incorporating data from plasma chemical-binding protein experiments, liver metabolism and clearance cell assays, and excretion-rate estimates. To parameterize the models to specific toxicants, we estimated hepatic clearance by first culturing and then exposing liver cells from fathead minnow and zebrafish to the munition 2,4,6-trinitrotoluene (TNT) and a model cytochrome p450 inhibitor, ketoconazole. In addition, we evaluated their binding affinity to plasma proteins. We then mathematically inverted these toxicokinetic models to describe a situation wherein tissue concentrations were approximated by the exposure concentrations of an in vitro cell-assay, and the exposure conditions leading to these concentrations are considered unknown, but can be predicted using this reverse-toxicokinetic framework. Finally, we contrasted results from these multi-compartment models with those obtained from a one-compartment (whole-body) model. Our reverse toxicokinetic models not only provide a theoretical framework for interpreting in vitro assay results, but may also be used to identify stressors responsible for individual level adverse wildlife outcomes.

585 Toxicokinetic modeling of contaminants in marine mammals: Why reverse dosimetry is often inevitable

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Reverse dosimetry is a well-known practice in the development of toxicokinetic models for marine mammals and can be used for two different applications: 1) for estimating values of input parameters in case there is a lack of such information, and 2) for predicting the dose that would elicit a certain toxic effect in the animal. The first is often beneficial when developing toxicokinetic models for wildlife. Due to their protected and even endangered status, the acquisition of suitable tissue samples for marine mammals is often logistically not feasible and the availability of biological information on these animals is usually scarce. In toxicokinetic modeling, a correct model input or dose is key to getting robust model predictions. However, such input requires data on what the daily consumption, on what prey species the animals eat as well as the degree of contamination in the prey, which is difficult to find for species with large home ranges and unknown population structures. Such information is only available for some (populations of) marine mammal species. For the remaining populations, reverse dosimetry can provide a better estimation of a potentially realistic dose. This first application is independent of any toxic threshold levels and is basically only meant to better fit the model predictions to the available datasets of contaminant levels in marine mammal tissues. The second application, however, depends on toxicity thresholds and predicts the levels that would be needed to cause a certain toxic effect within a given time frame. It is this application that can predict into the future, thereby making modeling efforts worthwhile for risk assessment purposes. From this perspective, for example, 2051 was found to be the year at which the level of PCB 153 in male harbour porpoises would be below toxicity thresholds based on current levels collated from the literature. It is with reverse dosimetry that toxicokinetic models can go further than the more traditional biomonitoring studies in marine mammals, and combine exposure with effects in these animals thereby increasing the usefulness of these models in environmental legislation and species conservation.

586 Applying models to quantitatively link in vitro bioassay results with chemical exposures to aquatic organisms

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There is a paucity of measured toxicity data compared to the large number of chemicals and endpoints required for chemical hazard assessment. Emerging alternative test methods are being developed and evaluated to reduce and eliminate unnecessary animal testing. Adverse outcome pathways integrate information relating to molecular initiating events through a series of responses and adaptations at different levels of biological organization including apical endpoints at the organism level. High throughput in vitro cell- or biochemical-based tests are producing chemical specific data for a range of "outcomes" at the cellular and molecular level. Reverse toxicokinetic (rTK) models for humans have been used to estimate steady-state blood concentrations and oral equivalent doses (OEDs) corresponding to the in vitro bioassay response by including estimates of relevant toxicokinetic parameters such as biotransformation rates. In vitro mass balance models have been used to estimate the dissolved chemical concentration (and chemical activity) corresponding to the in vitro assay response from the assumed nominal (administered, unmeasured) chemical concentration. We present a mass balance modeling method that quantitatively links in vitro bioassay results with external exposure concentrations for a fish. We first use a mass balance model for the in vitro bioassay to estimate the dissolved concentration (and chemical activity) corresponding with the bioassay response. We then use a 1-compartment toxicokinetic model, including estimated rates of biotransformation, to estimate the steady-state fish concentration and then the aggregate intake rate from environmental exposure concentrations corresponding to the internal concentrations (and chemical activities). The method is applied and illustrated for select case study chemicals. The evolution and extension of this approach using other models is also discussed.

587 PBTK Modeling Helps Prediction of Fish Growth From Cell Line Experiments

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Environmental risk assessment of chemicals is essential but often relies on ethically controversial and expensive animal based methods. We show that a combination of mathematical modeling and cell culture tests can replace tests with juvenile fish for determining fish growth retardation. We base our method on the assumption that the same chemical concentration in fish internal organs and in cells in culture would cause the same changes in cell growth and survival. Based on known external chemical concentrations we use a fish physiologically-based toxicokinetic (PBTK) model to determine the internal chemical concentration in fish. Then we use a cell culture TK model to determine chemical concentrations in cell culture medium that would lead to intracellular chemical concentrations corresponding to the internal organ concentration. We measure cell proliferation and survival of the cell populations in culture to inform two further mathematical models: a GUTS-SD survival model and a von Bertalanffy growth model, the latter of which we then use to predict growth in juvenile fish. We show that the model based predictions agree well with data obtained with a Fish Early Life Stage (FELS) test in a typical industrial setup for two pesticides: propiconazole and cyproconazole. We expect that the approach is also valid for a wide range of other chemicals that require toxicological testing but a concerted action is needed to confirm this hypothesis.

588 Development of screening level hazard thresholds using in vitro to in vivo extrapolation of zebrafish embryo transcriptional points of departure

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In vitro and non-regulated animal assays are increasingly being used to assess the potential hazards of new materials. These approaches provide information on the amount of chemical at the assay level that is needed to cause a biological effect. However, the amount of chemical that an animal is exposed to can be different from the amount available to cause effects at a tissue or molecular level due to metabolism and other physiological processes. In vitro to in vivo extrapolation (IVIVE) approaches