed to get the cumulative HI with interactions.

Figure 4: Excel Example

Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADE ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
1	0.016	31.31	2	10	70	4.57E-05	0.9659	1-2	1	1	0.9379	0.9659	0.000044
2	0.033	64.58	2	10	70	9.43E-05	0.0341	1-3	1	1	0.5034	0.0341	0.000002
3	0.0021	4.11	2	18	70	3.33E-06	0.0680	2-3	1	1	0.3632	0.0680	0.000006
	0.0511					1.43E-04	0.9320	2-1	1	1	0.9379	0.9320	0.000088
						Sum of HQ - simple	0.3265	3-1	1.1	1	0.5034	0.3426	0.000001
							0.6735	3-2	1	1	0.3632	0.6735	0.000002
													0.000143

Sum of HQ with Interaction

Results & Discussion

The measured environmental concentrations from the 30 sample sites in NJ (Figure 1) provide a diverse set of mixtures across most of the northern half of the state. Surface water is a large part of the supply for residential drinking water. The samples were taken only at one point in time as grab samples. This is one of the limitations of this study. The sampling was in the Fall of 2001, providing only a single point of data that is presumably the most concentrated sample for the year. As a risk assessment, this falsely increases the amount of pharmaceuticals and other chemicals that are available to the drinking water supply system. It does increase the concentrations of the individual components, making them easier to identify and measure in the water samples.

The calculations used in this work are very simplistic in application. The basic human chronic ADE, or acceptable daily intakes (ADI), is based on the lowest human or

animal low or no-observed-effect level in the public literature adjusted by UFs based on the data set of the individual pharmaceutical. Data from existing clinical trials but not available in the public literature or the data summaries may provide a better POD for the ADEs than the ones calculated in Table 2 for each of the pharmaceuticals in this dissertation. Additionally, other data could influence the UFs and the ADEs that were used. This variability could change individual risks, but overall the summary risk is probably not impacted in the mixtures.

The interaction matrix, as shown in Figure 2, is reasonable but could easily be missing some interactions. The pharmaceuticals that are not typically used together or the antibiotics that are primarily used by veterinarians may have interactions that have not been accounted for in this research. By the nature of their infrequency or lack of documentation, there could be some interactions missed. This potential limitation is accounted for by maximizing the interactions in the test case used.

The interaction range, as summarized in Table 3, is used to frame the default "M" values. These defaults could be changed if other data become available. The data from Mao does parallel the data from this dissertation. In Table 4, the listed interactions are few when compared to the possible interactions as shown in Figure 2. The 306 possible combinations are limited, so a few extra interactions, or changes to the defaults, up or down would change the calculation results.

The calculation for the cumulative HI (Equation 6) is a good screening tool. It is conservative, being a concentration addition type of calculation rather that one based

on independent action. Due to this assumption of additivity, the calculation is generating conservative risk values. To be more precise, the individual pairs in each sample mixture would have to be assessed. Those components that are additive in their biological effect would be well represented. Those components that would be best represented by an independent action calculation would be conservatively represented in the summary. While more precision could be gained, by either choosing a different calculation, or preparing a custom blend of both, little would be gained from an overall risk screening point of view such as those shown in the flow-chart in Figure 3. If the mixture does not predict a hazard, there is not a lot of value in improving the risk ratio currently calculated in this work.

The results of the cumulative risk assessment using the calculation from the EPA (Equation 6) in Excel, as presented in Figure 4, show that there is no expected risk from pharmaceuticals in NJ surface waters. The results of the calculations for each of the 30 stream locations are presented in Table 7. In the 30 stream samples, seven samples had no pharmaceutical components measured in them; two samples only had one detectable pharmaceutical. Twenty-one samples had two or more pharmaceuticals identified, with one sample having 11 individually measured pharmaceuticals. These individual spreadsheets are presented in Appendix 4 in the same order as in Table 7. The seven samples without pharmaceutical components do not have spreadsheets. When calculating the simple additive risk, none of the mixtures had an HI equal to or greater than one (Table 7). The highest single HI value calculated was 0.01003 in the Ramapo River. When including the DDI multiplier, as presented in this research, the HI

increases 1.02 fold to 0.01020 in the Ramapo River. Both values are about 100x lower than an HI of one that could indicate a potential human health risk. The Ramapo River has almost three times the HI, as does the next highest sample from the Hohokus Brook, location two, with an HI of 0.00375 and a DDI HI of 0.00403. The increase in the HI values is paralleled by the increase in the HI interactive values.

In Table 7, the data is summarized by sample location and also includes columns for the mass of the pharmaceuticals measured in the streams, the percentage of the mixture for the largest component, the number of components. The right side three columns represent the HI risk calculation results for each stream location. First is the simple additive HI, followed by the HI with the interaction potential "the M" included, followed by the ratio of the HIs with (HI interaction / HI additive = Ratio). Table 7 is sorted in order of lowest HI additive at the top down to the highest HI additive at the bottom.

This same data presented in Table 7 is displayed on the chart in Figure 5. The x-axis has the sample locations in order of low to high HI additive values. The Y-axis has the HI values from one down to 0.00001. Most of the values are indistinguishable from one another because they are so close together. The clearest observation is that none of the HI calculations is close to one, all having a clear safety margin of 100x up to 10,000x below the point where a hazard would be predicted. When ranked by the simple additive risk in Table 7, these higher HI values are associated with higher mass of

pharmaceutical materials in the water and in general with an increased number of contaminants.

To understand the risk potential at a theoretical maximum, the M value of all interactions was increased by 5 to match the EPA's upper limit. This is presented in Table 8 and the chart is shown as Figure 6. Instead of the intermittent interactions, as seen in the individual data sheets in Appendix 4, all of the potential interactions are considered greater than one. The EPA default of 5 is used for each pair of components in the mixtures in a two-way direction. That is pharmaceutical "A" effects pharmaceutical "B" and pharmaceutical "B" effects pharmaceutical "A", each by a five-fold increase in effect, as was shown in Table 4 with the list of DDI values. All but one of the values in Table 4 is below five, and only three of the 28 interactions listed are two-way interactions. This overuse of the interactions at a level well above most of the interaction dose shows an increase in the HI for all but a few of the stream samples. The HI value for the highest HI additive values, the Ramapo River, is the same at 0.01003. The HI with interactions included now has an HI value of 0.01200 or a 1.2 fold increase. This is up from 0.01020, a 1.02 fold increase, as presented in Table 7. The increase in the amount of interaction is more evident in Figure 6 where the two sets of results are distinctly separate. Even in this case, all but five of the streams have HI values below 0.01 or still having a safety margin of 100x or more.

One change between Table 7 and Table 8 that has occurred with the interactions being forced up to 5x, as presented in Table 8, is that the sample with the highest HI

with just additivity no longer is the highest HI with interactions. The Ramapo River, with a base HI of 0.01003 has an HI with interaction (5x) of 0.01200, while the Hohokus Brook-2 with a base HI of 0.00375 now has an HI with interaction (5x) of 0.01674. This is a 4.46 fold increase in the HI over the 1.2 fold increase in the Ramapo River. A review of the HI ratios (HI interaction / HI additive) at the 5x level (Table 8) shows a range of increase of 1.20 to 4.55, which is up from the ratio range of 1.00 to 1.17. This dose demonstrates that the increase in the interactions will change the interaction a measurable amount, but the mixture HIs are not increased a uniform 5x across the board.

The two streams show there is very little change between the HI additive values and the HI with interaction values because the mixtures are dominated by a single ingredient. In the case of the Musconetcong River, 92% of the mixture mass was dominated by caffeine at a concentration of 0.036 μg/L. The HI additive value is 0.00010 and the HI interaction value is 0.00013, only a 1.25 times increase even with a 5x interaction factor. The other river with very little change is the Ramapo River. The mixture in the Ramapo is dominated by carbamazepine at 99% of the mixture's mass at a concentration of 3.48 μg/L. The dominance of a single component of the mixture has driven the risk and any interaction potential for the whole mixture. The source of these high concentrations of pharmaceuticals was not in the USGS data. The Hohokus Brook at location two had high concentrations of three components, caffeine 0.27 μg/L (23% of the mixture), 0.3 μg/L (26%) of its metabolite 1, 7-dimethylxanthine, and 0.33 μg/L (28%) of the metabolite of erythromycin. Caffeine is ubiquitous in the environment, and

its variation in concentrations may be based on population served by the sewage treatment plants upstream of the sampling. The carbamazepine and erythromycin could be from medical facilities with a large resident population or hospitals or manufacturing facilities.

To understand the risk potential at a higher M value, all of the interactions were increased by 7 to match the FDA's "Strong Effects" average from Table 3. This is presented in Table 9 and the chart is shown as Figure 7 (Mao et al. 2012). The Ramapo River, as indicated in Tables 7 and 8, has the highest HI with no adjustment at 0.01003 and with the adjustment for interaction (7x) the HI interaction value is 0.01246. The highest HI interaction value is 0.02297 in the Hohokus Brook-2 sample. With this HI of 0.02297, the safety margin between 0.02297 and one drops from 100x to about 43x. As with the 5x analysis, the HI interaction values are more than the base HI values but with a range of 1.24 to 6.25; the interaction increase is higher than the base interaction range of 1.00 to 1.17 and all less than the 7x value being input into the "M" factor in the equations. In each of these cases, the highest individual DDI HI value was 0.01674 for the 5x case and 0.02297 in the case of the 7x calculation, both below the HI of one.

To analyze the potential drivers for the interaction, four river components were separately analyzed in Table 10. The four rivers included are the Whippany River at sample point 2, the Ramapo River, the Lamington River, and the Hohokus Brook at sample point 1. In Table 10, each river is titled with the individual components below the name and then a column for the in-stream concentration and a column for the

percentage of that component in the sample mixture. In these streams which have from 4 to 10 components, all have in common carbamazepine and cotinine, the nicotine metabolite. The antihistamine diphenhydramine and the pain reliever codeine are also in three of the four samples. There is no obvious correlation other than increased mass in the mixture generally related to increased risk. From the raw data, the most commonly found pharmaceuticals are caffeine in 19 of the 30 samples, cotinine in 18, carbamazepine in 18, 1,7-dimethylxanthine in 8, diphenhydramine in 6, and acetaminophen, codeine and dehydronifedipine in 5 of the samples.

The limitations of this risk assessment are many. The in-stream concentrations were taken in the Fall during low flow conditions. To be truly representative of the potential human exposure, a profile of the concentration over time, preferably annually, would be needed. The accuracy of the analysis can be improved by improving the ADI values that include biological effect concentration, a true NOEL, and smaller uncertainty factors to adjust this POD to a chronic human health equivalent. In addition, the M factor detailing the amount of interaction that does occur when two pharmaceuticals are mixed could be improved. Some of the interaction values are default estimates and measured internal dose changes based on interaction effects, which would improve the accuracy of these results. The risk assessment calculation used is based on the hazard index approach. A more accurate determination of the risk of these mixtures could be calculated by a combined approach of HI, CA, and IA methods, depending on the nature of the interacting pair or the HRPT method (Borgert et al. 2012). The other human health risk assessment recently publish, also used screening methods, found no risk

from mixtures in Dutch surface water but used different methods of assessment and did not examine drug-drug interactions (de Jongh et al. 2012). Although all these limitations exist, as a conservative screening tool, this approach would help guide where knowledge gathering and risk assessment fine tuning is needed.

Conclusion

Overall, this research has shown that there is no appreciable risk to human health from pharmaceuticals in surface water. The cumulative HI with interaction risk calculation has shown to function well as a screening exercise while including the interaction potential between the pharmaceuticals. The drug-drug interactions can account for a small amount of increase in the calculated risk. The amount of risk added by the EPA and FDA worst-case interaction settings would over-shadow the measured and estimated M values.

In practice, this HI approach does provide a level of knowledge on the risk of cumulative pharmaceuticals and their interactions in the surface water of NJ. The data estimate that there is a 100x safety margin between the calculated risk and the level of potential concern based on these concentrations of pharmaceuticals in water. In future risk assessments, drug interactions should be accounted for in examining mixtures. Based on this analysis, a factor of 1.2 would span the difference between the cumulative-risk calculations without interactions and with interactions.

To expand the understanding of the risk to human health from contaminants in NJ surface waters, the other components of the sample site should be assessed and

incorporated into a screening risk assessment. The other components measured in the USGS data included detergents, fuel products, fire retardants, pesticides, and fragrances. By incorporating these components into the risk assessment calculation, a clearer picture of the entire risk to human health from surface water can be estimated. Further, the amount of removal of any or most of these components by drinking water processing facilities need to be determined. By assessing the complete set of contaminants, a pattern may emerge as to what are the critical components or parameters of concern in the mixtures assessed here. Is it one group or family of chemicals or may be just a critical mass that in combination could tip an assessment of surface water into one of concern? Pharmaceuticals in themselves, by this analysis, do not present an obvious threat.

Table 7: Cumulative HI values by Stream Sample Point Data

Sample Location	Mass μg/L	Highest % of Single comp.	Number of comp.	Number of inter.	HI: Add Only	HI with Inter	Inter./Add
Wallkill R-1	0	0.00	0	0	0.00000	N/A	N/A
Cupsaw Bk	0	0.00	0	0	0.00000	N/A	N/A
Lamington R-2	0	0.00	0	0	0.00000	N/A	N/A
Beden Bk	0	0.00	0	0	0.00000	N/A	N/A
Maurice R	0	0.00	0	0	0.00000	N/A	N/A
Crosswicks Ck	0	0.00	0	0	0.00000	N/A	N/A
Haynes Ck	0	0.00	0	0	0.00000	N/A	N/A
N. Br Raritan R-2	0.002	100.0	1	0	0.00001	N/A	N/A
Delaware R	0.012	100.0	1	0	0.00003	N/A	N/A
Matchaponix Bk	0.032	84.4	2	1	0.00008	0.00009	1.01
Passaic R-1	0.035	68.4	3	1	0.00010	0.00010	1.00
Musconetcong R	0.039	92.3	2	0	0.00010	0.00010	1.01
Raritan R	0.039	64.9	3	1	0.00011	0.00011	1.00
Whippany R-1	0.051	64.6	3	1	0.00014	0.00014	1.00
N. Br Raritan R-1	0.258	85.4	4	0	0.00017	0.00017	1.00
Assunpink Ck	0.085	55.2	4	2	0.00017	0.00017	1.01
Passaic R-2	0.063	73.0	2	0	0.00018	0.00018	1.00
Millstone R	0.065	50.5	4	2	0.00019	0.00019	1.00
Whippany R-2	0.092	63.0	4	3	0.00019	0.00022	1.17
Dead R	0.194	61.5	5	2	0.00045	0.00045	1.00
Passain R-3	0.216	88.2	3	1	0.00061	0.00061	1.00
Singac Bk	0.420	42.8	4	1	0.00073	0.00073	1.00
Lamington R-1	0.362	30.4	10	15	0.00080	0.00083	1.04
Peckman R	0.562	53.4	5	3	0.00114	0.00116	1.01
Rockaway R	0.398	52.8	8	8	0.00125	0.00132	1.05
Hohokus Bk-1	0.663	39.2	9	11	0.00222	0.00245	1.10
N Br Rancocas Ck	0.881	55.3	7	3	0.00266	0.00266	1.00
Wallkill R-2	0.541	51.8	4	0	0.00324	0.00324	1.00
Hohokus Bk-2	1.158	28.5	11	19	0.00375	0.00403	1.07
Ramapo R	3.503	99.3	5	5	0.01003	0.01020	1.02

Component =	Comp
Interaction =	Inter
Additive =	Add

Average	0.00129	0.00139	1.024
Median	0.00045	0.00045	1.001
Min	0.00008	0.00009	1.000
Max	0.01003	0.01020	1.173

Table 8: Cumulative HI values by Stream Sample Point Data with 5x Interaction Assumed

