Supplemental Material

Pharmaceuticals in Tap Water: Human Health Risk Assessment and Proposed Monitoring Framework in China

Ho Wing Leung\textsuperscript{1,2,*}, Ling Jin\textsuperscript{1,2,3}, Si Wei\textsuperscript{4}, Mirabelle Mei Po Tsui\textsuperscript{1,2}, Bingsheng Zhou\textsuperscript{5}, Liping Jiao\textsuperscript{6,7}, Pak Chuen Cheung\textsuperscript{1,2}, Yiu Kan Chun\textsuperscript{1,2}, Margaret Burkhardt Murphy\textsuperscript{1,2}, and Paul Kwan Sing Lam\textsuperscript{1,2}

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METHODS

Selection of pharmaceuticals

We analyzed a total of 32 pharmaceuticals of 16 different therapeutic classes including 9 subclasses of antibiotics (viz. penicillins, cephalosporins, macrolides, sulfonamides, (fluoro)quinolones, amphenicols, nitroimidazoles, lincosamides, diaminopyrimidines), β-blockers, anti-hypertension drugs, diuretic drugs, lipid regulators, psychoactive stimulants, anticonvulsants and non-steroidal anti-inflammatory drugs (NSAIDs) (Supplemental Material, Table S1).

Sampling

The sampled cities were categorized into 4 groups according to their geographical locations: i) northern China: Beijing and Yancheng; ii) Yangtze River region: Nanjing, Hangzhou and Shanghai; iii) middle-southern China: Wuhan, Changsha and Xiamen; iv) Pearl River region in southern China: Guangzhou, Zhuhai, Macau, Shenzhen, and Hong Kong. Surface water is the dominant potable water source in the selected cities (>90% of total water supply), except for Beijing, which relies mainly on groundwater (67%) (NBSC 2009). Coagulation, sedimentation and chlorination are the most common processes in DWTPs but 18-49% of the water supplies in some sampled cities are further treated by ozonation, (bio-)activated carbon, and biofiltration (see Supplemental Material, Figure S1 and Table S2). We focused on household samples in relatively well-developed and densely-populated cities as pharmaceutical exposure could affect large populations in these locations. We also tried to maximize the geographical coverage of the samples by collecting tap water from areas with different water sources and treatment technologies under the constraint that samples had to be analyzed within 48 hours.
Analysis

The targeted pharmaceuticals were extracted with solid phase extraction methodology previously applied for sewage (Leung et al. 2012) with modifications for broadening the number of analytes and utilizing 9 isotopically-labeled standards instead of only $^{13}\text{C}$-caffeine for reducing analytical uncertainties. Briefly, 500 mL of each sample was combined with 5 mL 5\% (w/v) EDTA, acidified to pH 3-3.3 and then loaded on Hydrophilic-Lipophilic Balanced (HLB) cartridges preconditioned by methanol and water. After loading, the cartridge was rinsed with water and eluted with 4 mL methanol. The eluate was reduced to near-dryness (<0.1 mL) under a gentle stream of nitrogen, reconstituted to 0.5 mL with water and then centrifuged at 9000 rpm for 10 min. The final extract was spiked with 62.5 ng $^{13}\text{C}$-phenacetin, 100 ng $^{13}\text{C}_3$-ibuprofen and $^{13}\text{C}_3^{15}\text{N}$-ciprofloxacin, and 50 ng of each remaining internal standard in order to compensate for matrix effects during instrumental quantification. For matching internal standards with analytes, we followed the quantitative methods applied in Gros et al. (2009) with slight amendments in order to minimize matrix effects. First, the slope difference of two calibration curves separately constructed in Milli-Q water and in tap water extract was calculated for each analyte. This difference was regarded as a matrix-induced interference factor and we then selected an appropriate internal standard for instrumental quantification in order to minimize the factor as close as 0 as possible. If the analyte was subject to limited matrix effects and the external calibration curve alone was the best quantification method, no internal standard was assigned. A 10 $\mu$L aliquot of extract was injected into an Agilent 1100 HPLC system (Palo Alto, CA, USA) and chromatographic separation was performed using an XBridge™ C18 column (2.1 x 50 mm, 5 $\mu$m, Waters Corporation). Analytes were ionized in electrospray ionization (ESI) source operated in positive and negative modes. Two mass transitions of each parent compound were
monitored by an ABSciex 2000 QTRAP triple quadrupole tandem mass spectrometer (MS/MS) (Toronto, Canada) for quantification and confirmation in multiple reaction monitoring (MRM) mode except ibuprofen and the mass-labeled internal standards. Quantification was carried out by normalizing analyte peak area by the corresponding internal standard peak area in sample extracts and substituting into the linear equation of a seven-point external calibration curve (0-400 µg/L) constructed in Milli-Q water.

**Quality assurance/quality control**

Each individual sample was accompanied by a corresponding field blank (pure water fortified with ascorbic acid) and procedural blanks (n = 15) were analyzed with each sample batch. We found no background contaminations during sample collection, transportation and analysis. The matrix-matched limit of quantification (LOQ) was defined as the sum of the average and ten times the standard deviation of all procedural blank values and then corrected by the degree of matrix effects (Leung et al. 2012). LOQs ranged from 0.2 to 26.1 ng/L. Matrix-spiked absolute recoveries (n = 25, at 100 ng/L) ranged from 64.4% to 105%, with relative standard deviations mostly lower than 20% (Supplemental Material, Table S1).

