**SeweRx: Simulating baseline pharmaceutical concentrations, mass loads, and risk in American wastewater across sewershed scales**

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**Text S1** Additional details on the handling of the MEPS data.

1. Exclusion criteria for pharmaceuticals in PharmUse include:
   * prescriptions for compounds found in human diet and fecal matter, such as vitamins and minerals.
   * prescriptions for compounds naturally occurring in the body and background concentrations in wastewater, such as hormones. Notably, synthetic hormones (e.g., ethinyl estradiol) are included, while natural forms of hormones (e.g., estradiol) are excluded.
2. Miscoded prescriptions are included through manual curation. For example, combination pharmaceuticals are separated into their active ingredients to calculate mass per pharmaceutical.
3. Some drugs (such as birth control drugs) may not have the same dose each day. For simplicity, this analysis considers the average mass of drug prescribed, which indirectly accounts for some of this variability. Regardless, this remains an assumption of the model that can be changed for improved accuracy in future iterations. This assumption also may explain discrepancies in the predictions for these drugs.
4. Missing data are handled according to the following scheme:
   * If > 95% of data are missing for supply of medication, quantity, or strength for a given pharmaceutical in the MEPS data, then that pharmaceutical is eliminated from consideration.
   * If ≤ 95% of data are missing for any of these variables, the average value is computed from the available data for each pharmaceutical and imputed for the missing values.
   * Pharmaceuticals in the MEPS data that are listed without sufficient specificity (e.g., “analgesic,” “miscellaneous,” etc.) are excluded.