Sample Location	Mass μg/L	Highest % of Single comp.	Number of comp.	Number of inter.	HI: Add Only	HI with Inter	Inter./Add
Wallkill R-1	0	0.00	0	0	0.00000	N/A	N/A
Cupsaw Bk	0	0.00	0	0	0.00000	N/A	N/A
Lamington R-2	0	0.00	0	0	0.00000	N/A	N/A
Beden Bk	0	0.00	0	0	0.00000	N/A	N/A
Maurice R	0	0.00	0	0	0.00000	N/A	N/A
Crosswicks Ck	0	0.00	0	0	0.00000	N/A	N/A
Haynes Ck	0	0.00	0	0	0.00000	N/A	N/A
N. Br Raritan R-2	0.002	100.00	1	0	0.00001	N/A	N/A
Delaware R	0.012	100.00	1	0	0.00003	N/A	N/A
Matchaponix Bk	0.0320	84.38	2	1	0.00008	0.00021	2.52
Passaic R-1	0.0351	68.38	3	1	0.00010	0.00040	4.04
Musconetcong R	0.039	92.31	2	0	0.00010	0.00013	1.25
Raritan R	0.0385	64.94	3	0	0.00011	0.00042	3.95
Whippany R-1	0.0511	64.58	3	1	0.00014	0.00062	4.32
N. Br Raritan R-1	0.2576	85.40	4	0	0.00017	0.00076	4.55
Assunpink Ck	0.0851	55.23	4	2	0.00017	0.00055	3.27
Passaic R-2	0.0630	73.02	2	0	0.00018	0.00075	4.17
Millstone R	0.0654	50.46	4	0	0.00019	0.00082	4.46
Whippany R-2	0.092	63.04	4	1	0.00019	0.00050	2.67
Dead R	0.1935	61.50	5	2	0.00045	0.00134	2.96
Passain R-3	0.2155	88.17	3	1	0.00061	0.00163	2.66
Singac Bk	0.4202	42.84	4	1	0.00073	0.00255	3.51
Lamington R-1	0.3621	30.38	10	9	0.00080	0.00321	4.03
Peckman R	0.562	53.38	5	2	0.00114	0.00310	2.70
Rockaway R	0.3975	52.83	8	6	0.00125	0.00541	4.32
Hohokus Bk-1	0.6631	39.21	9	5	0.00222	0.00978	4.41
N Br Rancocas Ck	0.881	55.28	7	2	0.00266	0.01044	3.93
Wallkill R-2	0.541	51.76	4	0	0.00324	0.00684	2.11
Hohokus Bk-2	1.1582	28.49	11	7	0.00375	0.01674	4.46
Ramapo R	3.503	99.34	5	3	0.01003	0.01200	1.20

Component =	Comp
Interaction =	Inter
Additive =	Add

Average	0.00129	0.00372	3.40
Median	0.00045	0.00134	3.93
Min	0.00008	0.00013	1.20
max	0.01003	0.01674	4.55

Table 9: Cumulative HI values by Stream Sample Point Data with 7x Interaction Assumed

Sample Location	Mass μg/L	Highest % of Single comp.	Number of comp.	Number of inter.	HI: Add Only	HI with Inter	Inter./Add
Wallkill R-1	0	0.00	0	0	0.00000	N/A	N/A
Cupsaw Bk	0	0.00	0	0	0.00000	N/A	N/A
Lamington R-2	0	0.00	0	0	0.00000	N/A	N/A
Beden Bk	0	0.00	0	0	0.00000	N/A	N/A
Maurice R	0	0.00	0	0	0.00000	N/A	N/A
Crosswicks Ck	0	0.00	0	0	0.00000	N/A	N/A
Haynes Ck	0	0.00	0	0	0.00000	N/A	N/A
N. Br Raritan R-2	0.002	100.00	1	0	0.00001	N/A	N/A
Delaware R	0.012	100.00	1	0	0.00003	N/A	N/A
Matchaponix Bk	0.0320	84.38	2	1	0.00008	0.00026	3.06
Passaic R-1	0.0351	68.38	3	1	0.00010	0.00053	5.44
Musconetcong R	0.039	92.31	2	0	0.00010	0.00014	1.31
Raritan R	0.0385	64.94	3	0	0.00011	0.00056	5.29
Whippany R-1	0.0511	64.58	3	1	0.00014	0.00084	5.89
N. Br Raritan R-1	0.2576	85.40	4	0	0.00017	0.00104	6.25
Assunpink Ck	0.0851	55.23	4	2	0.00017	0.00071	4.22
Passaic R-2	0.0630	73.02	2	0	0.00018	0.00101	5.63
Millstone R	0.0654	50.46	4	0	0.00019	0.00113	6.10
Whippany R-2	0.092	63.04	4	1	0.00019	0.00062	3.29
Dead R	0.1935	61.50	5	2	0.00045	0.00169	3.74
Passain R-3	0.2155	88.17	3	1	0.00061	0.00200	3.27
Singac Bk	0.4202	42.84	4	1	0.00073	0.00334	4.59
Lamington R-1	0.3621	30.38	10	9	0.00080	0.00433	5.43
Peckman R	0.562	53.38	5	2	0.00114	0.00384	3.35
Rockaway R	0.3975	52.83	8	6	0.00125	0.00739	5.90
Hohokus Bk-1	0.6631	39.21	9	5	0.00222	0.01337	6.03
N Br Rancocas Ck	0.881	55.28	7	2	0.00266	0.01398	5.26
Wallkill R-2	0.541	51.76	4	0	0.00324	0.00802	2.47
Hohokus Bk-2	1.1582	28.49	11	7	0.00375	0.02297	6.12
Ramapo R	3.503	99.34	5	3	0.01003	0.01246	1.24

Component =	Comp
Interaction =	Inter
Additive =	Add

Average	0.00129	0.00477	4.47
Median	0.00045	0.00169	5.26
Min	0.00008	0.00014	1.24
max	0.01003	0.02297	6.25

Figure 5: HI Value by Sample Point Results

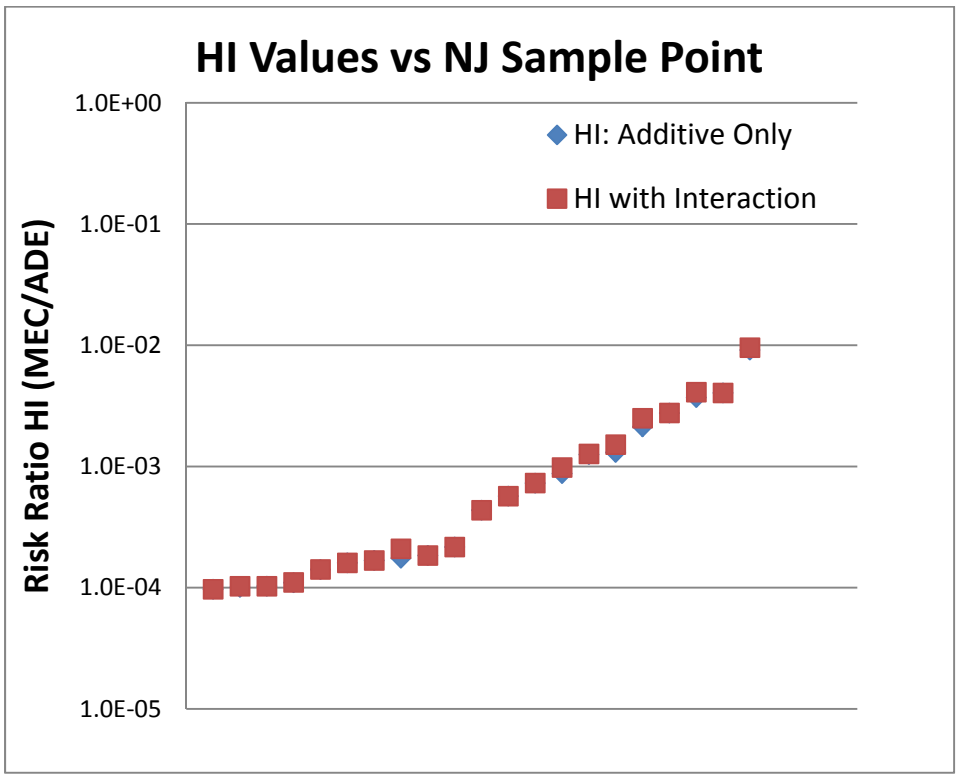


Figure 6: HI Value by Sample Point Results with 5x Interactions

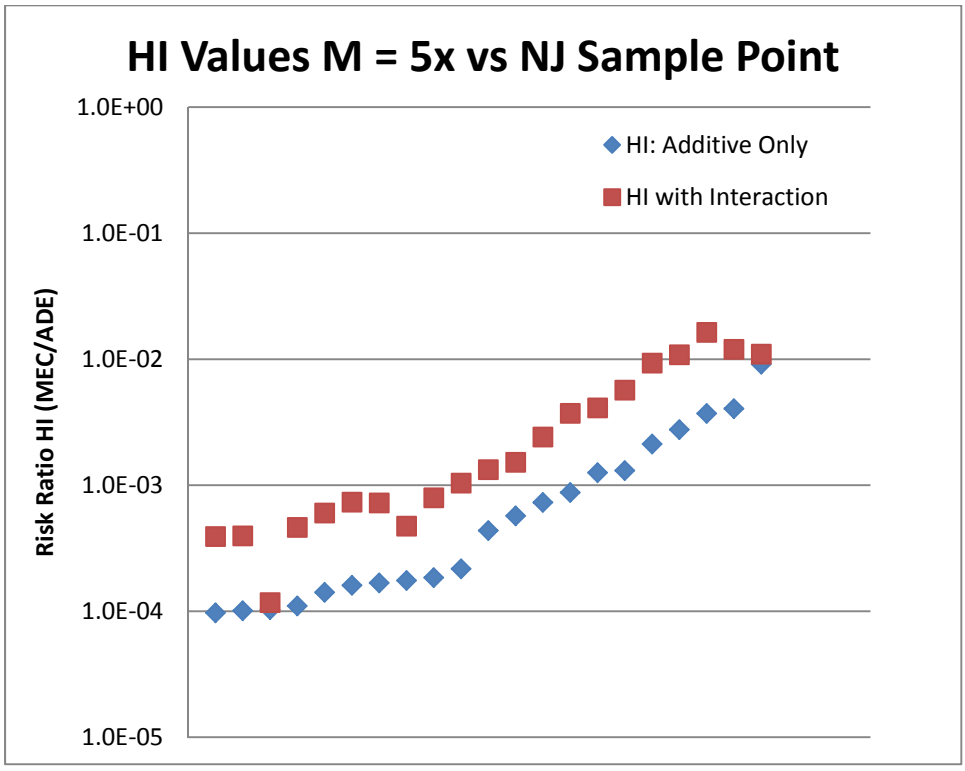


Figure 7: HI Value by Sample Point Results with x7 Interactions

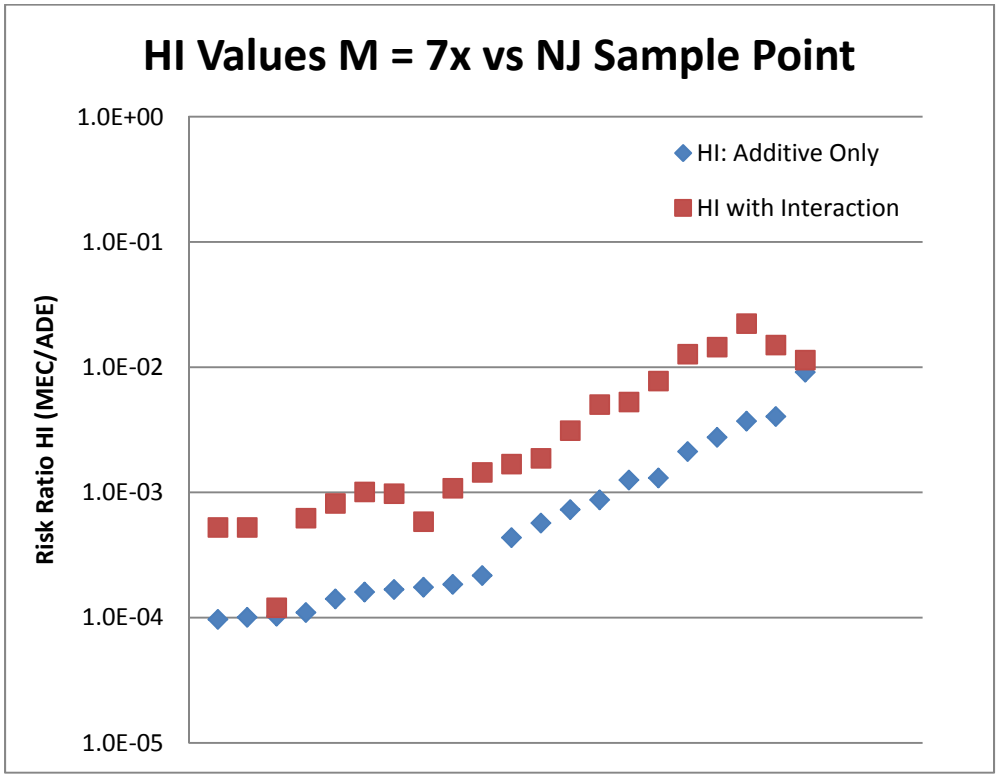


Table 10: Comparison of the Components of Four Rivers

Whippany-2	Stream Conc.	%	**Ramapo R**	Stream Conc.	%
	µg/L	mix		µg/L	mix
Carbamazepine	0.058	63.04%	Caffeine	0.015	0.43%
Cotinine	0.0005	0.54%	Carbamazepine	3.48	99.34%
Dehydronifedipine	0.0035	3.80%	Codeine	0.002	0.06%
Erythromycin-H2O	0.03	32.61%	Cotinine	0.003	0.09%
			Diphenhydramine	0.003	0.09%

Lamington R	Stream Conc.	%	**Hohokus Bk-1**	Stream Conc.	%
	µg/L	mix		µg/L	mix
Acetaminophen	0.023	6.35%	Caffeine	0.047	7.09%
Caffeine	0.110	30.38%	Carbamazepine	0.100	15.08%
Carbamazepine	0.059	16.29%	Ciprofloxacin	0.030	4.52%
Codeine	0.008	2.10%	Codeine	0.009	1.42%
Cotinine	0.030	8.29%	Cotinine	0.012	1.81%
Dehydronifedipine	0.002	0.47%	1,7-Dimethylxanthine	0.116	17.49%
Diltiazem	0.003	0.77%	Diphenhydramine	0.009	1.31%
1,7-Dimethylxanthine	0.035	9.67%	Erythromycin–H_2O	0.260	39.21%
Diphenhydramine	0.011	3.04%	Trimethoprim	0.080	12.06%
Ibuprofen	0.082	22.65%			

Appendix 1 USGS Full List

List of chemicals measured for in the original USGS data used in this research.

Compound	Commercial Use	In Risk Analysis
5-methyl-1H-benzotriazle	Antioxidant	
Bisphenol A	Antioxidant	
Fluoranthene	Combustion by-product	
Naphthalene	Combustion by-product	
Pyrene	Combustion by-product	
Ethyl citrate	Cosmetic	
NPEO2-total	Detergent	
OPEO2	Detergent	
Phenol	Disinfectant	
Triclosan	Disinfectant	
Bromoform	Disinfection byproduct	
Benzophenone	Fixative for fragrance/soap	
Ethanol,2-butoxy-,phosphate	Flame retardant	
Tri(2-chloroethyl)phosphate	Flame retardant	
Tri(dichlorisopropyl)phosphat	Flame retardant	
Tributylphosphate	Flame retardant	
Menthol	Flavorant	
Acetophenone	Fragrance	
AHTN	Fragrance	
HHCB	Fragrance	

Indole	Fragrance	
Isoquinoline	Fragrance	
Methyl salicylate	Fragrance	
skatol	Fragrance	
2-Methylnapthalene	Fuel component	
metalaxyl	Fungicide	
N,N-diethyltoluamide (DEET)	Insecticide	
1,7-dimethylxanthine	OTC pharmaceutical	X
Acetaminophen	OTC pharmaceutical	X
Caffeine	OTC pharmaceutical	X
Cotinine	OTC pharmaceutical	X
Ibuprofen	OTC pharmaceutical	X
Bromacil	Pesticide	
Carbaryl	Pesticide	
Chlorpyrifos	Pesticide	
Diazinon	Pesticide	
Metolachlor	Pesticide	
Prometon	Pesticide	
Carbamazapine	Pharmaceutical	X
Ciprofloxacin	Pharmaceutical	X
Codeine	Pharmaceutical	X
Dehydronifedipine	Pharmaceutical	X
Diltiazem	Pharmaceutical	X

Diphenhydramine	Pharmaceutical	X
Enrofloxacin	Pharmaceutical	X
Erythromycin-H_2O	Pharmaceutical	X
Fluoxetine	Pharmaceutical	X
Minocycline	Pharmaceutical	X
Sulfamethizole	Pharmaceutical	X
Sulfamethoxazole	Pharmaceutical	X
Trimethoprim	Pharmaceutical	X
Tetrachloroethylene	Solvent	
3-beta-coprostano	Steroid	
Beta-sitosterol	Steroid	
Cholesterol	Steroid	

List of chemical analyzed for by the USGS but not measured in any sample.