**Derivation of DWELs and risk assessment**

The acceptable daily intake (ADI) or risk-specific dose (RSD) were derived using toxicological, microbiological or therapeutic approaches applied previously (Bruce et al. 2010; Schriks et al. 2010; Schwab et al. 2005).

For non-cancer effects, the no-observable-adverse-effect level (NOAEL) or lowest-observable-adverse-effect level (LOAEL) for different toxicity endpoints such as developmental and reproductive effects in humans or other mammals was extrapolated to an ADI
by using equation S1, which includes five types of uncertainty factors (UFs): (UF1) extrapolation from LOAEL to NOAEL; (UF2) duration of exposure; (UF3) interspecies variation; (UF4) intraspecies variation; and (UF5) data quality (Schwab et al. 2005):

$$\text{ADI (µg/kg·d)} = \frac{\text{NOAEL or LOAEL}}{(UF1 \times UF2 \times UF3 \times UF4 \times UF5)} \quad \text{[S1]}$$

The values and considerations of each uncertainty factor were consistent with those recommended by the U.S. EPA and in recent literature (U.S. EPA 2002; Schwab et al. 2005).

Carcinogenicity risk was assessed using slope factors (SFs), referring to the tumorigenic risk per increment of dose, of a linear non-threshold dose-response curve of the observed data extrapolated to a RSD associated with an incremental lifetime cancer risk of $10^{-6}$ (equation S2).

$$\text{RSD (µg/kg·d)} = \frac{\text{SF}}{1 \times 10^{-6}} \quad \text{[S2]}$$

This approach assumes that the entire range of human variation is taken into consideration and can protect public health at low doses (U.S. EPA 2005). If only evidence of carcinogenicity but no tumor incidence data was obtained from toxicity tests, a virtually safe dose (equivalent to ADI) was estimated based on the maximum tolerated dose (MTD) determined in a 90-day bioassay study corresponding to an incremental cancer risk of $10^{-6}$ (Gaylor and Gold 1998; Bruce et al. 2010) (equation S3):

$$\text{ADI (µg/kg·d)} = \frac{\text{MTD}}{740000} \quad \text{[S3]}$$

For antibiotics, a microbiological ADI was also derived from MICs for the most sensitive human intestinal flora using equation S4 (Bruce et al. 2010; Schwab et al. 2005):

$$\text{ADI (µg/kg·d)} = \frac{\text{MIC}_{50} \times \text{MCC}}{(FA \times SF \times BW)} \quad \text{[S4]}$$
where MIC\textsubscript{50} is the concentration inhibiting 50% of strains; MCC is the mass colonic content = 220 g/d; FA is the fraction of the oral dose available to microorganisms in the intestines; SF is the safety factor, normally equal to 1 if MIC\textsubscript{50} data is adequate; and BW is body weight = 60 kg (approximately average between Chinese female: 57 kg; and male: 66 kg; based on a marketing survey in China, Alvanon 2008).

If toxicological and microbiological data were deficient for a given compound, the lowest therapeutic dose was regarded as the LOAEL for derivation of a therapeutic ADI (Schwab et al. 2005).
**Supplemental Material, Table S1. List of targeted pharmaceuticals and information about instrumental analysis and QA/QC parameters.**

