# Roche Position on Pharmaceuticals in the Environment (PIE)

## Roche's position

Pharmaceuticals may enter the environment from production, from patient use and excretion or from improper disposal. While such releases are generally unintended, Roche basically believes that the presence of pharmaceuticals in the environment is undesirable and therefore should be minimized whenever feasible. Those releases that still occur must be assessed in a careful, scientific and differentiated way; if indicated such releases must be actively managed, treated and reduced.

Pharmaceuticals are developed to treat or prevent human disease. Roche believes that the evidence available today indicates that the benefits derived from the use of active pharmaceutical ingredients (APIs) far outweigh the risks arising from their presence in trace amounts in the environment. Roche believes that the risk to human health associated with exposure to the levels of APIs currently found in typical waters (surface, ground and drinking water) is extremely low. This is primarily based on the wealth of human health data generated as part of the medicines approval process.

Roche strongly supports the need for continued research into the possible effects associated with long-term exposure to mixtures of APIs, especially on aquatic organisms. We believe that a collaborative effort, which includes academia, regulatory authorities and industry, will provide the greatest benefit. As a company, we remain committed to obtain reliable data on our products to use as a basis for scientific risk assessment accepted by regulators worldwide and for the implementation of appropriate risk management measures to minimize the amount of our products entering the environment.

## The global situation

Pharmaceuticals are developed to treat or prevent human (or animal) disease. Their production and use, however, results in releases to the environment that cannot be completely prevented. APIs may enter the environment in a variety of ways: from the manufacturing process, from improper disposal of unused medicines and from patients who take medicines that in the end pass through the human body. Patient use is universally recognized as the primary contributor to environmental exposure by APIs.

With the ever increasing sensitivity of analytical methods APIs and their metabolites have been detected in the environment in low (parts per billion) to extremely low (parts per trillion) concentrations by various researchers in many countries. They are present in rivers, lakes and streams, in marine and groundwaters as well as in the water we use in our homes. The presence of these biologically active compounds has raised concern regarding their

potential human health and environmental impact, mainly about the potential effects associated with long-term exposure of aquatic organisms and humans. There is also uncertainty about the possible effects of mixtures of many APIs and their metabolites that are present simultaneously in the environment in trace amounts.

As releases of APIs into the environment cannot totally be avoided, it is necessary to assess their potential impact in a scientific and differentiated way.

*From a public health perspective,* the risk posed to humans by exposure to the low concentrations of a variety of APIs in the environment must be thoroughly investigated and evaluated. The quantities that have been found in the environment are in general far below the level at which they have been shown to have a therapeutic or adverse effect in humans. Indeed, various peer-reviewed publications suggest that even a lifetime of consuming drinking water containing these trace concentrations of APIs would not correspond to one single daily therapeutic dose of the respective pharmaceuticals, while the World Health Organization has concluded that pharmaceuticals in drinking water do not pose a health threat. Nevertheless, the potential long-term effects of low concentrations of these substances and the potential combination effects need to be investigated further, in order to strengthen the fact base and decide on the necessity of future protective measures.

*From an environmental perspective,* research continues at an elevated rate as scientists attempt to better understand the environmental fate and effects associated with the low concentrations of APIs present in the environment, especially in water. Studying these potential impacts is very complex due to the large variety of aquatic species, the broad range of chemicals and the combinations of APIs and other substances that may be present in the water. To date, studies concur that the low levels of APIs generally found in the water do not cause short-term impact to aquatic life. More and more scientific studies are being conducted in an effort to further understand this issue and, in particular, to evaluate the potential effects associated with long-term exposure of aquatic organisms. There are indications that certain hormones (in particular sex hormones) and other substances exhibiting hormone-like activity may have detrimental long-term effects on local aquatic populations. While Roche has historically been involved in the manufacture of synthetic sex hormones, such products are not part of our current product portfolio.

*From a regulatory perspective,* many parts of the world, including the European Union, Switzerland and the United States, soon also Canada and Japan, require that environmental risk assessments be conducted in order to obtain a marketing authorization for a new drug product. These assessments are designed to predict the amount of APIs that may enter the environment, along with the impact that the presence of these compounds may have.

Additional regulations have been enacted to address the protection of the environment associated with emissions from manufacturing facilities and waste disposal. For example, several member states of the European Union have established 'take back' programs for

unused medicines, while patients are advised not to throw away or flush their unused medicines, but to return them using established collection systems. In the United States, the government has issued guidelines advising patients in general not to flush their unused medicines, but rather to dispose of them in the household trash and use 'take back' programs where they are available.

## The situation at Roche

*Regarding environmental exposure from pharmaceuticals production,* Roche manufacturing processes and facilities are designed and operated to ensure that, as far as practicable, the APIs are not discharged into the wastewater (especially from equipment cleaning processes). All aqueous manufacturing emissions are treated in wastewater treatment plants, where a significant part of this waste is degradable and thus readily removed via biological mechanisms. If required by risk assessments, Roche facilities pre-treat wastewater using additional technologies prior to discharge. For example, one of our new manufacturing facilities in Shanghai was equipped with an UV advanced-oxidation system designed to effectively eliminate the APIs before they reach surface waters. In other facilities, the APIs are chemically destroyed before the process wastewater is released to the treatment plant. In some instances, specific wastewaters are nanofiltrated or incinerated in order to remove or destroy compounds that cannot be eliminated otherwise. The performance regarding process safety, industrial hygiene and environmental protection including waste handling at all Roche sites is inspected and reported on a regular basis by our professional auditors.

