Data requirement and risk assessment in Pharmaceuticals.
Where can we use extrapolation tools?

Gerd Maack, Federal Environmental Agency (UBA), Germany

An Environmental Risk Assessment (ERA) for pharmaceuticals according to the EMA guidelines is a product based tiered approach, with an exposure estimation in phase I. Only if respective triggers are reached an in depth phase II assessment is necessary, involving effect and fate tests of different levels. Whereas for human pharmaceutical products, long term effect tests are obligatory, for veterinary medical products, due to a different exposure regime, normally acute effect tests are required. The effect tests have to cover all three trophic levels, i.e. plants, invertebrates and vertebrates. In both cases the guidelines clearly define which kind of tests, preferably according to OECD guidelines, are necessary. For substances with specific Mode of Action like endocrine active substances, antibiotics and anti-parasiticides a so called “tailored” ERA is foreseen, reflecting the respective specific mechanisms, not covered by the standard tests. Both guidelines are quite strict and explicitly require the specific tests mentioned in the respective parts of procedure. Read Across, Modelling and Extrapolations are not accepted.

On the other side, in Germany alone there are approximately 1200 human pharmaceutical substances on the market with a potential environmental impact, but sufficient data to adequately assess environmental risks is only available for a small proportion of these. This is especially true for those substances received marketing authorization, before an environmental risk assessment became obligatory in Europe in 2006. Even for well-known substances such as ibuprofen, diclofenac, and carbamazepine there are insufficient data available only.

It would be unrealistic to experimentally assess the hazards and environmental occurrence of all of these in a timely manner. Therefore, it is necessary to develop a concept that allows a proper judgment of the environmental impact of these substances, individually and in mixtures with other substances, including pesticides, biocides, and industrial chemicals without the need for extensive experimental testing. This prioritisation concept then could also be used to identify potential environmental risks of new APIs during the early stages of the development process. Yet, all of the existing models available like e.g. the fish plasma model, the drug target model and even more QSAR and Read Across approaches are lacking a proper validation and calibration.

Independent of the awaiting validation and calibration, this concept can only be used for ranking pharmaceutical active substances and to help deciding for which substances a full assessment with apical endpoints are necessary. Molecular and biochemical end points usually do not provide sufficient information for a quantitative environmental risk assessment for any specific pharmaceutical. This holds true for assessment according to the EMA guidelines, but also for substances evaluated according to the water framework directive.