An Update on CEFIC ECO16: Critical body residue validation for aquatic organisms exposed to chemicals causing toxicity by baseline narcosis.

Joop L.M. Hermens [1)], Jon A. Arnot [2)], Stephan A. van der Heijden[1)], Michiel T.O. Jonker[1)], Don Mackay[3)], Philipp Mayer[4)], Lynn S. McCarty[5)]

[1)] Utrecht University, The Netherlands

[2)] University of Toronto Scarborough, Canada

[3)] Trent University, Canada

[4)] NERI, Aarhus University, Denmark

[5)] L.S. McCarty Scientific Research & Consulting, Canada

WP1 - An Evaluated CBR Database

The objective is a data quality evaluation to identify CBRs for baseline neutral narcosis by screening out unsuitable, poor, or questionable quality data.

The most extensive publicly available environmental CBR compilation is the Environmental Residue Effects Database (ERED) from the U.S. Army Corps of Engineers and the U.S. EPA (http://el.erdc.usace.army.mil/ered/). Files of the October 2010 edition were downloaded and imported into spreadsheets for analysis. After removal of data for metals, inorganics, reptiles, birds, mammals, and other cleanups, the starting subset consisted of 7574 records for 318 organic chemicals from 651 references (about ½ of the records and ¾ of the chemicals). To identify records that met minimum requirements for data acceptability the following sets were removed: NOED toxicity endpoints, Injection exposures, Behaviour effects, Biochemical effects, Cellular effects, Developmental effects, Immunology effects, Lesions effects, Metabolism effects, Morphology effects, Pathology effects, Physiological effects, Tumor effects, and Mixture effects.

The first screen for minimal acceptability resulted in a subset of 2271 records for 182 chemicals from 294 references. Initial narcosis screening was carried out by removing records where the CBR was less than 0.1 mmol/kg (likely a specifically acting toxicant) and removing some other records for various reasons based on a case-by-case examination. Final narcosis identification used the final rules noted.

Final Narcosis Evaluation Rating Criteria

difficult to interpret endpoint	*response not statistically significant*
low response (LD, ED 35-20%)	*Verhaar Class 2, less inert compounds*
marginal statistical significance	*Verhaar Class 3, unspecific reactivity*
experimental problems, hormesis.	*Verhaar Class 4, respiratory-uncoupler*
low response (LD, ED < 20%; LOED)	*Verhaar Class 4, noncovalent binding*
mixture of isomers (surfactants)	*Verhaar Class 5, can't classify toxicity*
mortality during unfed 6-21d exposure	*UV-activated specific toxicity*
no adverse effect reported	

The final baseline neutral narcotic CBR subset consists of 166 records for 27 chemicals from 32 publications that were not rejected using the above criteria. These are not necessarily the only neutral narcotics in the database and may not cause baseline narcosis in all situations.

Table 1. *Final Baseline Neutral Narcotics Subset.*

Benzene	1,2-difluorobenzene
Ethylbenzene	1,4-difluorobenzene
Toluene	Ethane pentachloride
m-xylene	Octanol
o-xylene	Tetrachloroethane
p-xylene	PCB 31
1,2-dichlorobenzene	PCB 48
1,3-dichlorobenzene	PCB 105; 2,3,3`,4,4`-PeCB
1,4-dichlorobenzene	Fluoranthene
1,2,3-trichlorobenzene	Fluorene
1,2,4-trichlorobenzene	Naphthalene
1,2,3,4-tetrachlorobenzene	Phenanthrene
1,2-dibromobenzene	Pyrene
1,4-dibromobenzene	

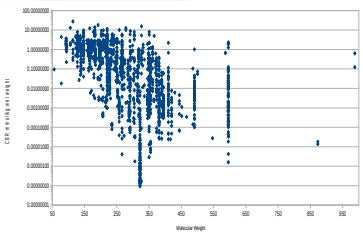

Figure 1. *ERED CBR Data Meeting Minimum Acceptability.*

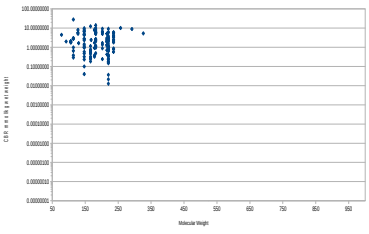

Figure 2. *Final Baseline Neutral Narcotic Subset.*

WP2 - CBR-Based Toxicity Models & Test Designs

The objective is development of CBR-based toxicity models that can be used to design toxicity tests and better interpret the results.