| Therapeutic class | Pharmaceutical | Supplier          | Retention time (min) | Precursor (m/z) | Transition 1 (m/z) | Transition 2 (m/z) | QA/QC parameters |
|-------------------|-----------------|-------------------|----------------------|-----------------|-------------------|-------------------|-----------------|
| Penicillins       | Ampicillina     | Sigma-Aldrich     | 6.47                 | 350.5           | 106.0             | 42 35            | 160.0           | 42 18            | 3.7 74.5 ± 9.5 |
|                   |                  |                   |                      |                 |                   |                   |                 |                 |                 |                 |
| Cephalosporins    | Cefalexina      | Riedel-de Haën    | 6.07                 | 348.1           | 158.3             | 66 15            | 174.2           | 66 17            | 3.7 72.2 ± 9.5 |
|                   | Cefotaximeb     | Fluka             | 6.37                 | 454.2           | 239.0             | -51 -16          | 394.1           | -36 -10          | 3.4 85.2 ± 10.5 |
|                   | Cefuroximeb     | Dr. Ehrenstorfer  | 6.55                 | 423.2           | 207.0             | -40 -20          | 318.0           | -40 -15          | 2.2 64.4 ± 17.2 |
|                   |                  |                   |                      |                 |                   |                   |                 |                 |                 |                 |
| Macrolides        | Clarithromycind | Sigma-Aldrich     | 10.50                | 748.8           | 590.3             | 76 31            | 558.5           | 76 31            | 0.7 81.2 ± 13.3 |
|                   | Roxithromycind  | Sigma-Aldrich     | 10.60                | 837.8           | 158.5             | 41 45            | 679.8           | 36 31            | 0.3 69.3 ± 12.0 |
|                   | Azithromycind   | Fluka             | 10.50                | 749.0           | 158.0             | -40 -20          | 591.4           | -36 -10          | 0.3 90.5 ± 18.4 |
|                   | Tylosinf        | Sigma-Aldrich     | 9.71                 | 916.3           | 174.1             | 96 53            | 772.3           | 81 53            | 0.9 72.7 ± 11.8 |
| Sulfonamides      | Sulfathiazolef  | Sigma-Aldrich     | 2.98                 | 256.0           | 156.0             | 46 17            | 108.0           | 41 17            | 3.7 84.6 ± 7.4  |
|                   | Sulfamethazinef | Sigma-Aldrich     | 5.23                 | 279.1           | 186.1             | 76 21            | 124.1           | 56 35            | 3.3 90.5 ± 18.4 |
|                   | Sulfamethoxazole| Sigma-Aldrich     | 6.38                 | 254.1           | 156.0             | 66 17            | 108.0           | 71 35            | 2.7 79.4 ± 15.0 |
| Fluoroquinolones  | Norfloxacinf    | Sigma-Aldrich     | 6.11                 | 320.2           | 302.2             | 51 30            | 276.0           | 46 17            | 21.3 105 ± 17.6 |
|                   | Flumequined     | Sigma-Aldrich     | 9.54                 | 262.4           | 202.1             | 30 45            | 244.2           | 30 28            | 14.4 86.5 ± 20.5 |
| Amphenicols       | Chloramphenicolb| Riedel-de Haën    | 7.81                 | 321.0           | 152.0             | -71 -22          | 257.1           | -76 -12          | 2.1 98.2 ± 19.6 |
|                   | Thiamphenicolb  | Sigma-Aldrich     | 4.80                 | 354.0           | 185.0             | -45 -26          | 79.0            | -80 -45          | 5.2 86.9 ± 14.4 |
| Nitroimidazoles   | Dimetridazolei  | Dr. Ehrenstorfer  | 2.08                 | 142.1           | 96.3              | 43 20            | 81.2            | 43 37            | 1.5 92.8 ± 13.5 |
|                   | Metronidazolel  | Dr. Ehrenstorfer  | 1.79                 | 172.2           | 128.0             | 40 20            | 82.0            | 40 32            | 0.4 91.8 ± 19.5 |
| Lincosamides      | Lincomycine     | Fluka             | 4.71                 | 407.0           | 126.2             | 50 40            | 359.4           | 50 30            | 0.2 80.9 ± 10.5 |
|                   | Clindamycind    | Sigma-Aldrich     | 8.77                 | 425.0           | 126.3             | 45 40            | 377.3           | 45 40            | 0.3 87.9 ± 13.6 |

**Notes:**
- **a** Dr. Ehrenstorfer
- **b** Sigma-Aldrich
- **c** Riedel-de Haën
- **d** Fluka
- **e** Sigma-Aldrich
- **f** Sigma-Aldrich
- **g** Sigma-Aldrich
- **h** Sigma-Aldrich
- **i** Sigma-Aldrich