Compound	Commercial Use
1,4-dichlorobenzene	
1-methylnapthalene	
2,6-dimethylnapthalene	
4-cumylpheno	
4-n-octylphenol	
4-tert-octylphenol	
Anthracene	
Anthraquinone	

Benzo(a)pyrene	
BHA	
Camphor	
Carbadox	
Carbazole	
Chlortetracycline	
Cimetidine	Pharmaceutical
Cumene	
Demeclocycline	
Dichlorvos	
Digoxigenin	Pharmaceutical
d-limonene	
Doxycycline	Pharmaceutical
Furosemide	
Gemfibrozil	Pharmaceutical
Isoborneol	
Isophorone	
Lincomycin	Pharmaceutical
Methotrexate	
Miconazole	
Norfloxaxin	Pharmaceutical
OPEO1	
Oxytetracycline	Pharmaceutical

para-Cresol	
para-Nonylphenol-total	
Pentachlorophenol	
Phenanthrene	
Ranitidine	Pharmaceutical
Roxarsone	
Roxithromycin	Pharmaceutical
Salbutamol	Pharmaceutical
Sarafloxacin	
Stigmastanol	
Sulfachlorpyradazine	
Sulfadimethoxine	Pharmaceutical
Sulfamerazine	Pharmaceutical
Sulfamethazine	Pharmaceutical
Sulfathiazole	
Tetracycline	Pharmaceutical
Thiabendazole	
Triphenyl phosphate	
Tylosin	
Virginiamycin	Pharmaceutical
Warfarin	Pharmaceutical

Appendix 2 Pharmaceutical ADEs

Acetaminophen

Acetaminophen (CAS# 103-90-2) is a non-steroidal analgesic and antipyretic used to treat pain and reduce fever. It is an odorless, white crystalline powder. Acetaminophen is freely soluble in alcohol and slightly soluble in water. Acetaminophen is the active ingredient in Tylenol® and other over-the-counter pharmaceuticals as well as prescription pharmaceuticals (NTP 1993). Acetaminophen is rapidly absorbed in the gastrointestinal tract after oral administration reaching its peak plasma levels in 30 to 120 minutes. Its half-life is 1-3 hours in human and animal models.

The lowest therapeutic dose of acetaminophen in a combination is 325 mg and a maximum daily dose of 4 grams (USFDA 2011). The lowest dose recommended not in a combination is 650 mg. At the 325 mg dose, assuming a 70 kg adult, the per-kilogram dose is 4.6 mg/kg. Acetaminophen has low toxicity and is well studied. Occupationally it has been shown to cause dermatitis among healthcare workers handling medications, but is not considered a dermal sensitizer (Gielen, Goossens 2001, BMS 2010, HSDB 2007). When exceeding recommended therapeutic doses, liver toxicity has been seen in animals and man. Acute liver toxicity has been observed in man at 210 mg/kg, assuming a 70 kg individual, but in some cases at 100 to 143 mg/kg levels. Acute toxicity LD_{50} in rats is 1944 mg/kg; in mice, the LD_{50} is 338 mg/kg (BMS 2010).

Acetaminophen has resulted in kidney failure among over-dose patients. This pharmaceutical was negative in in-vitro bacterial mutagenicity studies but with some clastogenic changes in mammalian cells. Unscheduled DNA synthesis was observed

during in-vitro studies. In long-term testing, acetaminophen was negative in a mouse carcinogenicity study and equivocal in a female rat and negative in male rats (NTP 1993). Reproductive effects in rats at 370 mg/kg included reduced weight gain, at 1400 mg/kg/day reduction in pup weight gain in F1 and in F2. Sperm abnormalities at the high dose do not classify acetaminophen as a reproductive or developmental toxin (NTP 1984). There is evidence of liver toxicity from high acute doses, and chronic exposure is increased by alcoholism (HSDB 2007).

The point of departure used was the lowest, single effective therapeutic dose as a combination drug in adults of 325 mg, or 4.6 mg/kg in a 70-kg adult, when taken once a day. This was adjusted by UF_L of 3 to extrapolate to a NOEL based on a typical descending dose regime in toxicity study design. As the POD is from human data a UF_A of 1 was used. For inter-individual uncertainty, a UF_H of 3 was used to adjust for sensitive individuals within the population and an UF_M of 1 used as there is extensive data on human endpoints for acetaminophen. With a POD of 4.6 mg/kg and a combined uncertainty of (3*3) 9, the acceptable daily exposure (ADE) for acetaminophen is 516 μg/kg/day.

Caffeine

Caffeine (CAS# 58-08-2), a stimulant of the central nervous system and the cardiovascular system, is a white powder with a bitter flavor (BMS 2008). It is soluble in water. The acute LD_{50} of caffeine to rats and mice is 309 and 132 mg/kg. Caffeine was

negative in Ames studies, but had negative and positive results in in-vitro and animal studies. There was not enough evidence to classify caffeine as a carcinogen (BMS 2008).

Cola beverages contain caffeine. The FDA permits the use of caffeine in these beverages up to 1.2 g (72 mg) per 12-ounce bottle (6 mg/oz). Low-calorie drinks are allowed only half (3 mg/oz) as much caffeine (HSDB 2006). Caffeine demonstrated in rats reduced pup weights in the female parent at ≥12.5 mg/kg and litter size and viability in the next generation at 50 mg/kg (NTP 1996a). In epidemiological studies, caffeine consumption has shown effects on newborns. A trial comparing in-vitro fertilization success and caffeine consumption demonstrated a reduced effectiveness of implantation at caffeine consumption equivalent of 2 mg/day (Klonoff-Cohen, Bleha & Lam-Kruglick 2002).

The point of departure was the no-effective dose in adults of 2 mg, or 0.029 mg/kg in a 70-kg adult, when taken once a day in the epidemiology study of in-vitro fertilization. There was an uncertainty factor used for the self-reported dosing levels in the epidemiology data as a UF_M of 3. No other uncertainty factors were added for species extrapolation or low-dose extrapolation, as this was based on a human end point with a NOEL. The endpoint used is also a very sensitive one, in-vitro fertilization implantation, so there is no uncertainty to account for a sensitive patient population. The ADI for caffeine is 0.029 mg/kg / 3 = 0.010 mg/kg or 10 μg/kg/day.

Carbamazepine

Carbamazepine (CAS# 298-46-4) is an anticonvulsant for epilepsy and an analgesic for trigeminal neuralgia (Novartis 2011). The acute toxicity in mice is an LD_{50} range for 1100-3750 mg/kg and in rats 3850-4025 mg/kg. The acute LD_{50} in dogs is >5000 mg/kg. The acute toxicity from inhalation exposure in rats is LC_{50} >2160 mg/kg. The lowest dose known to be lethal to humans (adult) is 3.2 gram. Carbamazepine is not mutagenic in bacterial and mammalian studies. When administered to rats (Sprague-Dawley) for two years in the diet at doses of 25, 75, and 250 mg/kg/day, observed a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males. Carbamazepine therefore, is considered to be carcinogenic in Sprague-Dawley rats but the significance to human health has not been established (Novartis 2011).

Carbamazepine is contraindicated for patients with historical bone marrow depression. Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with carbamazepine treatment. Patients with of Chinese decent have a strong association with developing TEN/SJS when they have an inherited variant of the HLA-B gene, HLA-B*1502, based on retrospective studies (Novartis 2011).

The reproductive label by the FDA is a Pregnancy Category D. Data from epidemiological studies suggest that carbamazepine is associated with pregnancy and congenital malformations, including spina bifida. For nursing mothers carbamazepine ad its epoxide metabolite are measured to breast milk. The estimated doses given to

newborns that are breast-feeding are 2-5 mg per day and 1-2 mg for the epoxide metabolite of carbamazepine (Novartis 2011). The typical adult starting dose is 400 mg/day with doses reaching 1000 mg/day and rarely up to 1600 mg/day. There have been several ADE published for carbamazepine, which range from 10 to 100 μg/kg/day (Cunningham et al. 2010, Snyder et al. 2008, Kumar, Xagoraraki 2010). The point of departure used in this research was the lowest level (LOAEL) with an expected risk of harm to a fetus during gestation in humans at 3.0 mg/kg/day based on clinical and epidemiology data (Snyder et al. 2008). In the Snyder article, this was adjusted by UF_L of 10 to extrapolate to a NOEL, UF_H of 3 to cover inter-species variability, UF_D of 3 for sub-chronic to chronic and UF_M of 3 for available data. The ADE for carbamazepine is 11 μg/kg/day.

Ciprofloxacin

Ciprofloxacin is a fluoroquinolone antibiotic (CAS# 85721-33-1): Ciprofloxacin is a slightly yellow crystalline powder, highly soluble in water, 30,000 mg/L, and is soluble in dilute hydrochloric acid but insoluble in ethanol. The LD_{50} in rats is >2000 mg/kg. Studies in rabbits, given oral doses of 30 and 100 mg/kg have shown that ciprofloxacin causes gastrointestinal disturbances, resulting in maternal weight loss and an increased incidence in abortion. However, these studies have not shown that ciprofloxacin is teratogenic at either dose. Studies using intravenous doses of up to 20 mg/kg have not shown that ciprofloxacin causes maternal toxicity, embryo-toxicity, or teratogenic effects (Pfizer 2009, Bayer HealthCare 2011). Ciprofloxacin was negative in in-vitro

bacterial mutagenicity assays, hamster cell transformation assay, positive in in-vitro mouse lymphoma forward mutation assay, and negative in two in-vivo assays, a mouse micronucleus and a mouse dominant lethal assay. Long-term studies in rats and mice indicated no carcinogenic or tumorigenic effects due to ciprofloxacin following daily oral dosages up to 250 and 750 mg/kg to rats and mice, respectively (Pfizer 2009, Bayer HealthCare 2011, Hospira 2011). Patients taking ciprofloxacin can become photosensitive to UV light (sunlight). Patients with renal impairment and elderly patients may have decreased elimination of ciprofloxacin, resulting in higher exposures. The typical adult dose range is from 200 mg every 12 hours to 400 mg every 8 hours (Bayer HealthCare 2011). The ADE of 1.6 μg/kg/day is based on NOEC for gastro-intestinal bacterial effects (Schwab et al. 2005, WHO 1997b, WHO 1997a, EMEA 1998). No additional UF adjustments have been used because this level of effect is well below toxic end-points or therapeutic levels identified in humans or animal species.

Codeine

Codeine (CAS# 76-57-3) as codeine sulfate is an opioid analgesic related to morphine, but with less potent analgesic properties. Codeine is selective for the mu receptor but with a much weaker affinity than morphine. The opioid receptors in the brain and spinal cord are suspected of playing a large part in the analgesic effects of codeine. Analgesia is often accompanied by drowsiness. The other central nervous system effects include anxiolysis, euphoria, and feelings of relaxation. Codeine sulfate

causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. Codeine also acts as a cough suppressant (Lannett Company 2010). In two-year National Toxicology Program (NTP) feed studies, there was no evidence of carcinogenic activity of codeine in male or female rats exposed to average doses of approximately 15, 35, and 75 mg codeine/kg/day. In mice the NTP found no evidence of carcinogenic activity of codeine in males or females fed at exposures of approximately 100, 200, and 400 mg codeine/kg/day (NTP 1996b). Codeine was negative in several mutagenicity studies including bacterial reverse mutation assay or clastogenic in the in-vitro Chinese hamster ovary cell chromosome aberration assay (Lannett Company 2010, NTP 1996b). In animal studies, codeine has been shown to have embryo lethal and have fetal toxicity at 2-4 times the maximum human adult daily dose in rats but not rabbits at the equivalent of 360 mg/day dose in man. In rats, at dosages of 120 mg/kg, in the toxic range for the adult animal, codeine was associated with an increase in embryo resorption at the time of implantation. In a mouse study, a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring. Withdrawal has been reported in newborns with irritability, excessive crying, tremors, hyper-reflexia, fever, and vomiting. The maximum recommended adult dose is 360 mg/day, and the lowest adult dosage is 15 mg taken up to four times a day (Schwab et al. 2005, Lannett Company 2010). The point of departure used was the adult lowest single therapeutic dose of 15 mg/day or 0.21 mg/kg/day. This was adjusted by UF_L of 10 to extrapolate to a NOEL from a therapeutic effect, as there is no clear no effect level. No adjustment was used for animal to human extrapolation or for duration. The data

end-point is human, which is from long-term patient information. The human intra-individual uncertainty (UF_H) was set at 10 to adjust for intra-individual variability (Schwab et al. 2005). The calculation is 0.21 mg/kg/day divided by 100 (10*10) to equal 0.002 mg/kg/day. This is adjusted to μg by multiplying by 1000. Therefore, the ADE for codeine is 2 μg/kg/day.

Cotinine

Cotinine (CAS# 486-56-6) is the main stable metabolite of nicotine that is a yellow, oily liquid with an ammonia-like odor (Chem Service 2012). Nicotine is a component of tobacco smoke. Nicotine received from smoking directly or from second-hand smoke has been identified as a public health issue. Cotinine has been shown to have a biological half-life of approximately 15-19 hours, much longer than nicotine, which has a half-life of 2-3 hours (Herzig et al. 1998). It has also been demonstrated to have a powerful effect on vascular smooth muscle cell (VSMC) proliferation (HSDB 2010). Once in the body, nicotine is metabolized to cotinine entering the environment through STPs. Nicotine can be absorbed into the body from the gastrointestinal tract and skin. The products containing nicotine include snuff, chewing tobacco, chewing gum, nasal sprays, and skin patches. It can also be an occupational hazard to workers who harvest tobacco, as they can be exposed to nicotine and become intoxicated as a result of the transdermal absorption of nicotine contained in the plant (CDC 2009). Cotinine has an oral LD50 in mice of 1604 mg/kg, and is negative in bacterial mutagenicity studies (HSDB 2010). It has been shown that memory changes have

occurred in healthy, non-smoking volunteers at 1.0 mg/kg oral dose of cotinine. A slight non-statistical improvement in memory was recorded at 0.5 mg/kg. The level of cotinine in the patient of study is 5-10 times higher than that of a regular smoker but without the confounding of the many other components of tobacco smoke (Herzig et al. 1998). The POD of 0.5 mg/kg was modified by UF_L = 3 because of the difference between doses in the study used. There is an inter-variability uncertainty UF_H which equals 3. There were no uncertainty factors for animals to humans or for interspecies variability. An UF_D of 10 has been used for the short duration of the studies and limited data for cotinine alone. The ADE for cotinine is 6 μg/kg/day.

Dehydronifedipine

Dehydronifedipine (CAS# 67035-22-7) is an inactive metabolite of nifedipine, which is used to treat angina and is an antihypertensive medicine. Dehydronifedipine is described as a pale yellow solid which is stable at room temperature. It had an oral LD_{50} of 300 mg/kg in mice, in rats of 980 mg/kg, and in rabbits an LD_{50} of 3200 mg/kg. Dehydronifedipine is also considered moderately irritating in a rabbit eye study (Clearsynth 2012). Dehydronifedipine is a very water soluble metabolite of nifedipine. Very little, less than one percent, of nifedipine is excreted (TEVA 2008). There is limited additional toxicological data for dehydronifedipine. The ADE is based on nifedipine data.