Models under development range in complexity from a simple one-compartment first-order uptake model to more complex multi-compartment models where the "toxicity trigger" may reside in a specific organism compartment. Model output consists of molar concentrations, chemical activities, and fugacities in compartments as a function of time. The corresponding probabilities of lethality are determined from the proximity of the estimated concentration or activity to a CBR defined for the specific chemical and compartment. A one-parameter Weibull probability distribution is used to quantify the variation in toxic response between individuals. This is a update of the model of Mackay, Puig and McCarty (1992) and is one of the "individual tolerance" toxicokinetic-toxicodynamic (TKTD) models recently reviewed by Jager *et al.* (2011).

Figure 1 illustrates a typical uptake for the simplest model and Figure 2 illustrates the corresponding probability of death curve which can be related directly to the observations of the test results.

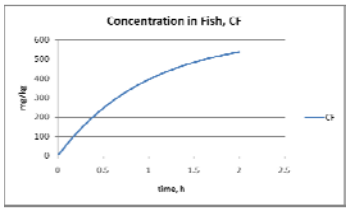

Figure 3. *Plot of computed organism concentration vs time.*

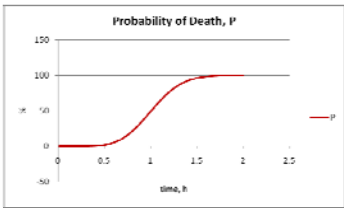

Figure 4. *Computed probability of death vs time for comparison with actual toxicity test results.*

The two key sets of quantities are as follows. First is the LC_{50}, i.e. the horizontal location of the probability curve as a function of time. This is controlled by the CBR (which is a function of the mode of action), the test concentration of the chemical, its partitioning properties, its biotransformation kinetics (when relevant), the kinetics of uptake as controlled by bioavailability, and effective respiration uptake rate constant.

Second is the steepness or spread of the curve which is a reflection of organism-to-organism differences in uptake kinetics and susceptibility to the toxic effect. A single Weibull parameter is fitted to the test results from either the slope at 50% lethality or from an appropriate regression of discrete probability - time data points.

The general aim is to provide the aquatic toxicologist with a tool to exploit the full set of data obtained from bioassays and to facilitate extrapolation to other chemicals and exposure conditions.

WP3 – Experimental CBR-based toxicity testing

The objective is to conduct CBR tests based on models developed for WP2. From the toxicity data, chemical burdens in biomembranes will be calculated using a simple equilibrium partitioning model based on sorption coefficients to the main compartments that make up an organism.

Partitioning of a wide range of narcotic chemicals to artificial membranes (POPC), triolein, protein (BSA), glycogen, and chitin will be measured. So far obtained data are plotted against the chemicals' $logK_{ow}$ values in Figure 5.

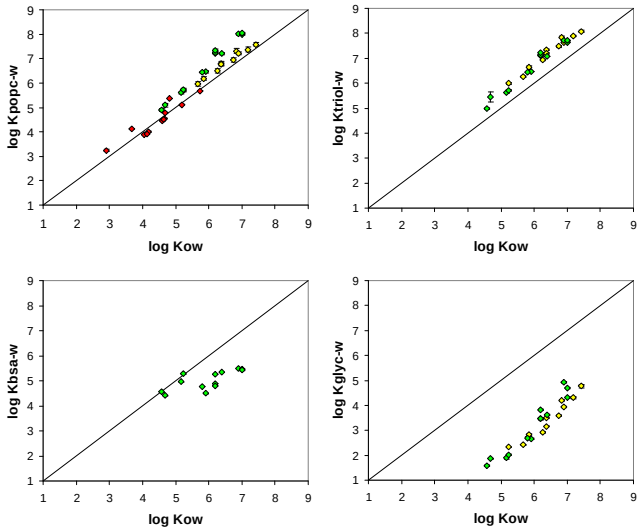

Figure 5. *Relationships between the $logK_{ow}$ and the logarithm of the POPC-water, triolein-water, BSA-water, and glycogen-water distribution coefficients for PAHs (green), PCBs (yellow), and chlorobenzenes/anilines (red). More data points for additional chemicals and matrixes are pending.*

Literature cited

Mackay, D., H. Puig, and L.S. McCarty, 1992. An equation describing the time course and variability in uptake and toxicity of narcotic chemicals to fish. Environ. Toxicol. Chem. 11:941-951.

Jager, T., C. Albert, T.G. Preuss, and R. Ashauer, 2011. General Unified Threshold Model of Survival - a Toxicokinetic-Toxicodynamic Framework for Ecotoxicology. Environ. Sci. Technol. 45:2529-2540.

Acknowledgments

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