**QA/QC parameters:**
- **Recovery (%):** Mean ± RSD
| Therapeutic class                        | Pharmaceutical     | Supplier          | Retention time (min) | Precursor (m/z) | Transition 1 (m/z) | Transition 2 (m/z) | QA/QC parameters |
|-----------------------------------------|--------------------|-------------------|----------------------|-----------------|-------------------|-------------------|------------------|
| Diaminopyrimidines                      | Trimethoprim<sup>a</sup>  | Sigma-Aldrich     | 5.36                 | 291.2           | 123.0             | 66                | 33               | 261.2 | 71 | 23 | 5.2 | 89.7 ± 12.5 |
| β-blockers                              | Metoprolol<sup>f</sup> | Sigma-Aldrich     | 6.78                 | 268.0           | 121.0             | 51                | 32               | 133.0 | 46 | 33 | 4.1 | 98.2 ± 8.9   |
|                                        | Acebutolol<sup>f</sup> | Sigma-Aldrich     | 6.86                 | 337.5           | 116.0             | 41                | 29               | 72.0     | 41 | 43 | 1.5 | 100 ± 10.7  |
| Anti-hypertensive drug                  | Enalapril<sup>d</sup>  | Sigma-Aldrich     | 8.75                 | 377.7           | 234.2             | 43                | 27               | 303.3    | 43 | 27 | 0.5 | 91.9 ± 8.0   |
| Diuretic drug                           | Hydrochlorothiazide<sup>b</sup> | Sigma-Aldrich | 2.28                 | 296.1           | 78.1              | -80               | -41              | 268.9    | -80 | -30 | 7.8 | 88.0 ± 15.5 |
| Lipid regulators                        | Clofibric acid<sup>d</sup> | Sigma-Aldrich     | 11.30                | 213.0           | 127.2             | -34              | -23              | 84.9     | -34 | -16 | 0.4 | 96.5 ± 10.1  |
|                                        | Gemfibrozil<sup>d</sup> | Sigma-Aldrich     | 13.50                | 249.2           | 121.1             | -45              | -25              | 127.4    | -45 | -15 | 1.3 | 84.9 ± 9.5   |
| Psychoactive stimulant                  | Caffeine<sup>d</sup>  | Fluka             | 5.75                 | 195.3           | 138.0             | 40               | 28               | 110.0    | 40 | 30 | 3.8 | 88.7 ± 7.4   |
| Antiepileptic drug                      | Carbamazepine<sup>d</sup> | Sigma-Aldrich     | 9.73                 | 237.3           | 194.1             | 53               | 30               | 179.2    | 53 | 50 | 0.7 | 93.8 ± 8.9   |
| Non-steroidal anti-inflammatory drugs   | Diclofenac<sup>d</sup> | Sigma-Aldrich     | 12.51                | 294.0           | 250.0             | -25              | -12              | 214.0    | -25 | -25 | 1.2 | 86.1 ± 7.9   |
| (NSAIDs)                                | Naproxen<sup>b</sup>  | Sigma-Aldrich     | 11.40                | 229.2           | 169.0             | -30              | -42              | 170.0    | -30 | -24 | 2.7 | 74.5 ± 20.8  |
| Non-steroidal anti-inflammatory drugs   | Ibuprofen<sup>d</sup> | Sigma-Aldrich     | 12.80                | 205.0           | 161.0             | -40              | -16              | 84.9     | -34 | -16 | 0.4 | 96.5 ± 10.1  |
| (NSAIDs)                                | Salicylic acid<sup>b</sup> | Sigma-Aldrich | 8.48                 | 137.1           | 93.1              | -30              | -25              | 65.2     | -30 | -24 | 13.0 | 73.0 ± 20.9  |
| Internal standards                      | 13C₂-Erythromycin-H₂O | CIL<sup>k</sup>  | 10.70                | 719.0           | 160.0             | 71               | 38               |          |    |    |     |          |
|                                        | 13C₆-Sulfamethoxazole | CIL                  | 6.37                 | 260.3           | 98.2              | 45               | 40               |          |    |    |     |          |
|                                        | 13C₃¹⁵N-Ciprofloxacin | CIL                  | 6.25                 | 336.5           | 318.0             | 56               | 34               |          |    |    |     |          |
|                                        | 13C₃-Trimethoprim     | CIL                  | 5.33                 | 294.5           | 126.0             | 60               | 35               |          |    |    |     |          |
|                                        | 13C₃-Caffeine         | CIL                  | 5.58                 | 198.1           | 140.1             | 61               | 19               |          |    |    |     |          |
|                                        | D₅-Chloramphenicol    | CIL                  | 7.73                 | 326.2           | 157.0             | -60              | -24              |          |    |    |     |          |
|                                        | 13C₃-Ibuprofen        | CIL                  | 12.80                | 208.0           | 163.0             | -26              | -16              |          |    |    |     |          |
| Therapeutic class | Pharmaceutical   | Supplier          | Retention time (min) | Precursor $(m/z)$ | Transition 1 $(m/z)$ | Transition 2 $(m/z)$ | QA/QC parameters |
|-------------------|-------------------|-------------------|----------------------|-------------------|----------------------|----------------------|------------------|
| $^{13}$C-Phenacetin | Sigma-Aldrich     | 8.05              | 181.3                | 110.2             | 60                   | 29                   |                  |
| D$_3$-Mecoprop    | Dr. Ehrenstorfer  | 11.80             | 216.0                | 144.0             | -30                  | -20                  |                  |

| LOQ (ng/L) | Recovery (%) | Mean ± RSD |
|------------|--------------|------------|
|            |              |            |

*a $^{13}$C$_6$-Sulfamethoxazole; b $^{13}$C$_3$-Ibuprofen; c Dr. Ehrenstorfer GmBH, Augsburg, Germany; d External calibration curve applied for quantification; e $^{13}$C$_2$-Erythromycin-H$_2$O; f $^{13}$C-Phenacetin; g $^{13}$C$_3$-$^{15}$N-ciprofloxacin; h D$_3$-mecoprop; i $^{13}$C$_3$-trimethoprim; j $^{13}$C$_3$-caffeine; k Cambridge Isotope Laboratory Inc.
### Supplemental Material, Table S2. Information for the 13 sampled cities in China.

| City   | Province   | Population (1x10^6) | Water supply (1x10^4 m³/day) | Treatment process\textsuperscript{d} |
|--------|------------|----------------------|------------------------------|----------------------------------|
| A Beijing | DCM\textsuperscript{a} | 1961                 | 343\textsuperscript{c}       | Conv, 49% O₃+(Bio)ActC           |
| B Yancheng | Jiangsu   | 159\textsuperscript{b} | 23.5\textsuperscript{b}     | Conv                            |
| C Nanjing | Jiangsu    | 771                  | 220                          | Conv                            |
| D Shanghai | DCM\textsuperscript{a} | 1921                 | 577\textsuperscript{b}       | Conv, 21% O₃+(Bio)ActC           |
| E Hangzhou | Zhejiang  | 429\textsuperscript{a} | 170                          | Conv, 41% O₃+(Bio)ActC           |
| F Wuhan  | Hubei      | 500\textsuperscript{a} | 375\textsuperscript{b}       | Conv                            |
| G Changsha | Hunan     | 362\textsuperscript{a} | 165                          | Conv, 18% O₃+(Bio)ActC           |
| H Xiamen | Fujian     | 252                  | 121                          | Conv                            |
| I Guangzhou | Guang-dong | 887                  | 465                          | Conv, 22% O₃+(Bio)ActC           |
| J Zhuhai | Guang-dong | 145                  | 52                           | Conv                            |
| K Macau  | SAR\textsuperscript{a} | 54                   | 33                           | Conv                            |
| L Shenzhen | Guang-dong | 891\textsuperscript{b} | 376                          | Conv, 38% O₃+(Bio)ActC           |
| M Hong Kong | SAR\textsuperscript{a} | 710                  | 261                          | Conv, 21% Biofil/ O₃+Biofil      |

See Supplemental Material, Figure S1 for map showing the location of each city.