Nifedipine (CAS# 21829-25-4), the parent compound, is a calcium channel blocker which inhibits the cross membrane transportation of calcium ions into vascular

smooth-muscle and cardiac muscle (TEVA 2008). It is also a yellow crystalline substance, mostly insoluble in water, but it is soluble in ethanol. Nifedipine is absorbed completely when taken orally, and its bioavailability has been recorded at between 84% and 89%. It reaches its peak concentration within 5 hours and has an elimination half-life of two hours, which can be extended to 7 hours with extended release tablet formulations that are not applicable to this research (TEVA 2008). Nifedipine has an acute toxicity as an LD_{50} of 1022 mg/kg in rats, 310 mg/kg in the mouse and an LD_{50} of 100 mg/kg in an undisclosed mammalian species (PCCA 2011). Nifedipine is not mutagenic in in-vivo studies nor was it carcinogenic in a two-year rat study. Reproductive and developmental effects have been observed. Nifedipine caused reductions in fertility in rats at doses that were about 30 times the maximum dose recommended in man of 90 mg/day (TEVA 2008).

The lowest therapeutic dose for nifedipine is 30 mg/day. The point of departure used was the NOEL in the longest term data available for the metabolite, which was at 100 mg/kg/day in rodent studies of up to four weeks in duration (Schwab et al. 2005). No adjustment was used for the end point, as it is a NOEL. The POD was adjusted for duration at study by UF_D of 10 to extrapolate from a short-term, four week study, to long-term data. Since the species is unclear, a UF_A of 10 is used to extrapolate between species and UF_H of 10 for intra-human variability, because the variability of the metabolite is uncertain. Based on the combined UF of 1000, the ADE for dehydronifedipine is 100 μg/kg/day.

Diltiazem

Diltiazem hydrochloride (CAS# 33286-22-5, base CAS# 42399-41-7) is an antihypertensive, anti-angina, anti-arrhythmic, and a calcium channel blocker. It is a white crystalline powder which is soluble in methanol, chloroform and water (HSDB 2003a, Cardinal Health 2010). Diltiazem is believed to operate by inhibiting the transportation of calcium ions across cell membranes (Cardinal Health 2010). The substance is well absorbed but is only 40% bioavailable due to the first-pass effect in the liver. About 2 - 4% of diltiazem appears in the urine unchanged after a plasma elimination half-life of 3.0 - 4.5 hours (Cardinal Health 2010).

The acute LD_{50} in mice was from 415 to 740 mg/kg; in rats, the LD_{50} is from 580 to 810 mg/kg (Cardinal Health 2010, RTECS 2011, ScienceLab.com 2012). The LD_{50} in dogs is as low as 50 mg/kg, and diltiazem is lethal to monkeys at 360 mg/kg. Diltiazem is not mutagenic in in vitro and in vivo studies. No evidence was found of carcinogenesis in a 24-month study in rats up to 100 mg/kg/day and in a 21-month study in mice up to 30 mg/kg/day. There is no observed effect on fertility in rats dosed up to 100 mg/kg/day. In reproductive studies in mice, rats, and rabbits, embryo and fetal lethality was observed at 4 to 6 times the maximum clinical trial dosage range at 480 mg/day or 8 mg/kg/day for a 60 kg person (Cardinal Health 2010).

Typical mono-therapy dosages start at 120 mg to 240 mg once daily, going as high 540 mg. The point of departure was the lowest therapeutic dose of 30 mg or 0.43 mg/kg given four times per day. This was adjusted by UF_L of 3 to extrapolate to a NOEL

and by UF_H of 10 to adjust for intra-individual variability (Schwab et al. 2005). No adjustment for animal to human data was indicated, as this data is a human clinical endpoint. No adjustment for duration of studies was indicated as there is long-term animal and human data supporting these values or for quality of data. The combined uncertainty is 30. The POD/UF (0.43 mg/kg/day/30) results in the ADE for diltiazem of 14 μg/kg/day.

1, 7-dimethylxanthine

This compound, 1, 7-dimethylxanthine (CAS# 611-59-6), is caffeine's primary metabolite. No toxicological data is available on 1, 7-dimethylxanthine. For the purposes of this research, the ADE of the parent compound, caffeine, will be used for the calculations of 1, 7-dimethylxanthine. The ADE is based on the ADE of caffeine and is 10 μg/kg/day.

Diphenhydramine

Diphenhydramine (CAS# 58-73-1) is a first-generation antihistamine (H1-receptor antagonist), also known commonly by the brand name Benadryl®. Diphenhydramine is a white, odorless crystalline powder which is soluble in alcohol and water. Diphenhydramine has sedative effects, with the lowest recommended therapeutic single dose in adults of 25 mg. There have been no adverse effects to fetus or effects in breast-fed infants. Studies in rats and rabbits at doses of up to five times the human recommended dose have shown no effects on fertility or to the fetus (Drug.com 2008).

The National Toxicology Program tested diphenhydramine in rats and mice for two years and was equivocal evidence in male rats based on an increased number of uncommon brain and lung neoplasms at 313 and 625 ppm in the diet. In female rats, it was equivocal increases in pituitary gland adenomas at concentrations up to 625 ppm. No evidence was present of carcinogenicity in male or female mice dosed up to 313 mg/kg (HSDB 2003b). The point of departure is the lowest single adult therapeutic dose of 25 mg or 0.36 mg/kg for a 70 kg person. This was adjusted by UF_L of 3 to extrapolate to a NOEL and by UF_H of 10 to adjust for intra-individual variability, as some people react differently to antihistamines. No adjustment was made for human to animal data, as the POD is a human endpoint, and no UFs for duration as long-term animal and human data are available on data quality. The ADE for diphenhydramine is 12 μg/kg/day.

Enrofloxacin

Enrofloxacin (CAS# 93106-60-6) is a synthetic, fluoroquinolone veterinary antibiotic, and is most effective against gram-negative bacteria. It is indicated for infections of the respiratory, gastrointestinal, and urinary tracts in cattle, pigs, and poultry. It is rapidly absorbed from the digestive tract, with 75% bioavailability, penetrating into all measured body tissues and fluids. The primary metabolite of enrofloxacin is ciprofloxacin.

The acute toxicity of enrofloxacin (LD_{50}) in rats is >5000 mg/kg from an oral dose and in mice oral LD_{50} >5000 mg/kg. The typical animal dose as an antibiotic is 2.5 to 5 mg/kg/day for 3 to 5 days for cattle and pigs, and for poultry it is 10 mg/kg/day for 3 to

10 days (WHO 1997a, Bayer HealthCare 2004). In rats, up to 577 mg/kg in males and up to 690 mg/kg over 90 days saw no overt toxicity in both appearance and behavior. Body weight gain at the highest level was reduced in this study (WHO 1997a). Adult dogs receiving enrofloxacin orally at a daily dosage rate of 52 mg/kg for 13 weeks had only isolated incidences of vomiting and loss of appetite. Adult dogs receiving the tablet formulation for 30 consecutive days at a daily treatment of 25 mg/kg did not exhibit significant clinical signs nor were there adverse effects upon the clinical chemistry, hematological or histological parameters. Daily doses of 125 mg/kg for up to 11 days induced vomiting, loss of appetite, depression, difficult locomotion, and death, while adult dogs receiving 50 mg/kg/day for 14 days had clinical signs of vomiting and loss of appetite.

No teratogenicity was observed in rats with a NOEL of 50 mg/kg/day, but fetal effect, reduced weight, along with maternal toxicity were observed at higher doses. There was no impact on fertility. The effect of enrofloxacin on the bacteria in the gastrointestinal system has been evaluated by the World Health Organization and the FDA for food safety. Their evaluation resulted in an ADE based on a NOEL of human gastrointestinal bacteria and did not include uncertainty factors. The ADE of enrofloxacin is 2.3 μg/kg/day (WHO 1997b, WHO 1997a, EMEA 1998).

Erythromycin-H_2O

Erythromycin-H_2O is a degradation product of the antibiotic Erythromycin (CAS# 114-07-8): No toxicological data are available on this degradent; therefore, the ADE is based on

the parent compound. Erythromycin is a white to off-white powder, slightly soluble in water, and soluble in alcohol, chloroform, and ether. Erythromycin inhibits the synthesis of protein in susceptible micro-organisms. It affects various gram-positive and gram negative organisms, among other infectious diseases. The oral LD_{50} is between 3000 and 9272 mg/kg for rats, mice, and hamsters (Abbott 2012). In rats, no evidence of tumors was observed in a two-year oral study. Erythromycin was negative in an Ames assay. Erythromycin is not teratogenic in animal studies, and there was no evidence of fertility effects in rats fed up to 0.25 ppm (Abbott 2012, Abbott Laboratories 2006, Abbott Laboratories 2006). The point of departure for this erythromycin metabolite was the lowest therapeutic dose of erythromycin, 250 mg/day or 3.6 mg/kg/day. Erythromycin is typically given at 250 mg, four times a day (Abbott Laboratories 2006). A single 250 mg dose which has adverse events associated with it was used as the POD for this ADE calculation. The antibiotic activity level of effect was not used to drive the ADI because this is a metabolite and the metabolite is not active as an antibiotic. The POD of 250 mg/day or 3.6 mg/kg/day was adjusted by a UF_L of 3 to extrapolate to a NOEL. A UF_D of 10 was used to extrapolate from short-term patterns of therapeutic use to potential chronic exposure in this risk scenario, and by a UF_H of 3 to adjust for intra-individual variability (Schwab et al. 2005). The ADE for erythromycin-H_2O is 40 μg/kg/day.

Fluoxetine

Fluoxetine (CAS# 54910-89-3) is a selective serotonin reuptake inhibitor (SSRI) used for treating depression in adults and children and for the treatment of premenstrual dysphoric disorder. The antidepressant, anti-obsessive-compulsive, and anti-bulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Fluoxetine is a white to off-white crystalline solid with a solubility of 14 mg/mL in water (Mallinckrodt 2007, TCI 2011). The elimination of fluoxetine is slow, with a half-life of 1 to 3 days; the active metabolite, norfluoxetine, has an elimination half-life of 4 to 16 days.

The starting daily dose is 20 mg/day. The acute oral LD_{50} in rats and mice is 452 and 248 mg/kg, respectively. Fluoxetine and norfluoxetine have not shown genotoxic effects in the assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells. Fluoxetine has shown no evidence of carcinogenicity in rats or mice over two years at doses up to 10 and 12 mg/kg/day. This is 1.2 and 0.7 times the MRHD maximum recommended human dose of 80 mg equivalent when compared on an mg/m^2 basis. In two fertility studies in rats at doses up to 7.5 and 12.5 mg/kg/day, no effects were observed (Mallinckrodt 2007). There was no evidence of teratogenicity following dosages of 12.5 and 15 mg/kg/day in rats and rabbits, respectively. There was an increase in stillborn pups at 7.5 mg/kg/day in reproduction studies. The no-effect level for pup mortality is 5 mg/kg/day, an equivalent of 0.6 times the maximum recommended human dose on an mg/m^2 basis.

Fluoxetine is measured in breast milk; therefore, nursing while taking fluoxetine is not recommended (Mallinckrodt 2007, TEVA 2011).

The point of departure was the lowest therapeutic dose of 20 mg/day or 0.29 mg/kg/day based on a 70 kg person (Schwab et al. 2005, Mallinckrodt 2007). The point of departure was adjusted by a UF_L of 10 to extrapolate to a NOEL to potentially protect nursing infants and by a UF_H of 10 to adjust for intra-individual variability. No adjustment was included for animal-to-human data, as the point of departure is based on clinical data. Long-term studies are available; therefore, no adjustment is used for duration of studies and no change for data quality. The POD for fluoxetine is 0.29 mg/kg/day divided by a total UF of 100 for an ADE of 2.9 μg/kg/day rounded to 3 μg/kg/day.

Ibuprofen

Ibuprofen (CAS# 15687-27-1) is both an anti-inflammatory and an analgesic that is non-steroidal. It is a colorless, crystalline solid, which is very soluble in alcohol and water at up to 21 mg/L (ECB 2000, Durg.com 2011). The oral LD_{50} in rats ranged from 636 mg/kg to 969 mg/kg. In mice, the LD_{50} range is from 740 mg/kg to 897 mg/kg. In acute dog studies, 20 and 50 mg/kg were non-toxic. Doses of 125, 200 and 320 mg/kg caused gastric damage in dogs (ECB 2000, Apotex 2011). Ibuprofen is not carcinogenic in a two-year rat study at up to 180 mg/kg/day or in an 80-week study in mice at up to 300 mg/kg/day. Ibuprofen is not mutagenic in bacterial mutagenicity (Ames), sister chromatid assay, and chromosomal aberration assays. In a 13-week study, rats at 540

mg/kg died or needed to be euthanized. In other long-term studies, liver effects and gastrointestinal erosions occurred at doses of 8 mg/kg/day. In dogs over a 26-week study, 16 mg/kg/day caused gastrointestinal tract ulcerations. No ulcerations were seen at 4 mg/kg/day. Ibuprofen was not considered teratogenic or effecting fertility in rats or mice (ECB 2000, Durg.com 2011).

The lowest therapeutic dose in adults was 200 mg, but it can be taken every four to six hours. This is based on a point-of-departure of 200 mg and divided by 70 kg for adult weight equals 2.86 mg/kg. The lowest recommended child dose is 5 mg/kg (Durg.com 2011). The adult low therapeutic dose is used for the point of departure. This was adjusted by a UF_L of 3 to extrapolate to a NOEL, a UF_H of 3 to adjust for intra-individual variability, and by a UF_M of 3 for lack of a complete dataset because ibuprofen is an old pharmaceutical which does not have a complete set of data available as a new pharmaceutical (Schwab et al. 2005). No adjustment was used for animal-to-human as a point of departure in clinical data. No adjustment was used for duration of studies, as long-term marketing data is available. The ADE for ibuprofen is 107 μg/kg/day.

Minocycline

Minocycline (CAS# 10118-90-8) is a broad spectrum tetracycline antibiotic. This drug is used to treat acne, other skin infections, and Lyme disease. Minocycline is a bright yellow-orange solid that is very soluble in water (~52,000 mg/L). It has a half-life of 16-18 hours. Minocycline: Low therapeutic dose is about 1 mg/kg. The probable lethal dose for humans is 5 to 15 g/kg (HSDB 2002). Minocycline should not be given to

women in the last half of pregnancy, as it could affect skeletal growth in fetuses and discolor teeth, similar to tetracycline. Minocycline does not impact fertility in males or females up to 300 mg/kg, which is estimated to be equivalent to 40 times the clinical dose in man. Minocycline does cross to the placenta. Developmental toxicity begins at 10 mg/kg/day; reproductive effects start at 50 mg/kg/day, and fertility effects begin at 100 mg/kg/day in rats and increase with increased dose in rats. The 10 mg/kg/day systemic exposure in rats is similar to clinical exposure in man. Tetracycline minocycline is expected to cross the placenta, distribute with breast milk, and will discolor teeth.

Minocycline is not mutagenic in in-vitro bacterial reverse mutation assay (Ames) or Chinese Hamster Ovary mammalian cell assay, with or without metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test. Minocycline was not tested for carcinogenicity, but for a structurally related compound, oxytetracycline, which was found to produce adrenal and pituitary tumors in rats. Dietary administration of Minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs (HSDB 2002, Medicis 2011).

The point of departure was the lowest therapeutic dose of 45 mg. In a 70 kg person, this equals 0.6 mg/kg/day (Medicis 2011, Monk et al. 1987). This was adjusted by a UF_L of 3 to extrapolate to a NOEL, by a UF_H of 3 to adjust for intra-individual variability, and a UF_M of 5 as minocycline will discolor teeth and produce an uncertain

level of reproductive effects in humans vs. rats. No UF was used for species changes, as the data are from clinical dose recommendations or for duration-of-study data. The POD of 0.6 mg/kg/day has been divided by a total UF of 45 for an ADE for minocycline of 14 μg/kg/day.

