Q&A with Mitch Kostich from the September 24th webinar "Pharmaceutical Residues in Municipal Wastewater"

Dendra Best: Are you working in partnership with USGS?

Not on the projects we described in the webinar. We do work closely with them on some related projects, though. For example, please refer to:
http://www.epa.gov/nerl/download_files/documents/FactSheet.FINAL.7.1.10.pdf

Catherine Zimmer: EPA staff: thank you for this webinar. Re: CWA--are changes to rules related to pass through chemicals (e.g. pharms), being considered?

Sorry, I am a researcher trying to inform the regulatory process, but I am not involved in the rule making process, so am poorly suited to answer this question. The best place to get the answer to your question is EPA's Office of Water: http://www2.epa.gov/aboutepa/about-office-water

Dendra Best: Also Canadian Experimental Lakes projects?

The Experimental Lakes project with EE2 was a very interesting project that one of the contributors (Jim Lazorchak) co-authored. We did not discuss estrogens in this webinar, because the results have not yet been published. Marc Mills will be publishing results from the analysis of estrogens and androgens in the effluent samples we studied. It may be interesting to compare to levels of EE2 used in the Experimental Lakes experiment.

Marjorie Copeland: Are you including excreted chemo therapy drugs or radiation therapy?

We modeled PECs for chemotherapy drugs, and the predicted concentrations were quite low relative to daily dose size, so none of those drugs made the cut for inclusion in the effluent study. There is only a little occurrence data for this class of drugs. Given that we put a daily dose of different drugs on the same footing (in order to simplify the analysis), given that many chemotherapy agents have fairly dramatic toxicity at the daily dose level (unlike most drugs we considered), and given that some chemotherapy agents (such as alkylating agents) probably do not have a definable threshold effect dose (again, unlike most of the drugs we considered), this class of drugs probably deserves a specialized analysis beyond the scope of what was described today. The marketing data we used did not include any radionuclide containing chemicals, so these were not covered by our work.

Jeff Brousal: The concentration may vary with seasons and usage .

You are correct that this is an important consideration, particularly for some classes of drugs (hay fever meds, flu meds, etc). We have not done any seasonal sampling ourselves. The 62 published studies we

summarized were conducted at various times of the year, and should therefore capture some of the seasonal variation. The measured concentrations reported in these studies are still consistent with our predicted concentrations, so we think the 10-fold application factor we propose accommodates not only geographic variation in concentration, but also temporal/seasonal variations.

Allen Gilliam: would like to see his basis for these "conclusions"

Please look over the papers (see links on webinar page) describing the scientific details, and contact me if you have specific questions (kostich.mitch@epa.gov)

Christine Gasparine: has the research addressed water conservation in developing the DPD?

Both increasing water conservation and increased use of medicines (due to aging populations, more drugs for more conditions, and wider availability of health insurance covering medications) could increase the concentrations of drugs found in the environment. However, for most drugs the potential exposure rates are so low compared to effect levels that the modest fold increase in concentration would not incite a major change our conclusions.

Scott Bessler: gut drug absorption is pretty variable across vertebrates.

Yes it is. This is why we assume 100% bioavailability/absorption when trying to model potential effects in aquatic life. Absorption cannot be higher than 100%, so this is a conservative default value that should capture the range of possibility.

Dendra Best: does the research address re-concentration in biosolids and then reintroduction to groundwater from biosolid spreading?

Not directly, and I think biosolids deserve some attention in this regard. However, the 62 studies we summarized that provide measurement data include a large number of surface water and ground water measurements that had the opportunity to reflect potential contributions from i.e. runoff from land-applied biosolids. We did not find any measurements that could not be accommodated by our wastewater model (with the exception of the one ethinyl estradiol concentration, but again, we have fairly good reasons to suspect this is a technical artifact), and therefore we did not find evidence of the biosolids to water route commonly resulting in water concentrations much different from what one would expect just modeling wastewater effluent. Still worth a closer more targeted look.