\textsuperscript{a} DCM: Directly-controlled municipality; SAR: Special Administrative Region; \textsuperscript{b} Refers to the metropolitan area of the city

\textsuperscript{c} Beijing: 65% from groundwater; Other cities: >90% from surface water; \textsuperscript{d} Percentage of raw water treated by non-conventional treatment. Conv (Conventional treatment): coagulation + flocculation + sedimentation + chlorination; O₃: ozonation; (Bio)ActC: (bio)activated carbon adsorption; Biofil: biofiltration; percentage of water supply treated by treatments other than chlorination.
Supplemental Material, Figure S1. Locations of the 13 sampled cities in China.

See Supplemental Material, Table S2 for key to the location names and additional information about each location.
| Age intervals           | Daily water ingestion per body weight (mL/kg·day) | Compound and corresponding ADI or RSD (µg/kg·day) | Toxicity endpoint                                      | References                                                                 | DWEL range throughout 12 age-intervals (ng/L) |
|------------------------|--------------------------------------------------|--------------------------------------------------|------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------|
| 1 to <3 months         | 205                                              | Clarithromycin 0.2                                | MIC<sub>50</sub> on *Peptostreptococcus spp.*       | Citron and Appleman 2001                                                  | 976 - 6452                                    |
| 3 to <6 months         | 159                                              | Roxithromycin 0.4                                 | MIC<sub>50</sub> on *Eubacterum spp.*               | Dubreuil 1987                                                             | 1951 - 12903                                  |
| 6 to <12 months        | 126                                              | Azithromycin 1.7                                  | MIC<sub>50</sub> on *Clostridium spp.*              | Kitris et al. 1990                                                        | 8293 - 54839                                  |
| 1 to <2 years          | 71                                               | Tylosin 0.85                                      | MIC<sub>50</sub> on *Bifidobacterium spp.* and *Clostridium spp.* | FAO/WHO 2008                                                              | 4146 - 27419                                  |
| 2 to <3 years          | 60                                               | Sulfathiazole 50                                  | Changes in thyroid tissue. Reference to the sulfamethazine which had a NOEL of 5 mg/kg for the thyroid effects in animal studies | Adopted from Schwab et al. 2005                                         | 243902 - 1612903                             |
| 3 to <6 years          | 61                                               | Sulfamethazine 1.6                                | Thyroid gland follicular adenoma in rats with tumor incidence data | Littlefield 1988                                                          | 7805 - 51613                                  |
| 6 to <11 years         | 43                                               | Sulfamethoxazole 130                              | Thyroid tumors in rats                                 | Adopted from Schwab et al. 2005                                          | 634146 - 4193548                              |
| 11 to <16 years        | 34                                               | Thiamphenicol 0.9                                 | Haemotoxic effects in rats and mice                  | Ando et al. 1997                                                          | 4390 - 29032                                  |
| 16 to <18 years        | 31                                               | Dimetridazole 0.006                               | Incidence of benign tumors of the mammary glands in rats, no slope factor | Lowe et al. 1976                                                          | 27.8 - 184                                   |
| 18 to <21 years        | 35                                               | Metronidazole 0.6                                 | MIC<sub>50</sub> for *Peptostreptococcus spp.*     | Jokipii and Jokipii 1987                                                  | 2927 - 19355                                  |
# Age-specific exposure scenario
(U.S. EPA 2009)

| Age intervals | Daily water ingestion per body weight (mL/kg·day)\(^a\) | Compound and corresponding ADI or RSD (µg/kg·day) | Toxicity endpoint | References | DWEL range throughout 12 age-intervals\(^b\) (ng/L) |
|---------------|-------------------------------------------------|-------------------------------------------------|------------------|------------|--------------------------------------------------|
| >21 years     | 39                                              | Trimethoprim 4.2                                 | MIC of the most sensitive species in human gut flora | Adopted from Schwab et al. 2005 | 20488 - 135484 |
| >65 years     | 37                                              | Metoprolol 14                                     | Lowest therapeutic dose | Adopted from Schriks et al. 2010 | 68293 - 451613 |
|               |                                                 | Clofibric acid 10                                 | Reduction effect on serum cholesterol and triglycerides in patients with type III hyperlipoproteinemia | Adopted from Schriks et al. 2010 | 48780 - 322581 |
|               |                                                 | Caffeine 150                                      | Developmental effects (cleft palate) in rats exposed gestationally | Skalko et al. 1984 | 73171 - 483871 |
|               |                                                 | Carbamazepine 0.3                                 | Carcinogenicity in rats, no tumour data | Adopted from Bruce et al. 2010 | 1659 - 10968 |
|               |                                                 | Diclofenac 67                                     | No observable effects in mice exposed gestationally | Adopted from Bruce et al. 2010 | 326829 - 2161290 |
|               |                                                 | Salicylic acid 26                                 | Reproductive effects (increased duration of labor, maternal peripartum death) | Davis et al. 1996 | 126829 - 838710 |