Sulfamethizole

Sulfamethizole (CAS# 144-82-1) is a broad spectrum antibiotic against gram-positive and gram-negative bacteria. Sulfamethizole is rapidly and almost completely absorbed by the body (70-100%). Most of sulfamethizole is also excreted in the urine, about 95% (Drug.com 1995). Sulfamethizole is not acutely toxic with an LD_{50} in rats of 3500 mg/kg and an LD_{50} in mice of 1000 mg/kg. It is also soluble in water and somewhat soluble in acetone and methanol (Science Lab.com 2005). Long-term studies to examine carcinogenicity have not been completed. Rats are susceptible to getting goiters after repeated sulfonamides exposure, and long-term administration has produced thyroid effects. Fertility and mutagenicity studies have not been conducted with sulfamethizole. In high dose animal studies, reproductive effects (cleft palate and other bony abnormalities) have been observed in sulfonamides in general. Epidemiology studies have shown a non-significant increase in miscarriages. Sulfonamides in general are distributed into breast milk. Sulfonamide use by pregnant women is not recommended (Drug.com 1995, Ratanajamit et al. 2003).

The point of departure would traditionally be the lowest therapeutic dose of 500 mg/day or 7.14 mg/kg/day. First, the point of departure was adjusted by a UF_L of 3 to

extrapolate to a NOEL and then by a UF_H of 3 to adjust for intra-individual variability. Then a UF_M of 10 is used as sulfamethizole has reproductive effects in animals at higher doses. The ADE as calculated is 79 μg/kg/day using the traditional approach. This ADE is higher than that of the food residue level recommended by the FDA. Based on the FDA Milk Safety References, a level of 10 μg/kg/day is used for the sulfamethizole ADE in this research (Hennes 2005).

Sulfamethoxazole

Sulfamethoxazole (CAS# 723-46-6) is a sulfur antibiotic that is a white to practically white fine crystalline powder. It is almost odorless and soluble in water up to 136 mg/L and easily soluble in acetone and slightly soluble in chloroform and ether. Its biological half-life in about 10 hours after being rapidly absorbed (Roche 2010a, Medisca 2007).

In rats the oral LD_{50} is 6300 mg/kg and the LD_{50} in mice is 2300 mg/kg; therefore, sulfamethoxazole is not considered acutely toxic. Sulfamethoxazole is not mutagenic in multiple in-vitro and in-vivo test systems. Rats are susceptible to getting goiters after repeated sulfonamides exposure, and long-term administration has produced adverse thyroid effects (Drug.com 1995). Sulfamethoxazole does not lower parental fertility at up to 200 mg/kg/day in rats. It is not teratogenic in man at therapeutic doses, but in high-dose animal studies, reproductive effects (cleft palate and other bony abnormalities) have been observed in sulfonamides, and epidemiology studies have

shown a non-significant increase in miscarriages (Ratanajamit et al. 2003, Roche 2010a, Merck).

The point of departure is a food residue level in meat based on a NOEL level in rats of 2.2 mg/kg/day (JECFA 1990). This was adjusted by a UF_A of 3 to extrapolate to humans from rats, by a UF_H of 3 to adjust for intra-individual variability, and a UF_M of 10 as sulfamethoxazole has a reproductive hazard potential in man, and at high doses, it can result in tumors (Schwab et al. 2005). There was no adjustment for duration of studies or quality of data, as this product has been on the veterinary market for a number of years. The ADE for sulfamethoxazole is 24 μg/kg/day.

Trimethoprim

Trimethoprim (CAS# 738-70-5), a di-amino-pyrimidine veterinary antibiotic, is often part of a fixed dose regiment (1:5) with a sulfonamide antibiotic (AR Scientific 2010). Trimethoprim is a white to cream-colored crystalline powder. It is soluble in most solvents including water at 300 mg/L, acetone at 2300 mg/L, ethanol 96% at 6200 mg/L and chloroform at 22200 mg/L (Roche 2010b, Watson 2000). Trimethoprim is rapidly and completely absorbed, reaching its peak in one to two hours. The elimination half-life is about 11 hours. The lowest typical therapeutic dose of trimethoprim is 100 mg as a maintenance dose (Watson 2000).

The LD_{50} for rat oral acute study is 2000 mg/kg and in mice the LD_{50} is 3960 mg/kg. No carcinogenicity studies have been conducted. Trimethoprim did not show

mutagenicity in an Ames assay. No chromosome damage was observed in the Chinese hamster ovary cell assay and concentrations about 500 times that of human plasma. At higher levels, some damage was seen in one study. No damage was seen in human leukocytes. In rat fertility and reproductive studies, adverse effects in males were not observed in oral dosages as high as 70 mg/kg/day, in females as high as 14 mg/kg/day (Watson 2000). At oral doses 40 times the typical dose in man, 200 mg/kg, teratogenic effects in rats such as cleft palates were observed. In rabbit studies, fetal loss was increased and associated with doses 6 times the therapeutic dose in man (Watson 2000). Based on the above data, a point of departure of 14 mg/kg/day with an uncertainty factor of a UF_L of 3 to extrapolation from a LOEL to a NOEL is used. To account for adjustment between animal and human data a UF_H of 3 was used. Long-term studies are available so there was no adjustment for the study duration. Rather, there was a UF for inter-human variability, which was used with a factor of 3. Finally, a UF_M of 10 for the reproduction hazard in children and pregnant women as a precaution resulted in an ADE of 52 μg/kg/day. In 1997 the European Agency for the Evaluation of Medicinal Products (EMEA) published an ADE for trimethoprim as a food residue (EMEA 1997). This is based on trimethoprim's microbial resistance potential where the in vitro minimum concentration caused 50% inhibition (MIC_{50}) in this case the human gut flora. This ADE is lower than ADEs based on the therapeutic dose or toxicological endpoints. The European Medicines Agency (EMA) food residue ADE is 4 μg/kg/day and is used for this assessment (EMEA 1997).

Appendix 3: Interaction Determination List

Strong Effects:

Erythromycin & Diltiazem: (5x)

Diltiazem is considered a potent inhibitor of CYP450-3A4 enzyme. Co-administration of diltiazem can increase the plasma levels of erythromycin. A prolonged QT interval has been observed after erythromycin use. It may trigger other cardiovascular effects as well (Drug.com 2011). An epidemiology retrospective study of 1476 cases looked at confirmed sudden death from cardiac causes (Osborne 2005). Erythromycin and (diltiazem or verapamil in these cases) was linked with an increase in the risk of sudden death from cardiac causes. The risk was calculated to be five times higher than those who did not use CYP450-3A4 inhibitors (Drug.com 2011, Osborne 2005).

Moderate Effects:

Erythromycin & Carbamazepine: (4.3x)

A significant increase in carbamazepine serum level can be caused by macrolide antibiotics. Carbamazepine and erythromycin are impacted by CYP450-3A4 enzyme metabolism. Severe toxicity effects from carbamazepine have been reported (Drug.com 2011). There are two case studies reported in the literature measured the increase in serum levels of carbamazepine after erythromycin co-administration. In both cases carbamazepine is increased multiple times when comparing the measured plasma

concentrations before and after erythromycin treatment. In cases cited 2.1 to 4.3 times the pre-dose levels of carbamazepine (MacNab et al. 1987, Zitelli et al. 1987). The increase resulted in carbamazepine toxicity that including lethargy, and cardiovascular effects.

In MacNab, the patient's carbamazepine plasma level was AUC = 9.0 μg/mL, when measured during routine blood work, three weeks before receiving erythromycin. The text of article states 9.0 mg/mL but normal therapeutic range 8 to 12 μg/mL is noted later in the article. After taking a prescription of erythromycin, dosed at 125 mg for 4x a day for 4 days, drowsiness increased. The patient's plasma level was AUC = 39 μg/mL a 4.3 fold increase in carbamazepine. In a case presented by Zitelli an increase from 11.9 mg/L (μg/mL) to 25.8 mg/L (μg/mL) was measured after 5 days of erythromycin. This is a 2.2 fold increase (Zitelli et al. 1987).

Erythromycin & Fluoxetine: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used. Effects also noted based on drug class (Drug.com 2011).

Fluoxetine & Carbamazepine: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used. Effects also noted based on drug class (Drug.com 2011).

Diphenhydramine & Fluoxetine: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used. Effects also noted based on drug class (Drug.com 2011).

Codeine & Diltiazem: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used (Drug.com 2011).

Ibuprofen & Diltiazem: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used (Drug.com 2011).

Ciprofloxacin & Erythromycin: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used. The database description considers this a two-way interaction (Drug.com 2011).

Codeine & Nifedipine: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used (Drug.com 2011).

Ibuprofen & Nifedipine: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used (Drug.com 2011).

Codeine & Carbamazepine: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used. The database description considers this a two-way interaction (Drug.com 2011).

Carbamazepine & Diltiazem: (3.1x Default)

Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used (Drug.com 2011).

Fluoxetine & Ibuprofen: (3.1x Default)

Serotonin reuptake inhibitors (SRI) have had bleeding reactions noted and NSAID have gastrointestinal tract bleeding history (Drug.com 2011). No identified AUC fold increases a default value of (3.1x) will be used (Drug.com 2011).

Carbamazepine & Diphenhydramine: (3.1x Default)

Diphenhydramine is a first generation H1 antihistamine limited by its sedative effects (Yap, Camm 1999). Carbamazepine has nervous system, narcotic effects, in some patients, including dizziness, drowsiness and fatigue among other adverse effects

(Novartis 2011). The combination of drugs affecting the central nervous system can have a compounding effect (Drug.com 2011). No quantifiable AUC change found in the literature. Based on the drug.com database classification a moderate default value of 3.1 from Table 3 will be used (Drug.com 2011).

Diltiazem & Nifedipine: (3x)

The increase in nifedipine AUC when given to patients on diltiazem ranges from (2.2x, 3.0x, 3.1x) in two studies (Fahmi et al. 2008, Tateishi et al. 1989). The database description also considers this a two-way interaction (Drug.com 2011).

Weak Effects:

Ibuprofen & Ciprofloxacin: (2x)

In a study looking at quinolone levels in facial tissue after dental work in rats, the serum levels of ciprofloxacin were doubled (2x) when co-administered with ibuprofen (Trichilis et al. 2003). In a mouse intravenous study looking for brain activity corresponding to convulsant activity the ED_{50} for ciprofloxacin changed from 17 nmol to 24.2 nmol a 1.4 fold increase when ciprofloxacin and ibuprofen were co-administered but was not considered significant in this study (Hori, Kizu & Kawamura 2003).

Erythromycin & Nifedipine: (1.7x)

When pretreated with erythromycin dogs have an increased nifedipine plasma (AUC) measurements at 1.66 times, rounded to 1.7, higher in plasma (Tsuruta et al. 1997).

Ciprofloxacin & Caffeine: (1.6x)

Caffeine plasma levels have been shown to be increased by quinolones. Pipemidic increases caffeine 2-3 times based on AUC and enoxicin increased caffeine 2-5 times in plasma (Drug.com 2011). The impact of ciprofloxacin on caffeine was found to be dose dependent in reducing clearance rate (Ludwig et al. 1990). At 250 mg bid of ciprofloxacin reduced the metabolism of caffeine hence increasing the AUC. At 100 mg no effect on caffeine was measured, but a slight change in *para*-xanthine the primary metabolite of caffeine. At doses less the 100 bib no effect on caffeine would be expected. Doses of 100, 250 and 500 mg were given to healthy volunteers (Hisaka et al. 2010). AUC increased from 21.4 to 25.0, 22.4 to 35.2 and 20.4 to 32.2 in three increasing doses of ciprofloxacin are (1.17, 1.57, and 1.57) times the AUC concentration of caffeine the values will be rounded to (1.6x) (Harder et al. 1988).

Sulfamethoxazole & Erythromycin: (1.5 x Default)

Based on the drug.com database classification a weak default value of 1.5 from Table 3 will be used (Drug.com 2011).

Sulfamethoxazole & Ciprofloxacin: (1.5x Default)

Based on the drug.com database classification a weak default value of 1.5 from Table 3 will be used (Drug.com 2011).

Fluoxetine & Codeine: (1.5x)

Codeine conversion to morphine is regulated by the CYP450-2D6. Reduced regulation by the 2D6 iso-enzyme can reduce the conversion to morphine and reduce pain relief in patients (Drug.com 2011). The interaction between codeine and fluoxetine is expected to be the same as methadone and fluoxetine (Ferrari et al. 2004).

Drugs that are inhibitors of CYP450 2D6 may interfere with the analgesic effect of codeine. The mechanism is decreased in vivo conversion of codeine to morphine, a metabolic reaction mediated by CYP450 2D6. The possibility of reduced or inadequate pain relief should be considered in patients receiving codeine with drugs that inhibit CYP450 2D6. An increase in the codeine dosage or a different analgesic agent may be necessary in patients requiring therapy with CYP450 2D6 inhibitors (Drug.com 2011).

Carbamazepine & Acetaminophen: (1.5x)

Data suggests the presence of carbamazepine could increase the hepatotoxicity potential of acetaminophen. It is thought that carbamazepine increases the CYP450

metabolism of acetaminophen which leads to an increase of hepatotoxic metabolites (Drug.com 2011).

Diphenhydramine & Diltiazem: (1.4x)

Diphenhydramine is a first generation H1 antihistamine limited by its sedative effects (Yap, Camm 1999). Diltiazem is considered a potent inhibitor of CYP450-3A4 enzyme. In an in-vitro rat liver infusion study, the addition of diphenhydramine to a steady state presence of diltiazem increase the diltiazem concentration levels by 45% with rabid onset after beginning infusion (Hussain et al. 1994).

No Effect:

Nicotine & Caffeine: (1.1x)

A study has noted significant interaction potential but there is no quantifiable data. As this is a common mixture serious adverse events would have been readily apparent (Drug.com 2011).

Trimethoprim and Sulfamethoxazole (1.1x)

There has been no interaction between trimethoprim and sulfamethoxazole identified with in the adverse effects and clinical measurement in one paper but effect are noted in these drug classes (Drug.com 2011, Bottiger et al. 2005).

Fluoxetine and Nifedipine (1.0x)

No increase expected/reported (Ohno, Hisaka & Suzuki 2007).

Codeine & Diphenhydramine: (0.7x)

Diphenhydramine is an inhibitors of CYP450 2D6 and may interfere with codeines therapeutic effect. The decreased conversion of codeine to morphine is mediated by CYP450 2D6 (Drug.com 2011). In intestinal and brain cell (in-vitro) diphenhydramine has shown interference of greater than 30% with codeine uptake potentially reducing codeine efficacy (Fischer et al. 2010).

Nifedipine & Carbamazepine: (0.4x)

Carbamazepine is an inducer of CYP450 3A4 and 2C19. When 3A4 inducers have been co-administered with nifedipine, increases in the nifedipine dose has been recommended because of reduced efficacy (TEVA 2008, Flockhart 2007). Nifedipine as a calcium channel blocker may conversely reduce 3A4 metabolism and increase carbamazepine plasma levels (Drug.com 2011, Flockhart 2007). The clinical simulation using nifedipine and similar inducers predict a 0.4x change nifedipine plasma levels (Xu et al. 2011).