**Text S2.** Additional details on the handling of the Drugs@FDA data.

1. Where available, and for most drugs, the currently available prescription forms of the drug as reported in the Drugs@FDA database. Since the market availability of the drug does not affect its pharmacokinetics, discontinued forms of the drug or over-the-counter forms of the drug were used when current prescription forms were unavailable.
2. Many drugs are administered as salts, prodrugs, etc. of the compound of interest. In these cases, the administered form is treated equivalently to the parent drug of interest. Where excretion data is provided for the active form of the drug without specifying if it is the parent or metabolite, then the active form is assumed to be the parent. Conjugates are not considered unchanged, parent drug.
3. Some of the pharmaceuticals may metabolize into each other (e.g., lisdexamfetamine and dextroamphetamine) or re-form the parent drug during metabolism. Additionally, some drugs are administered as racemic mixtures, whereas other drugs are administered as the pure R- or S-isomer. This is the case for ofloxacin and levofloxacin, albuterol and levalbuterol, amphetamine and dextroamphetamine, lansoprazole and dexlansoprazole, omeprazole and esomeprazole, methylphenidate and dexmethylphenidate, citalopram and escitalopram, and cetirizine and levocetirizine. These processes are neglected in this analysis for simplicity but may explain any discrepancies in influent concentration or mass load for these drugs.
4. When more than one value is reported for excretion percentage, then the highest value is reported to make the most conservative estimate for unchanged drug entering the wastewater collection system. If the excretion percentage is reported as an inequality, the numerical portion of the inequality is reported. When the excretion percentage is not directly reported, then the following assumptions may apply:
   1. Extent of metabolism may be used where excretion data is absent to infer the maximum amount of excretion of parent drug that may occur. If there are drugs whose extent of metabolism is reported to be low or extent of unchanged excretion is reported to be high, then 70% of the parent drug may be assumed to be excreted. Similarly, if there are drugs with high reported extent of metabolism or low reported extent of unchanged excretion, then 30% of the parent drug may be assumed to be excreted (Bamfo et al., 2021). If a drug is almost completely metabolized or has trace or negligible amounts excreted unchanged, then it is considered to be 1% excreted unchanged.
   2. If a drug's excretion percentage or extent of metabolism/excretion are completely unclear, then that drug is assigned an excretion percentage of 100% as the most conservative estimate for the maximum amount of the dose that can be excreted. Notably, this does not apply for cases where some metabolism information is provided (e.g., “40% is recovered in feces,” “3% is absorbed systemically”) or where an assumption applies (e.g., the drug is administered topically and may wash off up to 100%). These are the cases where there is not enough information to apply any assumptions at all. This is true for 81 of 525 combinations of pharmaceutical and administration route and true for all administration routes for 21 pharmaceuticals: penicillin v potassium, guaifenesin, diphenhydramine, benzonatate, primidone, hydroxyzine, meclizine, nortriptyline, prochlorperazine, senna, methimazole, methylprednisolone, loperamide, haloperidol, bisacodyl, triprolidine, levalbuterol, formoterol, nitroglycerin, formoterol, dulaglutide, and umeclidinium.
   3. If the majority of the drug is reported to be excreted unchanged by a certain route without specifying a number, then that drug is assumed to be totally excreted by that route to make the most conservative estimate of the unchanged drug entering the wastewater collection system. For example, if drug A is reported to be mostly excreted unchanged in feces, then 100% of drug A is assumed to be excreted unchanged if no additional information is given.
   4. If a drug is reported to be excreted as a mixture of unchanged drug and metabolites, then the reported value is used as the most conservative estimate of drug excreted. For example, if up to 30% of drug A is reported to be excreted as mixture of unchanged drug and metabolites, then 30% of drug A is assumed to be excreted unchanged if no additional information is given.
5. Excretion percentages for the same pharmaceutical but different administration routes cannot be substituted due to differences in metabolism that affect the unchanged excretion percentage (Le, 2024). If the administration route is not specified in the Clinical Pharmacology section of the label but an excretion percentage is provided, the administration route is assumed to be the same as the route listed at the top of the label (e.g., a label says tablets at the top and then simply provides a number for percentage excreted but does not specify if it is for an oral dose). If the administration route in the Clinical Pharmacology section of the label is different from the administration route at the top of the label, then the excretion percentage is considered unknown and assigned a value of 100% as the most conservative estimate (e.g., a label says tablets at the top and then provides excretion percentages following intravenous administration), except in limited cases where the two administration routes have been demonstrated to have similar pharmacokinetics.
6. Only urinary, fecal, and topical wash-off excretion routes are considered. Notably, if urinary excretion is reported but fecal is not, or vice versa, the other excretion route is considered negligible. Other excretion routes (sweat, breast milk, etc.) contribute negligibly to total drug excretion for most drugs (Barreto et al., 2021). For drugs that are taken orally, the unabsorbed portion is assumed to be excreted unchanged in feces (Ernstmeyer & Christman, 2023). For drugs that do not pass through the digestive system, the absorbed portion is reported as the maximum excretion percentage when excretion percentage is unspecified, and the unabsorbed portion is assumed to not enter the wastewater collection system. Topical drugs are the exception; the unabsorbed portion is assumed to be washed off (Daughton & Ruhoy, 2009). Otic, ophthalmic, vaginal, and dental drugs frequently lack excretion information; they may be up to 30%, 80%, 30%, and 1%, respectively, absorbed into the systemic circulation (Hussain & Ahsan, 2005; Le, 2024; Paderni et al., 2012; Vaajanen & Vapaatalo, 2017). Therefore, these absorption values were used in the absence of additional excretion data for these administration routes. Furthermore, epidural administration leads to high absorption into systemic circulation, and it can be substituted with the excretion percentage following intravenous administration. Epidural administration also results in higher absorption than intrathecal administration, which makes the excretion percentage following epidural administration a conservative approximation for the excretion percentage following intrathecal administration (Gustafsson, 1990). Additionally, intramuscular and subcutaneous administration involve absorption into the bloodstream, and so the excretion percentage following intravenous administration can be used to make a conservative approximation for the excretion percentage following these administration routes (Le, 2024).
7. The data included in the FDA labels is not necessarily nationally representative or inclusive of all demographics. Additionally, in most cases, the excretion percentages reported here are for ideal excretion (i.e., a typical healthy patient not taking any other, interacting drugs). If excretion percentages are differentiated for extensive versus poor metabolizers for certain drugs, the higher unchanged excretion percentage is reported.
8. There are some administration routes reported in MEPS for certain pharmaceuticals that are not reported for those pharmaceuticals in Drugs@FDA. In these cases, these pharmaceuticals were manually curated by matching their NDC codes to their FDA labels, and excretion percentages were assigned using the assumptions described above.