Jeff Brousal: bioaccumulation?

Food chain exposures were beyond the scope of the studies described in the webinar. Today's webinar was really focused on water column exposures. The extent of bioaccumulation of pharmaceuticals is one of our active areas of research.

Alicia Wilson: Is the DEA data available in the STOTEN article? Otherwise, how can we get the DEA data you used?

The data was downloaded from the DEA ARCOS database back in 2004. However, I cannot find live links to the data any more (the old link is dead). If you contact me directly (kostich.mitchell@epa.gov), I can send you a copy of the 2004 data we used.

JN Carleton: Are the MECs measured in undiluted wastewater, or ambient waters?

The MECs we presented from our effluent study are from undiluted finished wastewater effluent sampled from within the plant. The MECs we summarized from the 62 other studies looking at pharmaceutical occurrence included measurements in ambient surface water, ground water, finished drinking water, wastewater influent, and wastewater effluent.

Mark J: How do PECs relate to sensitive adults? There is a distribution in sensitivity just like there is a distribution of PECs

We used the minimum daily recommended dose as our benchmark, which is the lowest dose recommended for use in more sensitive but otherwise normal and healthy patients. For some people and some drugs the maximum dose rates may be much higher, in order to accommodate decreased sensitivity. For the most part, though, when we speak of sensitive subpopulations we are focused on pregnant women, small children, patients with impaired kidneys or livers, and people with allergies. Dose response in these populations is often not known (and hard to know without endangering test subjects), so it is harder to calculate risk quotients (concentration/dose) for these groups. This is a good subject for further investigation that physiological modeling may help us understand.

Christine Gasparine: Has there been any study on young adults who are not using prescribed drugs to find is these drugs are in their blood, urine and feces?

Not to my knowledge. It would be interesting but technically challenging to do.

Jeff Brousal: Nice analytic technique!

Thanks! Angela Batt developed the method, and has a separate publication describing the details of the method (Batt, Kostich, and Lazorchak. Analytical Chemistry, 2008).

Marjorie Copeland: Any chance your findings on APIs are shared with those working on the Unregulated Contaminant Monitoring Rule update?

Yes, we communicate our research results to the USEPA Office of Water.

Allen Gilliam: ok, so it's well established "normal" human consumption of APIs in potable water is probably not harmful. What about aquatic life such as the water flea and fathead minnow sublethality (growth and reproductivity)?

There is greater uncertainty regarding effects in aquatic life than there is for healthy adult humans. Nevertheless, our relatively conservative approach of comparing water concentrations to effective plasma concentrations suggests that water concentrations of the vast majority of pharmaceuticals are far below the effective plasma concentrations. For the dozen or so APIs whose environmental concentration approaches effective plasma concentrations, we are interested in gathering more detailed concentration response data. For the others, we continue to look out for data suggesting that comparison to effective plasma concentrations is an inadequate approach. We have not seen convincing data to suggest that though.

Alicia Wilson: Is the model available to other governmental entities for use in statewide or regional studies?

Yes. The model is simple, and we are happy to share it.

Akin Babatola: Perhaps a challenge that Mitch and cohorts overcome, but he is not presenting here is the measurement and sampling technologies they used in the wastewater studies. We have found that prolonged integrative sampling using such technologies as SPMD or POCIS will provide rather significantly different results (orders of magnitude higher in many cases) than the 24-hour composite samples and the data and narratives from this technology.

My understanding may not reflect the latest developments, however last time I investigated we came to the conclusion that Integrated sampling has complementary properties to composite and grab sampling of water, but is not a reasonable substitute in most cases. Composite and grab sampling of water provide direct measurement of water concentrations, and can be used to detect soluble analytes regardless of hydrophobicity. Integrated samplers typically use a solid matrix to 'extract' chemicals from the water. The efficiency of extraction by integrated samplers varies for different chemicals, and is typically poor for hydrophilic chemicals (the majority of pharmaceuticals). More problematic is that there is usually no reliable way to back-calculate the water concentration of an arbitrary contaminant based on the amount captured by the integrated samplers. So it is not clear to me how one could accurately compare numbers from integrated sampling and 24-hour composites. Integrated samplers are good for detecting presence of rarely occurring contaminants (a nice strength), but not so great for quantitation.