Appendix 4: Individual Sample Mixture Calculations

Matchaponix Brook

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.027	84.38	2	10	70	7.71E-05	1.000	1-2	1	1	0.8491	1.0000	0.0000771
Cotinine	2	0.005	15.63	2	6	70	2.38E-05	1.000	2-1	1.1	1	0.8491	1.0843	0.0000258
		0.032					1.01E-04							0.0001030
							Sum of HQ - simple							Sum of HQ with Interaction

Passaic River-1

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.0095	27.07	2	10	70	2.71E-05	0.8911	1-2	1	1	0.9194	0.8911	0.000024
Carbamazepine	2	0.024	68.38	2	11	70	6.23E-05	0.1089	1-3	1	1	0.8274	0.1089	0.000003
Cotinine	3	0.0016	4.56	2	6	70	7.62E-06	0.2192	2-3	1	1	0.6231	0.2192	0.000014
		0.0351					9.71E-05	0.7808	2-1	1	1	0.9194	0.7808	0.000049
							Sum of HQ - simple	0.3033	3-1	1.1	1	0.8274	0.3282	0.000003
								0.6967	3-2	1	1	0.6231	0.6967	0.000005
														0.000097

Sum of HQ with Interaction

Musconetcong River

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Acetaminophen	1	0.003	7.69	2	516	70	1.66E-07	1.000	1-2	1	1	0.0802	1.0000	0.000000
Caffeine	2	0.036	92.31	2	10	70	1.03E-04	1.000	2-1	1	1	0.0802	1.0000	0.000103
		0.039					1.03E-04							0.000103
							Sum of HQ - simple							Sum of HQ with Interaction

Raritan River

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.01	25.97	2	10	70	2.86E-05	0.7958	1-2	1	1	0.9213	0.7958	0.000023
Carbamazepine	2	0.025	64.94	2	11	70	6.49E-05	0.2042	1-3	1	1	0.9648	0.2042	0.000006
Cotinine	3	0.0035	9.09	2	6	70	1.67E-05	0.3684	2-3	1	1	0.8063	0.3684	0.000024
		0.0385					1.10E-04	0.6316	2-1	1	1	0.9213	0.6316	0.000041
							Sum of HQ - simple	0.3056	3-1	1.1	1	0.9648	0.3350	0.000006
								0.6944	3-2	1	1	0.8063	0.6944	0.000012
														0.000111

Sum of HQ with Interaction

Whippany River-1

	Chem Num	Stream Conc. µg/L	% mix	Ingdw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.016	31.31	2	10	70	4.57E-05	0.8955	1-2	1	1	0.9526	0.8955	0.000041
Carbamazepine	2	0.033	64.58	2	11	70	8.57E-05	0.1045	1-3	1	1	0.7675	0.1045	0.000005
Cotinine	3	0.0021	4.11	2	6	70	1.00E-05	0.1795	2-3	1	1	0.6118	0.1795	0.000015
		0.0511					1.41E-04	0.8205	2-1	1	1	0.9526	0.8205	0.000070
							Sum of HQ - simple	0.3478	3-1	1.1	1	0.7675	0.3742	0.000004
								0.6522	3-2	1	1	0.6118	0.6522	0.000007
														0.000142

Sum of HQ with Interaction

North Branch Raritan River-1

	Chem Num	Stream µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.0073	2.83	2	10	70	0.00002	0.4093	1-2	1	1	0.8852	0.4093	0.000009
Carbamazepine	2	0.022	8.54	2	11	70	0.00006	0.1699	1-3	1	1	0.9979	0.1699	0.000004
1,7-Dimethylxanthine	3	0.0083	3.22	2	10	70	0.00002	0.4208	1-4	1	1	0.8795	0.4208	0.000009
Ibuprofen	4	0.22	85.40	2	107	70	0.00006	0.2019	2-1	1	1	0.8852	0.2019	0.000012
		0.2576						0.2295	2-3	1	1	0.9105	0.2295	0.000013
							0.000160	0.5686	2-4	1	1	0.9999	0.5686	0.000032
							Sum of HQ - simple	0.1525	3-1	1	1	0.9979	0.1525	0.000004
								0.4179	3-2	1	1	0.9105	0.4179	0.000010
								0.4296	3-4	1	1	0.9053	0.4296	0.000010
								0.2051	4-1	1	1	0.8795	0.2051	0.000012
								0.5618	4-2	1	1	0.9999	0.5618	0.000033
								0.2331	4-3	1	1	0.9053	0.2331	0.000014
														0.00016
														Sum of HQ with Interaction

Assunpink Creek

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)
Acetaminophen	1	0.0124	14.57	2	516	70	6.87E-07
Carbamazepine	2	0.047	55.23	2	11	70	1.22E-04
Cotinine	3	0.0194	22.80	2	6	70	9.24E-05
Dehydronifedipine	4	0.0063	7.40	2	100	70	1.80E-06
		0.0851					
							2.17E-04
							Sum of HQ - simple

f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
0.5645	1-2	1	1	0.1492	0.5645	0.00000039
0.4272	1-3	1	1	0.1711	0.4272	0.00000029
0.0083	1-4	1	1	0.8942	0.0083	0.00000001
0.0072	2-1	1.5	1	0.1492	0.0077	0.00000094
0.9738	2-3	1	1	0.9904	0.9738	0.00011888
0.0190	2-4	1	1	0.2393	0.0190	0.00000232
0.0055	3-1	1	1	0.1711	0.0055	0.00000051
0.9800	3-2	1	1	0.9904	0.9800	0.00009054
0.0145	3-4	1	1	0.2738	0.0145	0.00000133
0.0032	4-1	1	1	0.8942	0.0032	0.00000001
0.5674	4-2	0.4	-1	0.2393	0.7065	0.00000127
0.4294	4-3	1	1	0.2738	0.4294	0.00000077
						0.00022
						Sum of HQ with Interaction

Passaic River-2

Chem	Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.017	26.98	2	10	70	0.000049	1.0000	1-2	1	1	0.9066	1.0000	0.000049
Carbamazepine	2	0.046	73.02	2	11	70	0.000119	1.0000	2-1	1	1	0.9066	1.0000	0.000119
		0.063					0.000168							0.000168
							Sum of HQ - simple							Sum of HQ with Interaction

Millstone River

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.033	50.46	2	10	70	9.43E-05	0.5979	1-2	1	1	0.9498	0.5979	0.0000564
Carbamazepine	2	0.019	29.05	2	11	70	4.94E-05	0.0245	1-3	1	1	0.4967	0.0245	0.0000023
Cotinine	3	0.0014	2.14	2	6	70	6.67E-06	0.3776	1-4	1	1	0.8844	0.3776	0.0000356
1,7-Dimethylxanthine	4	0.012	18.35	2	10	70	3.43E-05	0.7209	2-1	1	1	0.9498	0.7209	0.0000356
		0.0654						0.0170	2-3	1	1	0.6476	0.0170	0.0000008
							1.85E-04	0.2621	2-4	1	1	0.9836	0.2621	0.0000129
							Sum of HQ - simple	0.5156	3-1	1.1	1	0.4967	0.5406	0.0000036
								0.2969	3-2	1	1	0.6476	0.2969	0.0000020
								0.1875	3-4	1.1	1	0.7383	0.2012	0.0000013
								0.6253	4-1	1	1	0.8844	0.6253	0.0000214
								0.3600	4-2	1	1	0.9836	0.3600	0.0000123
								0.0147	4-3	1	1	0.7383	0.0147	0.0000005
														0.00018

Sum of HQ with Interaction

Whippany River-2

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Carbamazepine	1	0.058	63.04	2	11	70	1.51E-04	0.0960	1-2	1	1	0.2475	0.0960	0.0000145
Cotinine	2	0.0005	0.54	2	6	70	2.38E-06	0.0403	1-3	1	1	0.1619	0.0403	0.0000061
Dehydronifedipine	3	0.0035	3.80	2	100	70	1.00E-06	0.8637	1-4	1	1	0.6604	0.8637	0.0001301
Erythromycin-H2O	4	0.03	32.61	2	40	70	2.14E-05	0.8704	2-1	1	1	0.2475	0.8704	0.0000021
		0.092						0.0058	2-3	1	1	0.9128	0.0058	0.000000014
							1.89E-04	0.1238	2-4	1	1	0.6000	0.1238	0.0000003
								0.8635	3-1	0.4	-1	0.1619	1.0016	0.0000010
							Sum of HQ - simple	0.0042	3-2	1	1	0.9128	0.0136	0.000000014
								0.1228	3-4	1	1	0.4128	0.1228	0.0000001
								0.9781	4-1	4.3	1	0.6604	2.5626	0.0000549
								0.0155	4-2	1	1	0.6000	0.0155	0.0000003
								0.0065	4-3	1.7	1	0.4128	0.0081	0.0000002
														0.00021

Sum of HQ with Interaction

Dead River

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)
Caffeine	1	0.016	8.27	2	10	70	4.57E-05
Carbamazepine	2	0.119	61.50	2	11	70	3.09E-04
Cotinine	3	0.0043	2.22	2	6	70	2.05E-05
Dehydronifedipine	4	0.0042	2.17	2	100	70	1.20E-06
Sulfamethoxazole	5	0.05	25.84	2	24	70	5.95E-05
		0.194					
							0.000436
							Sum of HQ - simple

f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
0.7920	1-2	1	1	0.6701	0.7920	0.0000362
0.0525	1-3	1	1	0.9245	0.0525	0.0000024
0.0031	1-4	1	1	0.3157	0.0031	0.0000001
0.1525	1-5	1	1	0.9914	0.1525	0.0000070
0.3602	2-1	1	1	0.6701	0.3602	0.0001113
0.1613	2-3	1	1	0.4828	0.1613	0.0000499
0.0095	2-4	1	1	0.1241	0.0095	0.0000029
0.4690	2-5	1	1	0.7359	0.4690	0.0001450
0.1100	3-1	1.1	1	0.9245	0.1201	0.0000025
0.7438	3-2	1	1	0.4828	0.7438	0.0000152
0.0029	3-4	1	1	0.4574	0.0029	0.00000006
0.1432	3-5	1	1	0.8728	0.1432	0.0000029
0.1051	4-1	1	1	0.3157	0.1051	0.0000001
0.7109	4-2	0.4	-1	0.1241	0.7965	0.0000010
0.0471	4-3	1	1	0.4574	0.0471	0.00000006
0.1369	4-5	1	1	0.2784	0.1369	0.0000002
0.1214	5-1	1	1	0.9914	0.1214	0.0000072
0.8210	5-2	1	1	0.7359	0.8210	0.0000489
0.0544	5-3	1	1	0.8728	0.0544	0.0000032
0.0032	5-4	1	1	0.2784	0.0032	0.0000002
						0.000436
						Sum of HQ with Interaction

Passaic River-3

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.0233	10.81	2	10	70	0.000067	0.9792	1-2	1	1	0.6239	0.9936	0.000066
Carbamazepine	2	0.19	88.17	2	11	70	0.000494	0.0208	1-3	1	1	0.4352	0.0064	0.0000004
Cotinine	3	0.0022	1.02	2	6	70	0.000010	0.1360	2-3	1	1	0.1594	0.0498	0.000027
		0.2155					0.000571	0.8640	2-1	1	1	0.6239	0.9502	0.000516
								0.1189	3-1	1.1	1	0.4352	0.1139	0.0000004
								0.8811	3-2	1	1	0.1594	0.8908	0.000003
														0.000613

Singac Brook

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.18	42.84	2	10	70	5.14E-04	0.6623	1-2	1	1	0.8249	0.6623	0.00034
Carbamazepine	2	0.055	13.09	2	11	70	1.43E-04	0.1148	1-3	1	1	0.4187	0.1148	0.00006
Cotinine	3	0.0052	1.24	2	6	70	2.48E-05	0.2228	1-4	1	1	0.5592	0.2228	0.00011
Ibuprophen	4	0.18	42.84	2	107	70	4.81E-05	0.8760	2-1	1	1	0.8249	0.8760	0.00013
		0.4202						0.0422	2-3	1	1	0.7097	0.0422	0.000006
							0.000730	0.0819	2-4	1	1	0.8680	0.0819	0.00001
							Sum of HQ - simple	0.7293	3-1	1.1	1	0.4187	0.7590	0.00002
								0.2026	3-2	1	1	0.7097	0.2026	0.000005
								0.0682	3-4	1	1	0.9474	0.0682	0.000002
								0.7542	4-1	1	1	0.5592	0.7542	0.00004
								0.2095	4-2	1	1	0.8680	0.2095	0.00001
								0.0363	4-3	1	1	0.9474	0.0363	0.000002
														0.00073
														Sum of HQ with Interaction

Lamington River-1

	Chem Num	Stream Conc. µg/L	% mix	Ing dw L	ADI mg/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Acetaminophen	1	0.023	6.4	2	516	70	1.27E-06	0.3599	1-2	1	1	0.1268	0.3599	0.0000005
Caffeine	2	0.110	30.4	2	10	70	3.14E-04	0.1755	1-3	1	1	0.1808	0.1755	0.0000002
Carbamazepine	3	0.059	16.3	2	11	70	1.53E-04	0.1243	1-4	1	1	0.2141	0.1243	0.0000002
Codeine	4	0.008	2.1	2	2	70	1.09E-04	0.1636	1-5	1	1	0.1872	0.1636	0.0000002
Cotinine	5	0.030	8.3	2	6	70	1.43E-04	0.0006	1-6	1	1	0.8941	0.0006	0.000000001
Dehydronifedipine	6	0.002	0.5	2	100	70	4.86E-07	0.0065	1-7	1	1	0.7721	0.0065	0.00000001
Diltiazem	7	0.003	0.8	2	14	70	5.71E-06	0.1145	1-8	1	1	0.2229	0.1145	0.0000001
1,7-Dimethylxanthine	8	0.035	9.7	2	10	70	1.00E-04	0.0300	1-9	1	1	0.4206	0.0300	0.0000000
Diphenhydramine	9	0.011	3.0	2	12	70	2.62E-05	0.0251	1-10	1	1	0.4558	0.0251	0.0000000
Ibuprofen	10	0.082	22.6	2	107	70	2.19E-05	0.0023	2-1	1	1	0.1268	0.0023	0.0000007
		0.362						0.2735	2-3	1	1	0.9388	0.2735	0.0000860
							0.00087	0.1938	2-4	1	1	0.8737	0.1938	0.0000609
					Sum of HQ - simple			0.2550	2-5	1	1	0.9270	0.2550	0.0000801
								0.0009	2-6	1	1	0.0785	0.0009	0.0000003
								0.0102	2-7	1	1	0.2649	0.0102	0.0000032
								0.1785	2-8	1	1	0.8558	0.1785	0.0000561
								0.0467	2-9	1	1	0.5329	0.0467	0.0000147
								0.0391	2-10	1	1	0.4935	0.0391	0.0000123
								0.0018	3-1	1.5	1	0.1808	0.0019	0.0000003
								0.4357	3-2	1	1	0.9388	0.4357	0.0000668
								0.1505	3-4	3.1	1	0.9853	0.4590	0.0000703
								0.1981	3-5	1	1	0.9994	0.1981	0.0000304

0.0007	3-6	1	1	0.1122	0.0007	0.0000001
0.0079	3-7	3.1	1	0.3723	0.0121	0.0000019
0.1386	3-8	1	1	0.9776	0.1386	0.0000212
0.0363	3-9	3.1	1	0.7061	0.0807	0.0000124
0.0304	3-10	1	1	0.6615	0.0304	0.0000047
0.0017	4-1	1	1	0.2141	0.0017	0.0000002
0.4103	4-2	1	1	0.8737	0.4103	0.0000445
0.2001	4-3	3.1	1	0.9853	0.6100	0.0000662
0.1865	4-5	1	1	0.9907	0.1865	0.0000202
0.0006	4-6	3.1	1	0.1332	0.0007	0.0000001
0.0075	4-7	3.1	1	0.4359	0.0122	0.0000013
0.1306	4-8	1	1	0.9992	0.1306	0.0000142
0.0342	4-9	1	1	0.7914	0.0342	0.0000037
0.0286	4-10	1	1	0.7474	0.0286	0.0000031
0.0017	5-1	1	1	0.1872	0.0017	0.0000002
0.4295	5-2	1.1	1	0.9270	0.4692	0.0000670
0.2094	5-3	1	1	0.9994	0.2094	0.0000299
0.1484	5-4	1	1	0.9907	0.1484	0.0000212
0.0007	5-6	1	1	0.1162	0.0007	0.00000009
0.0078	5-7	1	1	0.3846	0.0078	0.0000011
0.1367	5-8	1.1	1	0.9843	0.1501	0.0000214
0.0358	5-9	1	1	0.7237	0.0358	0.0000051
0.0299	5-10	1	1	0.6789	0.0299	0.0000043
0.0015	6-1	1	1	0.8941	0.0015	0.000000001
0.3596	6-2	1	1	0.0785	0.3596	0.0000002
0.1753	6-3	0.4	-1	0.1122	0.1943	0.0000001
0.1242	6-4	1	1	0.1332	0.1242	0.0000001

