

**Pharmaceuticals in the Environment**  
**PhRMA Briefing Paper**  
**Human Health**

Chemicals used as active pharmaceutical ingredients (APIs) are among the most thoroughly studied substances in the world for their effects on human health. Billions of dollars are spent every year to discover and evaluate the efficacy and safety of new molecular entities that can stop the effects of human diseases. Government agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have rigorous regulations that guide the collection and evaluation of information required to support the safety and efficacy of new pharmaceutical compounds. The FDA creates summaries of its evaluations of new APIs and makes them available to the public when the molecule is approved for use as a new medicine in the United States.

Acceptable use of an API in patients is judged by comparing the benefits from therapy with the risk of potential side effects. Approval of a new API routinely requires testing the efficacy and safety of the molecule in laboratory models, animal studies and directly in human clinical studies. Depending on the targeted use of an API, this testing normally includes evaluation of the molecule for properties of therapeutic efficacy, of acute, chronic and reproductive toxicity, and of genotoxicity and carcinogenicity. Additional evaluations of therapeutic efficacy and side effects are determined for patients in clinical settings. In order to understand systemic exposure from administration of an API, animal and human studies are conducted to measure the time course of absorption into the body, distribution into the blood and throughout the body, metabolism by organs and tissues, and excretion of the molecule and its metabolites via the liver and kidney into feces and urine. APIs and the metabolites eliminated from humans are delivered to sewage treatment systems and then to surface waters. Detection of these chemicals has led to questions about their safety to humans who might be exposed through drinking water.

Questions about the safety of drinking water have been addressed over several years by authors from the pharmaceutical industry, academia, government and the non-government sector. To date, no published investigation has found that exposure to these detectable residues creates any appreciable risk to human health. In a report for the Drinking Water Inspectorate of the United Kingdom, Watts and Crane Associates (2007) concluded that even worst-case exposure ratios for most major pharmaceuticals provided a high margin of safety. Schwab et al. (2005) conducted human health risk assessments for 26 pharmaceuticals representing 14 general classes found in US waters by the USGS (Kolpin et al., 2002). They evaluated the safety of drinking water and fish consumption in a fashion equivalent to that used by the US EPA for drinking water under worst-case exposure conditions. The evaluation demonstrated that those detectable residues of pharmaceuticals in surface waters, and concentrations modeled under worst-case conditions, were safe and presented no appreciable risk to human health. In an evaluation of the safety of drinking water in Germany, Webb et al. (2003) concluded that risk is likely to be low from exposure to possible trace levels of pharmaceutical residues. Schulman et al. (2002) also evaluated the safety of potential residues of representative anti-cancer, lipid-regulating, anti-inflammatory, or analgesic drugs in

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drinking water in a fashion equivalent to that used by the US EPA. They found no appreciable risk to human health. In a paper published about a decade ago, Christensen (1998) concluded that there was negligible human health risk from environmental exposure to an antibiotic that can be an allergen (phenoxymethylpenicillin), a potent estrogen agonist (17 alpha-ethinylestradiol) or an anti-cancer drug (cyclophosphamide). For some perspective, Webb et al. (2003) calculated that more than 90% of the 64 pharmaceuticals they evaluated would have a safety margin of at least 150,000 to reach a single therapeutic dose from water. Or put another way, over a 70-year lifetime, less than 20 percent of a single therapeutic dose would be ingested in drinking water. All of the APIs that they evaluated had a safety margin of 1000 or more to reach a single therapeutic dose from water. These safety margins should not be a surprise even for potent pharmaceuticals, since total use of higher potency drugs is lower.

Even though questions about the safety of detectable residues of pharmaceuticals in surface waters to human health have been evaluated in published articles for at least a decade, there are still understandable questions raised by the public media about the possible impacts from the presence of these molecules. PhRMA and its member companies are committed to working with experts from appropriate scientific, regulatory, and trade organizations to openly consider and help answer these questions.

Some of these questions are addressed below:

**How do we determine what is safe?**

Techniques for establishing the safety of chemicals in drinking water and fish were published many years ago and updated by the US EPA (2000). As already mentioned, chemicals used as APIs are among the most thoroughly studied substances in the world for their effects on human health. This information can normally be directly used to establish a safe limit for APIs in drinking water and fish tissue. This has already been done for a total of about 30 APIs by Schwab et al. (2005) and Schulman et al. (2002).