**Text S3.** Additional details on the handling of the CompTox data.

1. Pharmaceuticals were added into PharmUse at two separate times in November 2024 and November 2025. Therefore, both versions v2.4.1 and v2.6.0 of CompTox were queried.
2. One DTXSID identifier is selected for pharmaceuticals with more than one DTXSID (e.g., sulfacetamide sodium). The “approved name” is selected over the available synonyms, or if multiple names are listed as approved, then the name with the most complete information is selected.
3. Dulaglutide and senna do not have DTXSID identifiers and are therefore excluded from the toxicity and physicochemical property datasets in CompTox.
4. Data missing from CompTox is not imputed but indicated by NA.
5. All toxicity values are converted to µg/L. Where necessary, the original papers were referenced to convert from less conventional units (e.g., ng/egg). If the concentration could not be determined from the given units (e.g., % diet), then those measurements were excluded. For toxicity values reported as mass per body weight, the conversion to LC50 or NOEC was conducted by assuming that the reported value is the concentration to which the organism is exposed in the water and that the organism takes up the full dose. In these cases, all values were converted to concentrations using the density of water.
6. Experimentally-derived physicochemical properties were used when available, and predicted properties were used otherwise. If multiple experimental or predicted values were available, then the median value was selected.
7. For the biotransformation prediction from OPERA, 0 indicates unlikely biotransformation, and 1 indicates likely biotransformation.

**Text S4.** Additional details on the handling of the enviPath and EPA CTS data.

1. enviPath was queried by providing the SMILES identifier for each pharmaceutical. Each search initially used the default enviPath package. For most pharmaceuticals, enviPath predicted a pathway in real-time using the anonymous package and the Global Default Setting, including the EAWAG-SOIL package. For select pharmaceuticals (e.g., ibuprofen, acetaminophen, and other commonly-studied pharmaceuticals), known pathways stored in the enviPath database from literature were used to report biotransformation likelihood. Biotransformation likelihood was assessed by the presence of an arrow-based pathway. If there were arrows, then biotransformation likelihood was high and assigned as 1; if not, then the likelihood was low and assigned as 0. The probability of each branch in the generated pathway was disregarded to maintain a binary approach but may be incorporated in future model iterations to add model complexity.
2. The EPA CTS was queried by running batch text files with 9-10 SMILES identifiers at a time under the Generate Transformation Products workflow and Abiotic Hydrolysis reaction library. All other settings were left at their default prior to submitting the job. The generation of transformation products and their likelihood of formation are the output of the CTS batch search; if the likelihood of at least one transformation product is “likely,” then hydrolysis likelihood is assigned 1 and otherwise is assigned 0. The CTS software was not compatible with the pharmaceuticals conjugated with metals and did not return results for bismuth subsalicylate, divalproex sodium, silver sulfadiazine, sulfacetamide sodium, and penicillin v potassium.
3. 9 pharmaceuticals (cadexomer iodine, dexlansoprazole, dulaglutide, gentamicin, ivermectin, povidone iodine, senna, spinosad, witch hazel) do not have SMILES identifiers. The biotransformation and hydrolysis predictions for these pharmaceuticals are indicated by NA.

**Text S5.** Calculations for average daily mass excreted, average duration of prescription, and total number of prescriptions.

