

irritation and may also be useful in studying individual susceptibility to develop chronic irritant contact dermatitis.

doi:10.1016/j.cbi.2007.06.014

Development of alternative assays for the lifetime rodent bioassay for carcinogenicity

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The traditional way to test compounds for carcinogenic properties is the lifetime rodent bioassay. This assay requires more than a thousand animals per compound, is time-consuming and expensive, and therefore creates a large need for alternative methods. One of the approaches taken in the development of alternatives is the usage of transgenic mouse models. A mutation in the genes Xpa and p53, involved in DNA repair and tumor suppression respectively, results in mice more sensitive to carcinogenic compounds, and it was shown that this reduces the number of mice and the time needed for the carcinogenicity test. The final aim of this project is to develop an alternative assay for detecting carcinogenic properties based on toxicogenomics. Gene expression profiles of known toxicants will be studied to find biomarkers: clusters of genes with a corresponding expression profile that can be used to discriminate between classes of toxicants. The *in vivo* approach of toxicogenomics encloses exposure of wild-type and transgenic mice (Xpa^{-/-}p53^{+/-}) to known toxicants for up to 4 weeks, followed by RNA isolation from various tissues. For the *in vitro* approach, primary mouse hepatocytes are isolated performing a two-step collagenase liver perfusion and are cultured in a collagen sandwich configuration. The hepatocytes are exposed to known toxicants and RNA is isolated. In both approaches, the RNA will be used for microarray analysis. Expression profiles from well-known toxicants will be compared to profiles of an unknown compound. If the profiles match, the compounds are assumed to have a similar mechanism of action. In the future, these toxicogenomics-based alternatives may, at least in cer-

tain circumstances, lead to a replacement of the chronic rodent bioassay.¹

doi:10.1016/j.cbi.2007.06.015

Measuring and modeling bioavailability in *in vitro* systems

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Although good correlations exist between *in vitro* and *in vivo* derived toxicity data, data obtained from cell tests have shown to be variable and less sensitive in a number of cases. Reasons for these drawbacks include possible differences in bioavailability of the test compound between *in vitro* and *in vivo* systems and within *in vitro* systems. Given that the free concentration determines toxicity and cell tests are to be used to predict the toxicity of compounds *in vivo*, it is necessary to quantify the free concentration in these tests. In this study, solid-phase microextraction (SPME) is used to determine the free concentration of a range of polycyclic aromatic hydrocarbons (PAHs) in a typical cell test set-up. SPME fibers are used as a dosing as well as a measuring device of free concentrations of PAHs in these tests. By systematically altering the different components of an *in vitro* assay (i.e. serum content, well plate contact, headspace, and lipid content), partitioning coefficients are determined for each PAH to each system component. In so doing, the relative influence each *in vitro* system component has on the free concentration of a PAH is assessed, modeled on the basis of the physicochemical properties of the test compound, and linked to effect concentrations (EC₅₀) in a Neutral Red Uptake (NRU) assay. Results indicate that PAHs readily bind to binding matrices of *in vitro* systems such as serum proteins, which significantly reduces their free concentration. This reduction is positively related to the hydrophobicity of the compound.

doi:10.1016/j.cbi.2007.06.016

¹ This work is supported by the Ministry of Public Health (VWS/VGP and VWS/VWA), the Netherlands Toxicogenomics Centre (NTC), Technology Foundation STW and Platform for Alternatives to Animal Testing (PAD).