For production on behalf of Roche by third parties, Roche asks for comparable standards regarding wastes and waste disposal (beside product quality, industrial hygiene and safety) as we stipulate for our own production sites. Third party manufacturers are also audited for safety, health and environmental performance by Roche specialists.

*Regarding environmental exposure from patient use,* there obviously are limits as APIs must be taken up by patients to perform their intended function. Moreover, the farther down our products are in the medical supply chain, the less influence Roche can take. However, the increasing rate of biopharmaceuticals (*e.g.,* highly specific monoclonal antibodies) in the range of Roche pharmaceuticals is a welcome development from an environmental point of view. Due to their chemical nature as proteins they are both widely metabolized in the human body and readily degraded during sewage treatment, hence their environmental exposure is negligible.

*Regarding environmental exposure from improper disposal,* this will need an increased awareness and cooperation between patients, prescribers and distributors, specifically in view of decreasing the rate of improper private disposal resulting from patient noncompliance with their doctors' prescriptions. Roche has also established financial incentives to ensure that

unused or outdated products are returned by retailers and others in the supply chain, while our policies require that any returned or waste pharmaceutical product be incinerated rather than disposed of in landfills. Roche participates in pharmaceutical take-back programs in the EU in cooperation with the European pharmaceutical industries umbrella organisations[1]; Roche also supports the use of existing local take-back programs in the US and elsewhere, as well as the implementation of take-back programs on national levels.

*Regarding developing a better understanding of PIE issues,* Roche carries out own investigations and supports or contributes to research programs to better understand the human and environmental health impacts of PIE and to promote appropriate approaches to wastewater treatment. New APIs are investigated for biodegradability and initial ecotoxicity during their development. For registration, a full state-of-the-art environmental risk assessment is developed based on chronic environmental effects and advanced environmental fate data, as required by the pertinent regulations. While not a regulatory requirement, Roche also investigates older APIs, normally at a simpler scale, in order to assess their environmental risks.

As part of our engagement, Roche has published several own in-depth environmental risk assessments of important older Roche APIs in the peer-reviewed scientific literature[2]. Roche also makes available to the public its Safety Data Sheets[3] and short versions of our Environmental Risk Assessments[4], which contain relevant environmental data on our APIs; this information source is being used regularly by academic researchers. In addition, during the past decade Roche has provided financial support, personal expertise and technical assistance for academic research programs and investigations into the presence, effects and risks of PIE.

Roche is actively engaged in a number of initiatives to better understand the PIE issue and to minimize the amount of our products that are released to the environment. We have participated in several international and national scientific bodies, programs and meetings dedicated to studying the impact of pharmaceuticals and trace chemicals in surface waters and groundwater. These organizations include

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1 See *medsdisposal.eu,* a campaign to raise awareness on how to correctly dispose of unused or expired medicines appropriately in Europe.

2 *e.g.,* Straub JO (2017): Combined environmental risk assessment for the antiviral pharmaceuticals ganciclovir and valganciclovir in Europe. Environ Toxicol Chem *36:* 2205–2216.
Straub JO (2016): Reduction in the environmental exposure of pharmaceuticals through diagnostics, Personalised Healthcare and other approaches. A mini review and discussion paper. Sust Chem Pharm *3:* 1–7.
Straub JO (2010): Combined environmental risk assessment for 5-fluorouracil and capecitabine for western Europe. In: Knacker T, Metcalfe C, eds: 'Environmental Risk Assessment of Pharmaceuticals (ERAPharm)'; Integr Environ Assess Manag *6(S1):* 540–566.
Straub JO (2009): An environmental risk assessment for oseltamivir (Tamiflu®) for sewage works and surface waters under seasonal influenza and pandemic use conditions. Ecotoxicol Environ Saf *72(6):* 1625–1634.
Straub JO (2008): Deterministic and probabilistic environmental risk assessment for diazepam. In Kümmerer K, ed: Pharmaceuticals in the Environment; Sources, Fate, Effects and Risks, 3rd ed. Heidelberg (D): Springer, pp 343–383.

3 http://www.roche.com/sustainability/for_communities_and_environment/environment/safety_data_sheets-row.htm

4 https://www.roche.com/sustainability/environment/environmental-risk-assessment-downloads.htm

- the iPiE (intelligence-led assessment of Pharmaceuticals in the Environment) Research Programme in the scope of the collaborative IMI framework between the European Commission and EFPIA, the European Federation of Pharmaceutical Industries and Associations (2015–2019);
- the Working Group on Pharmaceuticals in the Environment of the three European pharmaceuticals umbrella organisations: AESGP, Association of the European Self-Medication Industry; EFPIA, European Federation of Pharmaceutical Industries and Associations; Medicines for Europe, European Generics and Biosimilars Association; (2012– )
- the EU PHARMAS Research Program on human and environmental risks caused by antibiotics and cytostatics in the environment (2011–2014),
- the German START Program on reducing the occurrence of pharmaceuticals in drinking water (2007–2008); and others, including scientific societies and congresses.

## More information

Position papers on various environmental topics:

- Pollution – we protect air, water and soil: http://www.roche.com/position_pollution__prevention_and_reduction.pdf
- Water – the basis of all life: http://www.roche.com/position_paper_on_water.pdf

Environmental performance:

- Roche SHE performance : http://www.roche.com/corporate_responsibility/environment/she_performance.htm

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