Marjorie Copeland: So, there's not really a concern for human consumption of drinking water?

My opinion is that for healthy human adults there is no concern. For other human sub-populations, risks are harder to rule out, as details of dose response are not well defined, but we have no good data or models to suggest a cause for concern for consumption of drinking water.

Alicia Wilson: Could the model be used or tweaked to accommodate the integrative sampling technologies results?

The problem with integrative sampling (at least a few years back when I studied it) is that back-calculation of water concentrations based on how much material was captured by the integrated sampler is not very reliable. If we could back-calculate a water concentration reliably, accommodating integrated sampling results should be a straightforward extension of what was presented today.

Eric Agnew: Since so many of these are antibiotics, is the intent of the "notice" sent out yesterday intended to lower the presence identified or passed-through?

Eric Agnew: The "notice" is the antibiotic reduction piece sent out yesterday (sorry, didnt have time to read it).

I don't know anything about the notice, so cannot comment.

Marjorie Copeland: Still want to know about pass through chemo therapy drugs?

Please see the answer to your earlier question.

Kanak: What about direct potable reuse or water reuse plants? Would these chemicals be of more concern?

The concentrations we modeled and measured were wastewater effluent concentrations, so the concentrations being fed to the reuse plant may be comparable to those concentrations. When summarizing the 62 occurrence studies, we captured some data from studies looking at reuse scenarios. We did not find concentrations reported in these papers that are dramatically different from those reported in other scenarios (drinking water drawn from bodies of surface water).

Allen Gilliam: Marj: public perception from the "news" we see causes the concern I'm deducing.

It is easy to misinterpret frequent detection of an analyte (what is usually reported in the media) as implying a dangerously high level of an analyte, but often it just reflects a very, very sensitive chemical analytical method detecting vanishingly low concentrations.

Phillip Flanders: Does this approach address the effect of mixtures of drugs on aquatic life? My sense is that it does not.

We did not do as much mixture analysis when looking at aquatic life, because analyzing single drugs already suggests that for some individual drugs effects on aquatic life cannot be discounted and deserve further investigation. We did the mixture analysis on human consumption because one-drug-at-a-time analysis suggested little concern and we were interested in seeing whether concerns would be

dramatically higher for mixtures (they were not). We are interested in studying mixtures in aquatic life, but have several single drugs that we would like to evaluate first.

Credit Valley Conservation 2: Is there any data that speaks to the origin of the drugs (metabolized vs flushed down the toilet?)

Only rough estimates of proportions disposed vs. consumed are available. This is an active area of research for Christian Daughton (USEPA).

Catherine Wooster: It would be interesting to compare US results to results from another country.

We have not done this, but I think this has at least been touched on by researchers in Europe and Asia. I do not know of a recent synopsis off hand though.

Mike Carter: Credit Valley Conservation 2: don't forget to include the discharges from the Pharmaceutical plants manufacturing these drugs. The plant I worked at routinely "lost" 10KG of formulated product per batch. Less for injectbales, more for pastes.

Definitely a very different scenario that our work cannot provide much insight into. Certainly worth a look, and there are several research groups studying this.

Marjorie Copeland: Were any endocrine disruptors included?

Several estrogens and androgens were measured in our effluent samples by a collaborating research group (Marc Mills et al.), but those results have not been published yet, so I did not describe them. Please keep an eye out for a publication though.

Chris Cotelesse: What are the 10 APIs identified for future study and when will that happen?