0.1634	6-5	1	1	0.1162	0.1634	0.00000008
0.0065	6-7	3	1	0.5374	0.0118	0.00000001
0.1144	6-8	1	1	0.1387	0.1144	0.0000001
0.0300	6-9	1	1	0.2674	0.0300	0.00000001
0.0251	6-10	1	1	0.2914	0.0251	0.00000001
0.0015	7-1	1	1	0.7721	0.0015	0.00000001
0.3617	7-2	1	1	0.2649	0.3617	0.0000021
0.1764	7-3	1	1	0.3723	0.1764	0.0000010
0.1250	7-4	1	1	0.4359	0.1250	0.0000007
0.1644	7-5	1	1	0.3846	0.1644	0.0000009
0.0006	7-6	3	1	0.5374	0.0010	0.00000001
0.1151	7-8	1	1	0.4522	0.1151	0.0000007
0.0301	7-9	1	1	0.7669	0.0301	0.0000002
0.0252	7-10	1	1	0.8103	0.0252	0.0000001
0.0016	8-1	1	1	0.2229	0.0016	0.0000002
0.4058	8-2	1	1	0.8558	0.4058	0.0000406
0.1979	8-3	1	1	0.9776	0.1979	0.0000198
0.1402	8-4	1	1	0.9992	0.1402	0.0000140
0.1844	8-5	1	1	0.9843	0.1844	0.0000184
0.0006	8-6	1	1	0.1387	0.0006	0.0000001
0.0074	8-7	1	1	0.4522	0.0074	0.0000007
0.0338	8-9	1	1	0.8111	0.0338	0.0000034
0.0283	8-10	1	1	0.7678	0.0283	0.0000028
0.0015	9-1	1	1	0.4206	0.0015	0.0000000
0.3705	9-2	1	1	0.5329	0.3705	0.0000097
0.1806	9-3	1	1	0.7061	0.1806	0.0000047
0.1280	9-4	0.7	-1	0.7914	0.1697	0.0000044

0.1684	9-5	1	1	0.7237	0.1684	0.0000044
0.0006	9-6	1	1	0.2674	0.0006	0.00000001
0.0067	9-7	1.4	1	0.7669	0.0087	0.0000002
0.1179	9-8	1	1	0.8111	0.1179	0.0000031
0.0258	9-10	1	1	0.9960	0.0258	0.0000007
0.0015	10-1	1	1	0.4558	0.0015	0.0000000
0.3686	10-2	1	1	0.4935	0.3686	0.0000081
0.1797	10-3	1	1	0.6615	0.1797	0.0000039
0.1273	10-4	1	1	0.7474	0.1273	0.0000028
0.1675	10-5	1	1	0.6789	0.1675	0.0000037
0.0006	10-6	3.1	1	0.2914	0.0008	0.00000002
0.0067	10-7	3.1	1	0.8103	0.0168	0.0000004
0.1173	10-8	1	1	0.7678	0.1173	0.0000026
0.0307	10-9	1	1	0.9960	0.0307	0.0000007
						0.000983

Sum of HQ with Interaction

Peckman River

	Chem Num	Stream	%	Ing	ADI	BW	HQ	f(jk)	Chems	M(jk)	B(jk)	g(jk)	f*M^Bg	HQj
		µg/L	mix	L	ug/kg/day	kg	(j)		Paired		WOE			
Acetaminophen	1	0.15	26.7	2	516	70	8.31E-06	0.6859	1-2	1	1	0.1950	0.6859	0.00001
Caffeine	2	0.3	53.4	2	10	70	8.57E-04	0.1060	1-3	1	1	0.4713	0.1060	0.00000
Carbamazepine	3	0.051	9.1	2	11	70	1.32E-04	0.1715	1-4	1	1	0.3791	0.1715	0.00000
Cotinine	4	0.045	8.0	2	6	70	2.14E-04	0.0366	1-5	1	1	0.7214	0.0366	0.00000
1,7-Dimethylxanthine	5	0.016	2.8	2	10	70	4.57E-05	0.0207	2-1	1	1	0.1950	0.0207	0.00002
		0.562						0.3305	2-3	1	1	0.6810	0.3305	0.00028
							1.26E-03	0.5347	2-4	1	1	0.8000	0.5347	0.00046
							Sum of HQ -	0.1141	2-5	1	1	0.4385	0.1141	0.00010
								0.0074	3-1	1.5	1	0.4713	0.0089	0.000001
								0.7616	3-2	1	1	0.6810	0.7616	0.00010
								0.1904	3-4	1	1	0.9718	0.1904	0.00003
								0.0406	3-5	1	1	0.8735	0.0406	0.00001
								0.0080	4-1	1	1	0.3791	0.0080	0.000002
								0.8213	4-2	1.1	1	0.8000	0.8864	0.00019
								0.1269	4-3	1	1	0.9718	0.1269	0.00003
								0.0438	4-5	1.1	1	0.7613	0.0471	0.00001
								0.0069	5-1	1	1	0.7214	0.0069	0.00000
								0.7071	5-2	1	1	0.4385	0.7071	0.00003
								0.1093	5-3	1	1	0.8735	0.1093	0.000005
								0.1768	5-4	1	1	0.7613	0.1768	0.00001
														0.00127

Sum of HQ with Interaction

Rockaway River

	Chem Num	Stream Conc µg/L	% mix	Ing Rate L	ADI ug/kg/day	BW kg	HQ (j)
Caffeine	1	0.028	7.04	2	10	70	8.00E-05
Carbamazepine	2	0.055	13.84	2	11	70	1.43E-04
Codeine	3	0.029	7.30	2	2	70	4.14E-04
Cotinine	4	0.022	5.53	2	6	70	1.05E-04
Diltiazem	5	0.0043	1.08	2	14	70	8.78E-06
Diphenhydramin	6	0.0092	2.31	2	12	70	2.19E-05
Sulfamethoxazole	7	0.21	52.83	2	24	70	2.50E-04
Trimethoprim	8	0.04	10.06	2	4	70	2.86E-04
		0.3975					
							0.001253
							Sum of HQ - simple

f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
0.1163	1-2	1	1	0.9594	0.1163	0.000009
0.3373	1-3	1	1	0.7366	0.3373	0.000027
0.0853	1-4	1	1	0.9910	0.0853	0.000007
0.0071	1-5	1	1	0.5969	0.0071	0.000001
0.0178	1-6	1	1	0.8216	0.0178	0.000001
0.2035	1-7	1	1	0.8571	0.2035	0.000016
0.2326	1-8	1	1	0.8268	0.2326	0.000019
0.0686	2-1	1	1	0.9594	0.0686	0.000005
0.3555	2-3	3.1	1	0.8733	0.9548	0.000136
0.0899	2-4	1	1	0.9881	0.0899	0.000013
0.0075	2-5	3.1	1	0.4670	0.0128	0.000002
0.0188	2-6	3.1	1	0.6790	0.0405	0.000006
0.2145	2-7	1	1	0.9621	0.2145	0.000031
0.2452	2-8	1	1	0.9428	0.2452	0.000035
0.0895	3-1	1	1	0.7366	0.0895	0.000037
0.1598	3-2	3.1	1	0.8733	0.4292	0.000178
0.1172	3-4	1	1	0.8027	0.1172	0.000049
0.0098	3-5	3.1	1	0.2850	0.0136	0.000006
0.0245	3-6	1	1	0.4368	0.0245	0.000010
0.2796	3-7	1	1	0.9689	0.2796	0.000116
0.3196	3-8	1	1	0.9830	0.3196	0.000132
0.0665	4-1	1.1	1	0.9910	0.0731	0.000008
0.1187	4-2	1	1	0.9881	0.1187	0.000012
0.3442	4-3	1	1	0.8027	0.3442	0.000036
0.0073	4-5	1	1	0.5341	0.0073	0.000001
0.0182	4-6	1	1	0.7564	0.0182	0.000002

0.2077	4-7	1	1	0.9124	0.2077	0.000022
0.2374	4-8	1	1	0.8861	0.2374	0.000025
0.0616	5-1	1	1	0.5969	0.0616	0.000001
0.1099	5-2	1	1	0.4670	0.1099	0.000001
0.3188	5-3	1	1	0.2850	0.3188	0.000003
0.0806	5-4	1	1	0.5341	0.0806	0.000001
0.0169	5-6	1	1	0.90381	0.0169	0.000000
0.1924	5-7	1	1	0.36200	0.1924	0.000002
0.2199	5-8	1	1	0.34006	0.2199	0.000002
0.0622	6-1	1	1	0.82158	0.0622	0.000001
0.1111	6-2	1	1	0.67904	0.1111	0.000002
0.3221	6-3	0.7	-1	0.43679	0.3763	0.000008
0.0814	6-4	1	1	0.75638	0.0814	0.000002
0.0068	6-5	1.4	1	0.90381	0.0092	0.000000
0.1943	6-7	1	1	0.54432	0.1943	0.000004
0.2221	6-8	1	1	0.51434	0.2221	0.000005
0.0756	7-1	1	1	0.85710	0.0756	0.000019
0.1350	7-2	1	1	0.96209	0.1350	0.000034
0.3915	7-3	1	1	0.96894	0.3915	0.000098
0.0990	7-4	1	1	0.91236	0.0990	0.000025
0.0083	7-5	1	1	0.36200	0.0083	0.000002
0.0207	7-6	1	1	0.54432	0.0207	0.000005
0.2700	7-8	1	1	0.99778	0.2700	0.000067
0.0782	8-1	1	1	0.82680	0.0782	0.000022
0.1397	8-2	1	1	0.94281	0.1397	0.000040
0.4051	8-3	1	1	0.98299	0.4051	0.000116
0.1024	8-4	1	1	0.88614	0.1024	0.000029
0.0086	8-5	1	1	0.34006	0.0086	0.000002
0.0214	8-6	1	1	0.51434	0.0214	0.000006

0.2445	8-7	1.1	1	0.99778	0.2689	0.000077
						0.001516

Sum of HQ with Interaction

Hohokus Brook-1

	Chem Num	Stream µg/L	% mix	Ing dw L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Caffeine	1	0.047	7.1	2	10	70	1.34E-04	0.1306	1-2	1	1	0.9480	0.1306	0.000018
Carbamazepine	2	0.100	15.1	2	11	70	2.60E-04	0.2155	1-3	1	1	0.8524	0.2155	0.000029
Ciprofloxacin	3	0.030	4.5	2	2	70	4.29E-04	0.0675	1-4	1	1	1.0000	0.0675	0.000009
Codeine	4	0.009	1.4	2	2	70	1.34E-04	0.0287	1-5	1	1	0.9152	0.0287	0.000004
Cotinine	5	0.012	1.8	2	6	70	5.71E-05	0.1666	1-6	1	1	0.9060	0.1666	0.000022
1,7-Dimethylxanthine	6	0.116	17.5	2	10	70	3.31E-04	0.0104	1-7	1	1	0.6805	0.0104	0.000001
Diphenhydramine	7	0.009	1.3	2	12	70	2.07E-05	0.0934	1-8	1	1	0.9870	0.0934	0.000013
Erythromycin–	8	0.260	39.2	2	40	70	1.86E-04	0.2873	1-9	1	1	0.7850	0.2873	0.000039
Trimethoprim	9	0.080	12.1	2	4	70	5.71E-04	0.0721	2-1	1	1	0.9480	0.0721	0.000019
		0.663						0.2300	2-3	1	1	0.9695	0.2300	0.000060
							2.12E-03	0.0721	2-4	3.1	1	0.9480	0.2106	0.000055
							Sum of HQ - Simple	0.0307	2-5	1	1	0.7689	0.0307	0.000008
								0.1778	2-6	1	1	0.9926	0.1778	0.000046
								0.0111	2-7	3.1	1	0.5231	0.0201	0.000005
								0.0997	2-8	1	1	0.9861	0.0997	0.000026
								0.3066	2-9	1	1	0.9270	0.3066	0.000080
								0.0792	3-1	1.6	1	0.8524	0.1183	0.000051
								0.1533	3-2	1	1	0.9695	0.1533	0.000066
								0.0792	3-4	1	1	0.8524	0.0792	0.000034
								0.0337	3-5	1	1	0.6444	0.0337	0.000014
								0.1956	3-6	1.6	1	0.9918	0.3117	0.000134
								0.0122	3-7	1	1	0.4194	0.0122	0.000005
								0.1096	3-8	3.1	1	0.9185	0.3098	0.000133
								0.3372	3-9	1	1	0.9897	0.3372	0.000145
								0.0675	4-1	1	1	1.0000	0.0675	0.000009

0.1306	4-2	3.1	1	0.9480	0.3817	0.000051
0.2155	4-3	1	1	0.8524	0.2155	0.000029
0.0287	4-5	1	1	0.9152	0.0287	0.000004
0.1666	4-6	1	1	0.9060	0.1666	0.000022
0.0104	4-7	1	1	0.6805	0.0104	0.000001
0.0934	4-8	1	1	0.9870	0.0934	0.000013
0.2873	4-9	1	1	0.7850	0.2873	0.000039
0.0650	5-1	1.1	1	0.9152	0.0709	0.000004
0.1257	5-2	1	1	0.7689	0.1257	0.000007
0.2074	5-3	1	1	0.6444	0.2074	0.000012
0.0650	5-4	1	1	0.9152	0.0650	0.000004
0.1604	5-6	1.1	1	0.7083	0.1716	0.000010
0.0100	5-7	1	1	0.8838	0.0100	0.0000006
0.0899	5-8	1	1	0.8484	0.0899	0.000005
0.2766	5-9	1	1	0.5750	0.2766	0.000016
0.0749	6-1	1	1	0.9060	0.0749	0.000025
0.1450	6-2	1	1	0.9926	0.1450	0.000048
0.2392	6-3	1	1	0.9918	0.2392	0.000079
0.0749	6-4	1	1	0.9060	0.0749	0.000025
0.0319	6-5	1	1	0.7083	0.0319	0.000011
0.0116	6-7	1	1	0.4706	0.0116	0.000004
0.1036	6-8	1	1	0.9595	0.1036	0.000034
0.3189	6-9	1	1	0.9640	0.3189	0.000106
0.0639	7-1	1	1	0.6805	0.0639	0.000001
0.1235	7-2	1	1	0.5231	0.1235	0.000003
0.2038	7-3	1	1	0.4194	0.2038	0.000004
0.0639	7-4	0.7	-1	0.6805	0.0814	0.000002
0.0272	7-5	1	1	0.8838	0.0272	0.000001
0.1576	7-6	1	1	0.4706	0.1576	0.000003
0.0883	7-8	1	1	0.6009	0.0883	0.000002

0.2718	7-9	1	1	0.3675	0.2718	0.000006
0.0693	8-1	1	1	0.9870	0.0693	0.000013
0.1341	8-2	4.3	1	0.9861	0.5649	0.000105
0.2212	8-3	3.1	1	0.9185	0.6253	0.000116
0.0693	8-4	1	1	0.9870	0.0693	0.000013
0.0295	8-5	1	1	0.8484	0.0295	0.000005
0.1711	8-6	1	1	0.9595	0.1711	0.000032
0.0107	8-7	1	1	0.6009	0.0107	0.000002
0.2949	8-9	1	1	0.8605	0.2949	0.000055
0.0865	9-1	1	1	0.7850	0.0865	0.000049
0.1674	9-2	1	1	0.9270	0.1674	0.000096
0.2762	9-3	1	1	0.9897	0.2762	0.000158
0.0865	9-4	1	1	0.7850	0.0865	0.000049
0.0368	9-5	1	1	0.5750	0.0368	0.000021
0.2136	9-6	1	1	0.9640	0.2136	0.000122
0.0133	9-7	1	1	0.3675	0.0133	0.000008
0.1197	9-8	1	1	0.8605	0.1197	0.000068
						0.00250

