Predicting Acute Toxicity from a Process-Based Perspective

Tjalling Jager[1], Hélène Magaud[2], Erik van de Plassche[2], Bas Kooijman[1]

[1] Theoretical Biology, Vrije Universiteit De Boelelaan 1085, NL-1081 HV, Amsterdam, The Netherlands,
email: tjalling@bio.vu.nl - http://www.bio.vu.nl/thb http://www.cem-nl.eu

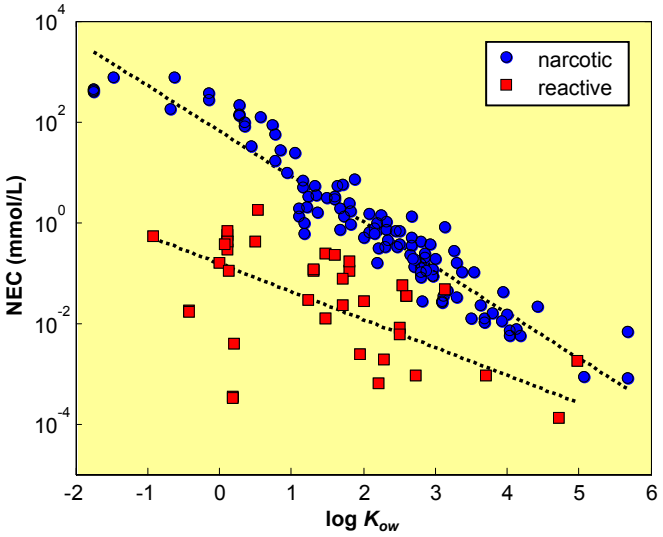
[2] European Chemicals Bureau, European Commission Joint Research Center, Ispra, Italy

Introduction

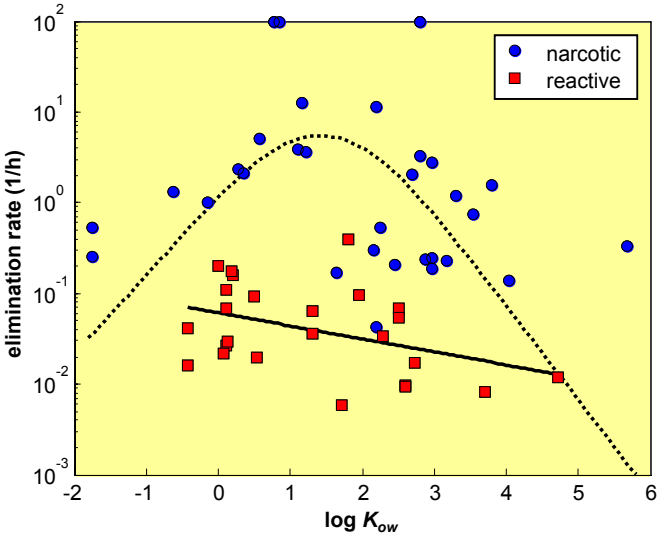
QSARs for acute toxicity link LC50 after fixed exposure time to chemical properties (e.g., hydrophobicity). Development in this field focuses on finding equations for new species and new chemical groups, or finding better descriptors; the LC50 data themselves are viewed as given facts. This overlooks two important aspects:

- *LC50s decrease in time in a manner depending on toxicant and species, introducing bias in QSARs.*
- *Toxicity data include much more information than only the LC50 after a fixed test duration.*

To develop better prediction methods, it is advisable to focus on parameters with a closer link to the underlying processes and use all information in the survival pattern over time. Here, we explore the possibilities of biology-based models in QSAR development.



NEC decreases with increasing K_{ow}. For narcotics, K_{ow} is a good descriptor. For reactive compounds, the NECs are generally lower and the relationship with K_{ow} quite poor.

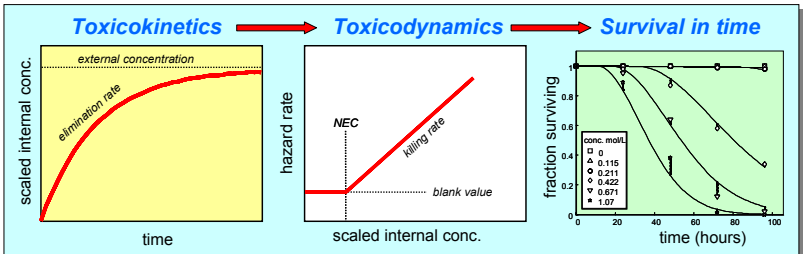


The elimination rate is often poorly identified from the data. Narcotics show a reasonable correspondence to an allometric model (2), parameterised for minnows.