\(^a\) 95\(^{th}\)-percentile values recommended;
\(^b\) DWEL was calculated using the following equation: DWEL (ng/L) = [(ADI or RSD)\(\times\)RSC\(_{DW}\)\(\times\)BW\(\times\)1000]/IngRD\(_{DW}\), where RSC\(_{DW}\): relative source contribution of acceptable dose from drinking water, assumed to be 100% (most compounds) or 10% (caffeine only) for screening purposes; BW: body weight at each age-intervals; and IngRD\(_{DW}\): daily ingestion rate of drinking water per day. The highest level of each pharmaceutical in tap water was compared to the corresponding DWEL for each age interval to determine RQs at different life-stages.
| Sampling city (DI) and season |  | Clarithromycin | Roxithromycin | Azithromycin | Tylosin | Sulfadiazine | Sulfamethoxazole | Thiampenicol | Dimetridazole | Metronidazole | Trimethoprim | Clofibrate acid | Caffeine | Carbamazepine | Diclofenac | Salicylic acid |
|------------------------------|---|----------------|---------------|-------------|--------|-------------|-----------------|-------------|---------------|--------------|-------------|----------------|---------|---------------|----------|---------------|
| All All                      | 113 num<sup>b</sup> | 8            | 8             | 8           | 4      | 1           | 6               | 10          | 13            | 22           | 45          | 2              | 1       | 31            | 98       | 26            | 2        | 37            |
| Dry                         | med<sup>b</sup> | 6.7          | 2.8           | 7.0         | 6.4    | <3.7<sup>c</sup> | 9.4             | 8.0         | 17.8          | 6.9          | 1.8         | 10.2           | 1.2     | 24.4          | 1.3      | 3.2           | 16.6     |
|                             | max<sup>b</sup> | 11.9         | 15.1          | 11.7        | 7.0    | 27.4        | 89.6            | 21.2        | 104.3         | 14.7         | 19.3        | 14.2           | 8.5     | 3.3           | 562.5    | 6.7           | 3.7      | 41.2          |
| Wet                         | num | 6            | 8             | 7           | 4      | 1           | 5               | 8           | 8             | 12          | 27          | 2              | 1       | 26            | 55       | 18            | 2        | 19            |
|                             | med | 8.5          | 2.8           | 7.9         | 6.4    | <3.7<sup>c</sup> | 11.2            | 6.6         | 33.6          | 7.8          | 2.2         | 10.2           | 1.7     | 24.5          | 1.7      | 3.2           | 15.6     |
|                             | max | 11.9         | 15.1          | 11.7        | 7.0    | 27.4        | 89.6            | 21.2        | 104.3         | 14.7         | 19.3        | 14.2           | 8.5     | 3.3           | 562.5    | 6.7           | 3.7      | 41.2          |
| Beijing (0.4)       | Dry | 5 num        | 2            | 0            | 1      | 0           | 0               | 1           | 2             | 5           | 10          | 18             | 0       | 0             | 5        | 43            | 0        | 18            |
|                             | med | 1.8<sup>b</sup> | <0.3         | <0.3        | <0.9   | <3.7<sup>c</sup> | 9.0              | 6.8         | 1.8           | <5.2<sup>b</sup> | 10.2<sup>b</sup> | <4.1<sup>b</sup> | 0.7     | 20.4          | 1.1      | <1.2<sup>b</sup> | 19.0     |
|                             | max | 1.9<sup>b</sup> | <0.3         | 1.2         | <0.9   | <3.7<sup>c</sup> | 5.5              | 9.1         | 26.5          | 9.7          | 8.4         | <5.2<sup>b</sup> | 4.1     | 1.2           | 79.9     | 1.8<sup>b</sup> | <1.2<sup>b</sup> | 35.4         |
| Yancheng (2.6)     | Dry | 5 num        | 0            | 0            | 0      | 0           | 0               | 0           | 0             | 0           | 0           | 0              | 0       | 0             | 1        | 0             | 1        | 1             |
|                             | med | <0.7         | <0.3         | <0.3        | <0.9   | <3.7<sup>c</sup> | <3.3            | <2.7        | <5.2<sup>b</sup> | <1.5<sup>b</sup> | <0.4<sup>b</sup> | <5.2<sup>b</sup> | <4.1<sup>b</sup> | <0.4<sup>b</sup> | <3.8<sup>b</sup> | <0.7<sup>b</sup> | <1.2<sup>b</sup> | <13.0<sup>b</sup> |
|                             | max | <0.7         | <0.3         | <0.3        | <0.9   | <3.7<sup>c</sup> | <3.3            | <2.7        | <5.2<sup>b</sup> | <1.5<sup>b</sup> | <0.4<sup>b</sup> | <5.2<sup>b</sup> | <4.1<sup>b</sup> | <0.4<sup>b</sup> | <3.8<sup>b</sup> | 1.9<sup>b</sup> | <1.2<sup>b</sup> | 38.2<sup>b</sup> |
| Shanghai (2.9)     | Dry | 5 num        | 0            | 0            | 0      | 0           | 0               | 0           | 0             | 0           | 3           | 0              | 0       | 0             | 5        | 5             | 0        | 0             |
|                             | med | <0.7         | <0.3         | <0.3        | <0.9   | <3.7<sup>c</sup> | 50.4            | 20.8        | 5.0           | <0.4        | <5.2        | <4.1           | 0.8     | 24.1          | 4.0      | <1.2<sup>b</sup> | 15.6     |
|                             | max | <0.7         | <0.3         | <0.3        | <0.9   | <3.7<sup>c</sup> | 89.6            | 20.8        | 5.2           | <0.4        | <5.2        | <4.1           | 1.0     | 62.7          | 6.7      | <1.2<sup>b</sup> | 16.4     |