Sum of HQ with Interaction

North Branch Rancocas Creek

	Chem Num	Stream Conc µg/L	% mix	Ing rate L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Acetaminophen	1	0.055	6.2	2	516	70	3.05E-06	0.5047	1-2	1	1	0.0934	0.5047	0.0000015
Caffeine	2	0.487	55.3	2	10	70	1.39E-03	0.1503	1-3	1	1	0.1702	0.1503	0.0000005
Codeine	3	0.029	3.3	2	2	70	4.14E-04	0.0604	1-4	1	1	0.2655	0.0604	0.0000002
Cotinine	4	0.035	4.0	2	6	70	1.67E-04	0.2207	1-5	1	1	0.1408	0.2207	0.0000007
1,7-	5	0.213	24.2	2	10	70	6.09E-04	0.0017	1-6	1	1	0.9755	0.0017	0.00000001
Diphenhydramin	6	0.002	0.2	2	12	70	4.76E-06	0.0622	1-7	1	1	0.2619	0.0622	0.0000002
Sulfamethizole	7	0.06	6.8	2	10	70	1.71E-04	0.0022	2-1	1	1	0.0934	0.0022	0.0000031
		0.881						0.3027	2-3	1	1	0.8409	0.3027	0.0004211
							2.76E-03	0.1218	2-4	1	1	0.6181	0.1218	0.0001694
							Sum of HQ - simple	0.4446	2-5	1	1	0.9202	0.4446	0.0006187
								0.0035	2-6	1	1	0.1166	0.0035	0.0000048
								0.1252	2-7	1	1	0.6250	0.1252	0.0001743
								0.0013	3-1	1	1	0.1702	0.0013	0.0000005
								0.5931	3-2	1	1	0.8409	0.5931	0.0002457
								0.0710	3-4	1	1	0.9046	0.0710	0.0000294
								0.2594	3-5	1	1	0.9818	0.2594	0.0001075
								0.0020	3-6	1	1	0.2120	0.0020	0.0000008
								0.0731	3-7	1	1	0.9100	0.0731	0.0000303
								0.0012	4-1	1	1	0.2655	0.0012	0.0000002
								0.5365	4-2	1.1	1	0.6181	0.5691	0.0000948
								0.1597	4-3	1	1	0.9046	0.1597	0.0000266
								0.2347	4-5	1.1	1	0.8216	0.2538	0.0000423
								0.0018	4-6	1	1	0.3287	0.0018	0.0000003
								0.0661	4-7	1	1	0.9999	0.0661	0.0000110
								0.0014	5-1	1	1	0.1408	0.0014	0.0000009
								0.6467	5-2	1	1	0.9202	0.6467	0.0003936

0.1925	5-3	1	1	0.9818	0.1925	0.0001172
0.0775	5-4	1	1	0.8216	0.0775	0.0000471
0.0022	5-6	1	1	0.1755	0.0022	0.0000013
0.0797	5-7	1	1	0.8282	0.0797	0.0000485
0.0011	6-1	1	1	0.9755	0.0011	0.00000001
0.5050	6-2	1	1	0.1166	0.5050	0.0000024
0.1504	6-3	0.7	-1	0.2120	0.1622	0.0000008
0.0605	6-4	1	1	0.3287	0.0605	0.0000003
0.2209	6-5	1	1	0.1755	0.2209	0.0000011
0.0622	6-7	1	1	0.3243	0.0622	0.0000003
0.0012	7-1	1	1	0.2619	0.0012	0.0000002
0.5375	7-2	1	1	0.6250	0.5375	0.0000921
0.1600	7-3	1	1	0.9100	0.1600	0.0000274
0.0644	7-4	1	1	0.9999	0.0644	0.0000110
0.2351	7-5	1	1	0.8282	0.2351	0.0000403
0.0018	7-6	1	1	0.3243	0.0018	0.0000003
						0.0028

Sum of HQ with Interaction

Wallkill River-2

	Chem Num	Stream Conc µg/L	% mix	Ing Int L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj *SumFMBg
Dehydronifedipine	1	0.005	0.9	2	100	70	1.43E-06	0.0113	1-2	1	1	0.3428	0.0113	0.00000002
1,7-Dimethylxanthine	2	0.016	3.0	2	10	70	4.57E-05	0.8475	1-3	1	1	0.0408	0.8475	0.0000012
Enrofloxacin	3	0.24	44.4	2	2	70	3.43E-03	0.1412	1-4	1	1	0.0998	0.1412	0.0000002
Minocycline	4	0.28	51.8	2	14	70	5.71E-04	0.0004	2-1	1	1	0.3428	0.0004	0.00000002
		0.541						0.8568	2-3	1	1	0.2279	0.8568	0.0000392
							4.05E-03	0.1428	2-4	1	1	0.5238	0.1428	0.0000065
							Sum of HQ - Simple	0.0023	3-1	1	1	0.0408	0.0023	0.0000079
								0.0739	3-2	1	1	0.2279	0.0739	0.0002534
								0.9238	3-4	1	1	0.6999	0.9238	0.0031673
								0.0004	4-1	1	1	0.0998	0.0004	0.0000002
								0.0132	4-2	1	1	0.5238	0.0132	0.0000075
								0.9864	4-3	1	1	0.6999	0.9864	0.0005637
														0.00405
														Sum of HQ with Interaction

Hohokus Brook-2

	Chem Num	Stream C	% mix	Ing L	ADI ug/kg/day	BW kg	HQ (j)	f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj * SumFMBg
		µg/L												
Caffeine	1	0.27	23.3	2	10	70	7.71E-04	0.0645	1-2	1	1	0.7959	0.0645	0.000050
Carbamazepine	2	0.073	6.3	2	11	70	1.90E-04	0.1459	1-3	1	1	0.9583	0.1459	0.000113
Ciprofloxacin	3	0.03	2.6	2	1	70	4.29E-04	0.1945	1-4	1	1	0.9888	0.1945	0.000150
Codeine	4	0.04	3.5	2	2	70	5.71E-04	0.0438	1-5	1	1	0.6999	0.0438	0.000034
Cotinine	5	0.027	2.3	2	6	70	1.29E-04	0.0032	1-6	1	1	0.2180	0.0032	0.000002
Diltiazem	6	0.0046	0.4	2	14	70	9.39E-06	0.2917	1-7	1	1	0.9986	0.2917	0.000225
1,7-Dimethylxanthine	7	0.3	25.9	2	10	70	8.57E-04	0.0154	1-8	1	1	0.4575	0.0154	0.000012
Diphenhydramine	8	0.019	1.6	2	12	70	4.52E-05	0.0802	1-9	1	1	0.8468	0.0802	0.000062
Erythromycin–	9	0.33	28.5	2	40	70	2.36E-04	0.0149	1-10	1	1	0.4510	0.0149	0.000012
Fluoxetine	10	0.0046	0.4	2	3	70	4.38E-05	0.1459	1-11	1	1	0.9583	0.1459	0.000113
Trimethoprim	11	0.06	5.2	2	4	70	4.29E-04	0.2192	2-1	1	1	0.7959	0.2192	0.000042
		1.158						0.1218	2-3	1	1	0.9223	0.1218	0.000023
							3.71E-03	0.1623	2-4	3.1	1	0.8650	0.4320	0.000082
							Sum of HQ - simple	0.0365	2-5	1	1	0.9814	0.0365	0.000007
								0.0027	2-6	3.1	1	0.4240	0.0043	0.000001
								0.2435	2-7	1	1	0.7703	0.2435	0.000046
								0.0129	2-8	3.1	1	0.7887	0.0314	0.000006
								0.0670	2-9	1	1	0.9941	0.0670	0.000013
								0.0124	2-10	1	1	0.7809	0.0124	0.000002
								0.1218	2-11	1	1	0.9223	0.1218	0.000023
								0.2351	3-1	1.6	1	0.9583	0.3689	0.000158
								0.0578	3-2	1	1	0.9223	0.0578	0.000025
								0.1742	3-4	1	1	0.9897	0.1742	0.000075
								0.0392	3-5	1	1	0.8427	0.0392	0.000017
								0.0029	3-6	1	1	0.2897	0.0029	0.000001

0.2613	3-7	1.6	1	0.9428	0.4069	0.000174
0.0138	3-8	1	1	0.5877	0.0138	0.000006
0.0718	3-9	3.1	1	0.9569	0.2121	0.000091
0.0134	3-10	1	1	0.5801	0.0134	0.000006
0.1306	3-11	1	1	1.0000	0.1306	0.000056
0.2458	4-1	1	1	0.9888	0.2458	0.000140
0.0604	4-2	3.1	1	0.8650	0.1608	0.000092
0.1366	4-3	1	1	0.9897	0.1366	0.000078
0.0410	4-5	1	1	0.7744	0.0410	0.000023
0.0030	4-6	3.1	1	0.2522	0.0040	0.000002
0.2731	4-7	1	1	0.9798	0.2731	0.000156
0.0144	4-8	1	1	0.5214	0.0144	0.000008
0.0751	4-9	1	1	0.9094	0.0751	0.000043
0.0140	4-10	1	1	0.5143	0.0140	0.000008
0.1366	4-11	1	1	0.9897	0.1366	0.000078
0.2154	5-1	1.1	1	0.6999	0.2303	0.000030
0.0530	5-2	1	1	0.9814	0.0530	0.000007
0.1197	5-3	1	1	0.8427	0.1197	0.000015
0.1596	5-4	1	1	0.7744	0.1596	0.000021
0.0026	5-6	1	1	0.5037	0.0026	0.000000
0.2394	5-7	1.1	1	0.6736	0.2552	0.000033
0.0126	5-8	1	1	0.8776	0.0126	0.000002
0.0658	5-9	1	1	0.9558	0.0658	0.000008
0.0122	5-10	1	1	0.8708	0.0122	0.000002
0.1197	5-11	1	1	0.8427	0.1197	0.000015
0.2085	6-1	1	1	0.2180	0.2085	0.000002
0.0512	6-2	1	1	0.4240	0.0512	0.000000
0.1158	6-3	1	1	0.2897	0.1158	0.000001
0.1544	6-4	1	1	0.2522	0.1544	0.000001
0.0347	6-5	1	1	0.5037	0.0347	0.000000

0.2317	6-7	1	1	0.2070	0.2317	0.000002
0.0122	6-8	1	1	0.7545	0.0122	0.000000
0.0637	6-9	5	1	0.3838	0.1182	0.000001
0.0118	6-10	1	1	0.7624	0.0118	0.000000
0.1158	6-11	1	1	0.2897	0.1158	0.000001
0.2705	7-1	1	1	0.9986	0.2705	0.000232
0.0665	7-2	1	1	0.7703	0.0665	0.000057
0.1503	7-3	1	1	0.9428	0.1503	0.000129
0.2003	7-4	1	1	0.9798	0.2003	0.000172
0.0451	7-5	1	1	0.6736	0.0451	0.000039
0.0033	7-6	1	1	0.2070	0.0033	0.000003
0.0159	7-8	1	1	0.4364	0.0159	0.000014
0.0826	7-9	1	1	0.8226	0.0826	0.000071
0.0154	7-10	1	1	0.4302	0.0154	0.000013
0.1503	7-11	1	1	0.9428	0.1503	0.000129
0.2105	8-1	1	1	0.4575	0.2105	0.000010
0.0517	8-2	1	1	0.7887	0.0517	0.000002
0.1170	8-3	1	1	0.5877	0.1170	0.000005
0.1559	8-4	0.7	-1	0.5214	0.1878	0.000008
0.0351	8-5	1	1	0.8776	0.0351	0.000002
0.0026	8-6	1.4	1	0.7545	0.0033	0.000000
0.2339	8-7	1	1	0.4364	0.2339	0.000011
0.0643	8-9	1	1	0.7351	0.0643	0.000003
0.0120	8-10	3.1	1	0.9999	0.0371	0.000002
0.1170	8-11	1	1	0.5877	0.1170	0.000005
0.2221	9-1	1	1	0.8468	0.2221	0.000052
0.0546	9-2	4.3	1	0.9941	0.2327	0.000055
0.1234	9-3	3.1	1	0.9569	0.3643	0.000086
0.1645	9-4	1	1	0.9094	0.1645	0.000039
0.0370	9-5	1	1	0.9558	0.0370	0.000009

0.0027	9-6	1	1	0.3838	0.0027	0.000001
0.2467	9-7	1	1	0.8226	0.2467	0.000058
0.0130	9-8	1	1	0.7351	0.0130	0.000003
0.0126	9-10	3.1	1	0.7271	0.0287	0.000007
0.1234	9-11	1	1	0.9569	0.1234	0.000029
0.2104	10-1	1	1	0.4510	0.2104	0.000009
0.0517	10-2	3.1	1	0.7809	0.1251	0.000005
0.1169	10-3	1	1	0.5801	0.1169	0.000005
0.1559	10-4	1.5	1	0.5143	0.1920	0.000008
0.0351	10-5	1	1	0.8708	0.0351	0.000002
0.0026	10-6	1	1	0.7624	0.0026	0.000000
0.2338	10-7	1	1	0.4302	0.2338	0.000010
0.0123	10-8	1	1	0.9999	0.0123	0.000001
0.0643	10-9	1	1	0.7271	0.0643	0.000003
0.1169	10-11	1	1	0.5801	0.1169	0.000005
0.2351	11-1	1	1	0.9583	0.2351	0.000101
0.0578	11-2	1	1	0.9223	0.0578	0.000025
0.1306	11-3	1	1	1.0000	0.1306	0.000056
0.1742	11-4	1	1	0.9897	0.1742	0.000075
0.0392	11-5	1	1	0.8427	0.0392	0.000017
0.0029	11-6	1	1	0.2897	0.0029	0.000001
0.2613	11-7	1	1	0.9428	0.2613	0.000112
0.0138	11-8	1	1	0.5877	0.0138	0.000006
0.0718	11-9	1	1	0.9569	0.0718	0.000031
0.0134	11-10	1	1	0.5801	0.0134	0.000006
						0.004117

Sum of HQ with Interaction

Ramapo River

	Chem Num	Stream Conc. µg/L	% mix	Ing Int. L	ADI ug/kg/day	BW kg	HQ (j)
Caffeine	1	0.015	0.43	2	10	70	4.29E-05
Carbamazepine	2	3.48	99.34	2	11	70	9.04E-03
Codeine	3	0.002	0.06	2	2	70	2.86E-05
Cotinine	4	0.003	0.09	2	6	70	1.43E-05
Diphenhydramin	5	0.003	0.09	2	12	70	7.14E-06
		3.503					
							9.13E-03
							Sum of HQ - simple

f(jk)	Chems Paired	M(jk)	B(jk) WOE	g(jk)	f*M^Bg	HQj * SumFMBg
0.9945	1-2	1	1	0.1371	0.9945	0.00004262
0.0031	1-3	1	1	0.9798	0.0031	0.00000013
0.0016	1-4	1	1	0.8660	0.0016	0.00000007
0.0008	1-5	1	1	0.6999	0.0008	0.00000003
0.4615	2-1	1	1	0.1371	0.4615	0.00417183
0.3077	2-3	3.1	1	0.1121	0.3493	0.00315727
0.1538	2-4	1	1	0.0794	0.1538	0.00139061
0.0769	2-5	3.1	1	0.0562	0.0820	0.00074093
0.0047	3-1	1	1	0.9798	0.0047	0.00000013
0.9929	3-2	3.1	1	0.1121	1.1272	0.00003221
0.0016	3-4	1	1	0.9428	0.0016	0.00000004
0.0008	3-5	1	1	0.8000	0.0008	0.00000002
0.0047	4-1	1.1	1	0.8660	0.0051	0.00000007
0.9914	4-2	1	1	0.0794	0.9914	0.00001416
0.0031	4-3	1	1	0.9428	0.0031	0.00000004
0.0008	4-5	1	1	0.9428	0.0008	0.000000011
0.0047	5-1	1	1	0.6999	0.0047	0.00000003
0.9906	5-2	1	1	0.0562	0.9906	0.00000708
0.0031	5-3	0.7	-1	0.8000	0.0042	0.00000003
0.0016	5-4	1	1	0.9428	0.0016	0.000000011
						0.00956
						Sum of HQ with Interaction

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