MIXTURE EFFECTS – DETECTABLE USING TOXICOGENOMIC APPROACHES?

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Introduction

The assessment of mixture exposure with regard to the occurrence of potential combined effects is on the agenda for prospective chemical risk regulation as well as in the water quality management[1]. Intensive research was carried out in several fields of environmental toxicology during the last decade studying various organic and inorganic compounds, mixtures of binary, multiple and complex composition as well as employing an array of bioassays to detect combined effects. Observational studies demonstrate that combined effects may occur in the environment, while experimental work with bioassays using apical endpoints shows that combined effects may be predicted from the biological activities of the mixture components using toxicological non-interaction models[2,3]. For risk assessment this leads to assume that the concept of concentration addition may provide a reasonable default assumption in dealing with potential mixture toxicity[4].

Remaining disputable issues in the assessment of combined effects from mixture exposure concern our dealing with synergism and how to account for low dose mixture effects when the mixture components act via dissimilar modes of action[5]. With the advent of toxicogenomic methods, that is tools to study transcriptomic, proteomic or metabolomic responses in a non-targeted fashion, novel perspectives to resolve some of the related questions may be developed. The objective of this paper therefore is to provide a comprehensive overview of achievements made in using toxicogenomic approaches to address mixture toxicity.

Materials and Methods

A data-base literature search was carried out to retrieve experimental studies employing toxicogenomic methodologies. These studies were systematically analysed for the selected compounds, mixture and exposure design, the data treatment, as well as the response observations made. Furthermore, the conceptual premises and the derived mixture assessments were reviewed.

Results and Discussion

The literature search retrieved 40 original mixture studies, which covered mixtures of organic as well as inorganic compounds. Binary and multiple mixture were studied with equal efforts, and also mixtures which where only incompletely resolved as to their composition were investigated. The compounds covered include heavy metals, pesticides, endocrine disruptors, PAHs, POPs, and flame retardents.

Mostly transcriptomic methodologies such as gene arrays or qPCR on a multiple set of transcripts were employed in the existing studies. Pioneering work for proteomic and metabolomic combined effects detection could also be identified. The exposure design with respect to selected concentrations is highly reflective of potential problems, exposure durations were mainly equivalent to short-term toxicity testing under a static regime. Several different mixture designs where chosen, however, rarely with provision of a study-related rational.

In response to the complex and often multivariate information retrieved in the assays, various signal analysis techniques can be found to cope with variance issues, data description and pattern recognition. In particular, major developments in bioinformatics tools can be described.

The assessment terminology employed by the authors is highly ambiguous due to a lack of reference to an initial hypothesis. We therefore developed a conceptual framework (Figure 1) which might help to overcome future confusion in evaluating mixture responses. Assessments based on interpreting the occurrence of different signal can be distinguished from those based on grading responses for given signals. 11 of the studies employed a concentration graduation to study toxicogenomic effects, an effort to describe concentration-response relationships could, however, only be found in 2 studies and none utilised these for the mixture assessment. A clear picture as to the detectability of low dose effects for mixtures or the provision of proxy measures for synergism could thus not be derived.

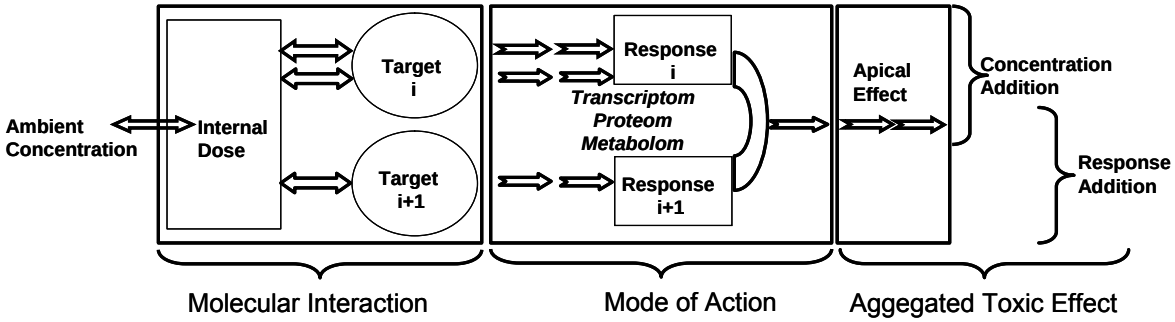

Figure 1: A conceptual framework suggested for devising and analysing toxicogenomic mixture response studies.

The current evidence for assessment of mixture effects by using toxicogenomic tools is mainly anecdotal. In order to further progress the understanding and tap the potential of these approaches we suggest to employ more quantitative means of describing the relationship between exposure concentration or duration and observable graded effects. Moreover, utilization of existing mixture models and linkage to known combination effects for apical endpoints is suggested.

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