**What about sensitive subpopulations that could be exposed to residues of potent pharmaceuticals such as steroids or anticancer drugs?**

It will always be important to evaluate the hazards from specific potent pharmaceuticals to ensure that any measured or calculated residues are safe. This has already been done for several of these compounds by Webb et al. (2003), Schulman et al. (2002), Christensen (1998), and Watts and Crane Associates (2007). All of the risk assessments conducted by Schwab et al. (2005) were based on the potential for children to be exposed to pharmaceutical residues in surface water. All of the authors found no appreciable risk from the APIs that they considered. PhRMA, through its Task Force on Pharmaceuticals in the Environment, is continuing to evaluate more examples of these types of potent pharmaceuticals.

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**What about metabolites?**

Metabolites are created in human patients and the responses of humans to exposure to an API and its metabolites are considered when establishing a safe limit for the API. Metabolites are also created by animals in the preclinical safety studies used to estimate any potential toxicity of an API to patients. Since the time course of exposure to metabolites in the plasma is normally measured in human and animal studies, it is possible to establish the safety of metabolites themselves from studies that have been conducted with the APIs. Many, but not all, metabolites have about the same or less potency than the parent molecule. In those cases, the safe water concentration for the parent molecule should also be safe for the metabolite.

**What about mixtures?**

Hundreds or thousands of water soluble chemicals from nature, agriculture, confined animal feeding operations, industrial settings, municipal discharges, and humans continue to enter surface waters and, therefore, potentially exist at very low, if not measurable, concentrations in drinking water sources. With the availability of new detection technologies, it is likely that more and more of these chemicals will be found. The potential for interactive responses to exposure of mixtures of trace levels of these chemicals in water continues to be a complicated and difficult scientific question. In part, this is due to the number of potential exposure combinations and the low level of information available for absorption, metabolism and target tissue mode of action for most chemicals. In the future, the large databases available for pharmaceuticals might help clarify some of the scientific assumptions associated with evaluating the potential for effects of complex mixtures at concentrations where individual chemicals are not expected to have effects.

**What about human cell responses found *in vitro*?**

Testing individual human cell lines with abnormally high concentrations of mixtures of human pharmaceuticals does not present an accurate picture of human health risks. A human is not made up of a single cell type. The large variety of human cells in tissues and organs throughout the body operate in concert to respond to exposures to many different types of natural and man-made chemicals that are routinely ingested on a daily basis. Extrapolating from a response by a cell line to impacts on human health ignores all the whole-organism safety and efficacy research already available for every pharmaceutical.

**Shouldn't we set drinking water limits for all pharmaceuticals?**

The US EPA recently evaluated a large list of chemicals, including pharmaceuticals, which could potentially meet the criteria for being placed on the Drinking Water Contaminant Candidate List (Feb 21, 2008;

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Fed. Reg. Vol. 73, No. 35, pp. 9628-9654). The only chemicals considered for the draft list that are used as pharmaceuticals were quinoline and nitroglycerin. Both are also used for industrial purposes. This demonstrates that almost all pharmaceuticals are used in such low amounts that they are unlikely to exist in surface waters in high enough concentrations to justify inclusion on a draft list of chemicals being considered for regulatory guideline limits for drinking water.

There can be special areas of the world where the water resources are so limited that they have to be recycled. For example, a draft national water quality management strategy was recently published in Australian Guidelines (2007) to propose guidelines for water recycling. In this case, water would be reused to augment drinking water supplies. So in order to get public comment, the Australian Health Ministers Conference, the Environmental Protection and Heritage Council, and the Natural Resource Management Ministerial Council published draft guidance levels for trace residues of all chemicals that could be in recycled water, including pharmaceuticals.

**What about the next new detection?**

Questions routinely occur around the safety of APIs detected for the first time in surface water using increasingly sensitive instruments. PhRMA, through its Task Force on Pharmaceuticals in the Environment, is continuing to evaluate new detections of pharmaceuticals. Scientists at some member companies are beginning to proactively publish risk assessments for pharmaceuticals (Bercu et al., 2008), even if residues have not been detected in surface waters.

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