| Sampling city (D1) and season | n | Chloramphenicol | Oxolinic acid | Tetracycline | Sulfamethazine | Sulfamethoxazole | Thiabendazole | Dimetridazole | Metronidazole | Trimethoprim | Metoprolol | Clofibric acid | Caffeine | Carbamazepine | Diclofenac | Salicylic acid |
|-----------------------------|---|----------------|---------------|--------------|----------------|-----------------|---------------|---------------|---------------|--------------|------------|----------------|----------|---------------|-------------|----------------|
| **Wuhan** (3.0)             | 6 | num            | 0             | 0            | 0              | 0               | 0             | 0             | 0             | 0            | 0          | 0              | 0        | 0             | 0           | 0              |
|                             |   | med            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 13.1          | <1.5         | <0.4       | <5.2            | 4.1      | 0.6           | 0.9         | <1.2          | <13.0       |
|                             |   | max            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 26.5          | <1.5         | <0.4       | <5.2            | 4.1      | 0.7           | 5.7         | <1.2          | <13.0       |
| **Xiamen** (1.0)            | 5 | num            | 0             | 0            | 0              | 0               | 0             | 0             | 0             | 0            | 0          | 0              | 0        | 0             | 0           | 0              |
|                             |   | med            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 13.1          | <1.5         | <0.4       | <5.2            | 4.1      | 0.6           | 0.9         | <1.2          | <13.0       |
|                             |   | max            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 26.5          | <1.5         | <0.4       | <5.2            | 4.1      | 0.7           | 5.7         | <1.2          | <13.0       |
| **Nanjing** (4.4)           | 5 | num            | 0             | 0            | 0              | 0               | 0             | 0             | 0             | 0            | 0          | 0              | 0        | 0             | 0           | 0              |
|                             |   | med            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 23.4          | 11.6         | 15.5       | <5.2            | 4.1      | <0.4          | 33.6        | <1.2          | 19.2        |
|                             |   | max            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 38.2          | 14.7         | 17.5       | <5.2            | 4.1      | <0.4          | 53.1        | <1.2          | 41.2        |
| **Xiamen** (1.0)            | 5 | num            | 0             | 0            | 0              | 0               | 0             | 0             | 0             | 0            | 0          | 0              | 0        | 0             | 0           | 0              |
|                             |   | med            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 16.8          | 9.5          | 8.4        | <5.2            | 4.1      | <0.4          | 15.9        | 1.4           | 15.1        |
|                             |   | max            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 16.8          | 9.5          | 8.4        | <5.2            | 4.1      | <0.4          | 15.9        | 1.4           | 15.1        |
| **Wuhan** (3.0)             | 6 | num            | 0             | 0            | 0              | 0               | 0             | 0             | 0             | 0            | 0          | 0              | 0        | 0             | 0           | 0              |
|                             |   | med            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 16.8          | 9.5          | 8.4        | <5.2            | 4.1      | <0.4          | 15.9        | 1.4           | 15.1        |
|                             |   | max            | <0.7          | <0.3         | <0.9          | <3.7            | <3.3          | <2.7          | 16.8          | 9.5          | 8.4        | <5.2            | 4.1      | <0.4          | 15.9        | 1.4           | 15.1        |
| Sampling city (DI) and season | n  | max  | <0.7 | 0.3 | 0.9 | <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | <3.0 | <4.1 | <0.4 | 0.4 | 41.6 | 0.7 | <1.2 | 16.8 |
|-----------------------------|----|------|------|-----|-----|------|------|------|------|------|------|------|------|-----|------|-----|------|------|
|                             |    | max  | <0.7 | 0.3 | 0.9 | <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | <3.0 | <4.1 | <0.4 | 0.4 | 41.6 | 0.7 | <1.2 | 16.8 |
| Changsha (2.6) Dry 5 num   | 1  | 1    | 0    | 0   | 0   | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 3   | 4    | 0   | 0    | 1    |
|                             | 2  | <0.7 | 1.9  | 0.3 | 0.9 | <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | 3.0  | <5.2 | <4.1 | <0.4 | 74.1 | <0.7 | <1.2 | <13.0 |
|                             | 3  | 1.0  | 2.9  | 1.1 | <0.9| <3.7 | <3.3 | 6.2  | <5.2 | <1.5 | 3.6  | <5.2 | <4.1 | 0.5  | 99.1 | <0.7 | <1.2 | 24.0  |