The top six are listed on slide 25 of our presentation (top mec/epc). It is not really clear how much deeper we need to dig, as what constitutes a 'safe' risk ratio is somewhat subjective, but the complete listing is in our effluent publication. There are some other academic research groups that are already looking at some of these other drugs (for instance propanolol) in fish. We do not have firm plans yet. We have a number of projects underway where we are trying to compare risks of pharmaceuticals to risks posed by other contaminant classes that we would like to complete before prioritizing further work.

Tanya Spano (MWCOG): Is anyone doing anything to see if there are contributions via other water routes (e.g.stormwater)?

Yes, I think runoff from land applied biosolids is an area of active research, but I am not up to date on the scope or progress of that research.

Tucker Burch: Mitch, you mentioned that you dealt with uncertainty by using protective defaults for uncertain parameters. Have you ever considered using a Monte Carlo simulation to incorporate uncertainty into your risk analysis?

Answered in a separate e-mail chain.

Tanya Spano (MWCOG): Are there any studies being done to address the potential accumulation or concentration of any of these compounds in reuse situations? Also, what level of treatment where those WWTPs operating at? Evaluations in the Chesapeake Bay region seemed to indicate that enhanced nutrient removal did breakdown some compounds. Is that still the case?

There has been some work by various research groups looking at concentrations in reuse situations, but I am not familiar enough with the details to describe them.

Xueyuan Yu: What's your opinion on those in vitro bio-analytical screening (cell-based bioassays) which are of high throughput?

In some cases in vitro bioassays can have a significant per sample cost advantage over standard chemical analysis. They can also integrate effects from different contaminants with a common mode of action. Their drawbacks primarily relate to the difficulty in getting precise quantitation, particularly when there may be interference from other substances (potentially naturally occurring) in the water, and lack of structural specificity – when you detect i.e. estrogenic activity with such an assay, you do not know which estrogen may be causing the effect. For studies such as ours, accurate quantitation and analyte identification were important, so we went with chemical analysis. For other studies, those considerations may not be as important, and in vitro biological assays may have considerable value.

Scott Seery: I hoped for clarification on the waste water sampled for the study. Because I arrived a bit in the presentation due to audio issues, I wasn't clear if these samples were collected from final treated waste water or untreated, and also whether all WWTP employed tertiary treatment practices. Thank you.

Yes, the samples were collected from final treated wastewater. We did not collect treatment details for the plants we sampled.

Marjorie Copeland: Were any samples taken at sites on streams below pharmaceutical plants ?

I am not sure of the location of pharmaceutical plants relative to our wastewater plants.

Alicia Wilson: Were whole water grab samples taken and compared to the results of the composite samplers to see the differences in concentrations? If so, what was the outcome?

We only collected composite samples. Comparison to other published data suggests that grab samples at smaller plants sometimes result in concentration up to about twice what we observed in composite samples at these large plants. It is not clear if the differences are due to composite vs. grab sampling, or due to large vs. small plant, or something else.

Eric Agnew: Were the names of the 50 largest WWTPs disclosed?

No, they participated in the study on the condition of non-disclosure of plant identities.

Chris Angel: Mitch did a great job covering lots of info. Thank You!

Thank you for your interest and kind words!

Jim Mullowney: I would argue that the modeling does not work for Cytotoxic drugs because we are not considering the side effects of the drug verses the therapeutic dose, OSHA has a zero exposure limit for cyclophosphamide and the effective dose is 4000 mg. A side effective dose is any amount

Among the different drug classes, our approach is least applicable to cytotoxic drugs for the reasons you mention. I believe a more detailed approach taking the peculiar properties of cytotoxic drugs into account is warranted and is tractable. I hope to get to such an analysis in the near future.

Wale Adewunmi: Were the PECs compared in any way with published concentrations that have triggered endocrine disruption in aquatic organisms?

Unfortunately, although estrogens and androgens were analyzed in our effluent samples by a collaborating group, the results are not yet published. Marc Mills is the researcher who led that effort. We did conduct a review of published concentrations of estrogens and compared them to effect levels proposed by Caldwell et al. The results can be found in Kostich, Flick, and Martinson (2013). Environmental Pollution 178:271.