For reactives, K_{ow} is a rather poor descriptor; elimination rates are remarkably constant, and generally lower than for narcotics. Likely, the elimination rate represents a rate-limiting step in the reactivity process.

References

(1) Bedaux, JJM, SALM Kooijman (1994). *Environ. Ecol. Stat.* 1:303-314.
(2) Sijm, DTHM, A Van der Linde (1995). *Environ. Sci. Technol.* 29:2769-2777.
(3) Russom, CL *et al.* (1997). *Environ. Toxicol. Chem.* 16:948-967.



DEBtox

The DEBtox method (*1*) for survival data is based on the following assumptions:

1. Chemicals need to be *taken up* before they can exert a toxic effect (toxicokinetics).
2. Internal concentration above a threshold increases the *probability* to die (toxicodynamics).

DEBtox uses all of the observations in time to fit four time-independent parameters: an elimination rate, a no-effect concentration (NEC), a killing rate and blank hazard rate (as shown above). We expect the parameter values for different chemicals to behave as follows:

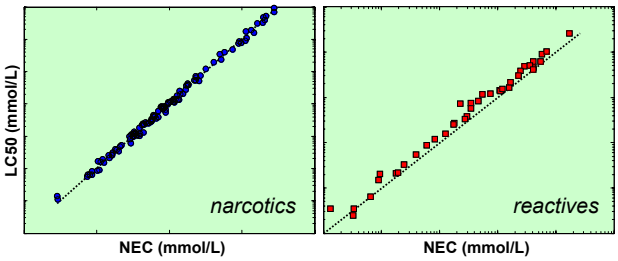
1. NEC equals incipient LC50. With slow toxicokinetics, 4-day LC50 will be higher than NEC.
2. The elimination rate from toxicity data reflects whole-body residues (see e.g. *2*).
3. For chemicals that act through the same mechanism of action, NEC and killing rate are inversely proportional. Such chemicals differ only in their ability to reach the target site.

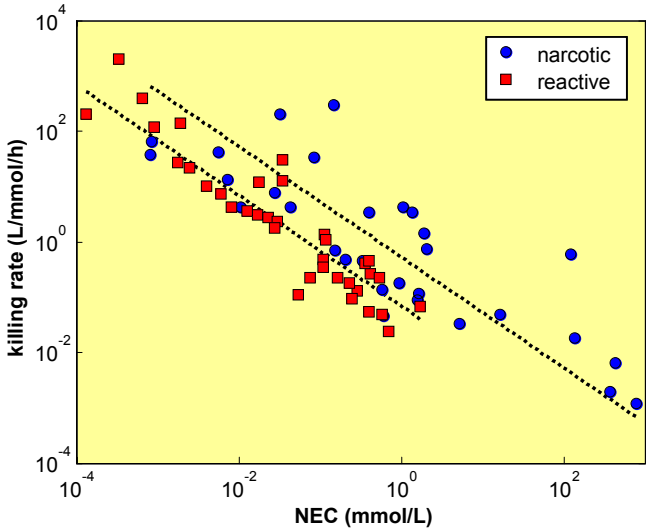
Fathead minnow data

Data for fathead minnows (*Pimephales promelas*) were obtained from the reports of the Center for Lake Superior Environmental Studies (see *3*), which include the raw mortality data in time. We only consider chemicals classified as aliphatic hydrocarbons, ethers, alcohols, aldehydes, ketones and benzenes. Further, we only show chemicals classified as non-polar narcotics or (pro-)electrophile reactives (*3*) (confidence level A or B). Parameter estimates are only shown if the 95% confidence intervals span less than a factor of 10.

For narcotics, NEC is almost identical to the 4-day LC50. Bias in this data set is thus small.

For reactives, the 4-day LC50 is somewhat higher than the NEC, reflecting slower toxicokinetics.





Killing rates generally increase with K_{ow} (not shown), but especially for reactives, the relationship is poor. Plotting the killing rate versus NEC yields better relationships. The line through the data has a forced slope of -1, expected for compounds sharing a mechanism of action. The relationship for reactives appears to differ from that of narcotics, indicating a different mechanism.

Conclusions

- The NEC is a more robust summary statistic than the LC50. Neverteless, the bias in the minnow data set is small.
- Reactives show slower kinetics of mortality, unrelated to K_{ow}. Thus, bias in the LC50 is not restricted to very hydrophobic chemicals.
- Relationships between DEBtox parameters reveal information on underlying mechanisms which may aid classification and prediction.
- Metabolism and misclassified compounds may obscure patterns.