The average daily mass excreted (M) of active pharmaceutical ingredient (API) associated with each prescription can be computed from the MEPS data by Equation S1:

where e is the excretion fraction for the given pharmaceutical and administration route, r is the number of prescriptions of each pharmaceutical, a is the mass of API per dose, q is the quantity of doses in each prescription, and d is the supply of medication in days. The average duration of prescription for each pharmaceutical was computed by averaging the medication supply column in the MEPS data for each pharmaceutical. The number of prescriptions per pharmaceutical was computed by summing the prescription events associated with each pharmaceutical.

**Text S6.** Additional details on dataset generated from the PRISMA literature search.

1. The literature-reported influent concentrations are often average or median concentration values reported in the papers. If a range is reported, the average concentration value is used. If the minimum concentration is ND, then the maximum value is used. When ranges are too large to have a meaningful average, they are excluded (there is one case where this occurs with a range of 78-10900 ng/L).
2. Influent from hospitals and landfill leachate are included in the literature-reported data and may be higher than influent from other sources (e.g., residential use). However, the hospital and landfill streams still enter the municipal wastewater flow and therefore are still included.
3. Pseudoephedrine + ephedrine refers to reports of these pharmaceuticals combined, which are assumed to be 50% pseudoephedrine and 50% ephedrine. These assumptions are carried out in the pharmflush.R script and only pseudoephedrine is retained.Ephedrine is not included in PharmFlush.

**Text S7.** Full lists of pharmaceuticals exhibiting predicted and/or reported mass loads greater than the NOEL and for which the predicted mass load for smaller sewersheds exceeds the predicted mass load for larger sewersheds.

The following 28 pharmaceuticals have at least one predicted mass load that exceeds at least one NOEL:

* acetaminophen
* amoxicillin
* atenolol
* atorvastatin
* carbamazepine
* citalopram
* diazepam
* diclofenac
* enalapril
* fluorouracil
* fluoxetine
* furosemide
* gemfibrozil
* hydrochlorothiazide
* hydrocortisone
* ibuprofen
* levonorgestrel
* losartan
* metformin
* methocarbamol
* naproxen
* norethindrone
* nortriptyline
* ranitidine
* simvastatin
* spironolactone
* venlafaxine
* verapamil

The following 16 pharmaceuticals have at least one predicted mass load and at least one reported mass load that exceeds at least one NOEL:

* acetaminophen
* atenolol
* atorvastatin
* carbamazepine
* citalopram
* diclofenac
* fluoxetine
* gemfibrozil
* ibuprofen
* metformin
* methocarbamol
* naproxen
* ranitidine
* simvastatin
* venlafaxine
* verapamil

The following 7 pharmaceuticals have predicted mass loads below all NOEL values and at least one reported mass load that exceeds at least one NOEL:

* ketoprofen
* metoprolol
* propranolol
* sertraline
* sulfamethoxazole
* temazepam
* trimethoprim

The following 14 pharmaceuticals have at least one predicted mass load exceeding at least one NOEL for smaller sewersheds (100 or 1,000 people) with predicted mass loads for larger sewersheds (100,000 or 1,000,000 people) remaining below all NOEL values:

* acetaminophen
* amoxicillin
* citalopram
* diazepam
* enalapril
* hydrochlorothiazide
* hydrocortisone
* levonorgestrel
* losartan
* naproxen
* norethindrone
* nortriptyline
* simvastatin
* venlafaxine

**Figure S1**. The reported mass load (black), predicted mass load (blue), human NOEL (red), vertebrate NOEL (orange), and invertebrate NOEL (violet) for the 313 considered pharmaceuticals (where available). The predicted mass loads are modelled for sewersheds of size 100, 1,000, 110,000, and 1,000,000 as labeled on the graphs. Notably, the sewershed with 110,000 residents represents the average population for each sewershed considered in the literature search (110,262 people). For these predictions, the actual value of 110,262 was used in PharmFlush. In all cases, only those reported mass loads with detectable measurements are included, and zero-valued predicted and reported mass loads are excluded due to logarithmic scaling. Figure S1 continues from this page through page 52.

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