|                             | 4  | <0.7 | <0.3 | <0.9| <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | 1.5  | <5.2 | <4.1 | <0.4 | 32.4 | <0.7 | <1.2 | <13.0 |
|                             | 5  | <0.7 | <0.3 | <0.9| <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | 1.8  | <5.2 | <4.1 | <0.4 | 34.2 | <0.7 | <1.2 | 14.2  |
| Guangzhou (5.2) Dry 5 num  | 1  | 1    | 0    | 0   | 0   | 0    | 2    | 4    | 0    | 1    | 2    | 2    | 1    | 4    | 5    | 2    | 2    | 3    |
|                             | 2  | 2    | 10.6 | 4.5 | <0.9| <3.7 | 41.9 | 6.3  | <5.2 | <1.5 | 6.5  | 10.2 | <4.1 | 2.3  | 23.4 | 2.6  | 3.2  | 16.0  |
|                             | 3  | 7.3  | 15.1 | 7.9 | <0.9| <3.7 | 77.2 | 21.2 | <5.2 | 11.6 | 10.4 | 14.2 | 8.5  | 3.0  | 185.7 | 3.3  | 3.7  | 19.6  |
|                             | 4  | <0.7 | <0.3 | <0.9| <3.7 | <3.3 | 9.0  | <5.2 | 5.6  | 2.2  | <5.2 | <4.1 | <0.4 | 20.1 | <0.7 | <1.2 | <13.0 |
|                             | 5  | <0.7 | <0.3 | <0.9| <3.7 | <3.3 | 5.5  | 9.1  | <5.2 | 9.7  | 5.1  | <5.2 | <4.1 | 0.7  | 41.8 | 1.8  | <1.2 | 20.4  |
| Zuhai (1.9) Dry 5 num       | 1  | 0    | 0    | 0   | 0   | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 5    | 5    | 0    | 0    | 1    |
|                             | 2  | <0.7 | <0.3 | <0.9| <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | <0.4 | <5.2 | <4.1 | 2.1  | 24.3 | <0.7 | <1.2 | <13.0 |
|                             | 3  | <0.7 | <0.3 | <0.9| <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | <0.4 | <5.2 | <4.1 | 2.5  | 28.5 | <0.7 | <1.2 | 14.2  |
|                             | 4  | <0.7 | <0.3 | <0.9| <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | <0.4 | <5.2 | <4.1 | <0.4 | 32.2 | <0.7 | <1.2 | 24.4  |
|                             | 5  | <0.7 | <0.3 | <0.9| <3.7 | <3.3 | <2.7 | <5.2 | <1.5 | <0.4 | <5.2 | <4.1 | <0.4 | 48.0 | <0.7 | <1.2 | 26.8  |
| Macau (2.2) Dry 5 num       | 1  | 0    | 0    | 0   | 0   | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 5    | 5    | 0    | 0    | 2    |
|                             | 2  | 0    | 0    | 0   | 0   | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 5    | 5    | 0    | 0    | 2    |
| Sampling city (DI) and season | n | Chloramphenicol | Roxithromycin | Azithromycin | Tylosin | Sulfadiazine | Sulfamethoxazole | Thiabendazole | Dinitroazin | Metronidazole | Trimethoprim | Metoprolol | Clofibric acid | Caffeine | Carbamazepine | Diclofenac | Salicylic-acid |
|------------------------------|---|-----------------|---------------|-------------|--------|-------------|-----------------|---------------|-------------|--------------|-------------|-------------|----------------|----------|----------------|-------------|--------------|
| Wet 5                        | num | <0.7           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 2.7      | 22.2          | <0.7      | <1.2         | 14.3        |
| med                          | 0   | 0              | 0             | 0           | 0      | 0           | 0               | 0             | 0           | 0           | 0           | 0           | 0               | 5        | 0             | 0          | 5            |
| max                          | <0.7| <0.3           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 3.3      | 25.8          | <0.7      | <1.2         | 15.2        |
| Shenzhen (1.6) Dry 5         | num | <0.7           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 37.7          | <0.7      | <1.2         | 20.3        |
| med                          | <0.7| <0.3           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 46.7          | <0.7      | <1.2         | 26.0        |
| max                          | <0.7| <0.3           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 46.7          | <0.7      | <1.2         | 26.0        |
| Hong Kong (1.3) Dry 6        | num | <0.7           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 51.4          | <0.7      | <1.2         | 13.0        |
| med                          | <0.7| <0.3           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 64.1          | <0.7      | <1.2         | 13.2        |
| max                          | <0.7| <0.3           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 64.1          | <0.7      | <1.2         | 13.2        |
| Wet 6                        | num | <0.7           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 8.4           | <0.7      | <1.2         | 13.0        |
| med                          | <0.7| <0.3           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 10.0          | <0.7      | <1.2         | 13.0        |
| max                          | <0.7| <0.3           | <0.3          | <0.3        | <0.9   | <3.7        | <3.3            | <2.7          | <5.2        | <1.5        | <0.4        | <5.2        | <4.1          | 0.4      | 20.2          | <1.2      | <1.2         | 17.8        |

\[a\] DI: positive detection index, calculated by dividing total number of positive detections (levels ≥LOQ) of all compounds by the total sample number (both season) in each city. \[b\] num: number of positive detection; med: median; max: maximum \[c\] <LOQ
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