J. ENVIRON. TOXICOL.
Vol. 21, No. 2, 185~195 (2006)

Body Residue-based Approach as an Alternative of the External Concentration-based Approach for the Ecological Risk Assessment

Jong-Hyeon Lee※

Neo Environmental Business Co. Institute of Environmental Protection and Safety, Rm 904, Byuksan Digital Valley II, Gasan dong 481-10, Geumcheon gu, Seoul 153-783, Korea

외부환경농도에 기반한 생태위해성 평가방법의 대안으로서 생체잔류량 접근법

이 종 현

(주)네오엔비즈, 환경안전연구소

요 약

환경오염물질로부터 수생태계 보호를 위한 표준적인 평가 및 관리 수단인 수질환경기준은 오염물질의 독성작용이 일어나는 표적기관에서의 오염물질의 농도에 대한 대체측정치로서 환경 내 오염물질의 농도를 이용해 왔다. 이러한 '외부환경농도에 기반한 접근방법'은 표적기관에서의 독성물질의 농도가 생물체 내 농도에 비례하고, 결국 외부환경농도에도 비례할 것이라고 가정한다. 따라서 환경오염물질의 생물이용도나 생물축적 양상의 차이 때문에 고유 독성치를 비교·평가하는데 한계가 있다. 이와 달리 '생물체내 농도에 기반한 접근방법(이하 생체잔류량 접근법)'은 환경오염물질의 생물이용도나 종 특이적 생물축적 양상과 관련된 불확실성을 제거하고, 환경오염물질 고유의 독성을 비교·평가할 수 있게 해준다. 특히 생체잔류량 접근법을 독성동태학 및 독성역학 모델과 함께 사용하는 경우는 실제 현장에서 일어나는 복잡한 노출조건에서의 독성영향을 예측하는데 활용할 수 있다. '생체잔류량 접근법'은 독성기작별 임계잔류량(Critical Body Residue)을 결정함으로써 생물모니터링의 결과를 해석하는데 적용되고 있다. 또한 생태위해성평가를 위해서 필요한 '무영향예측농도(Predicted No-effect Concentration, PNEC)를 예측하기 위한 방법으로 생체 내 잔류량에 기반해서 농도-시간-반응관계를 기술하고, 예측할 수 있는 새로운 유형의 독성역학 및 독성동태학 모델을 제시하고, 생체내 '무영향농도(No Effect Concentration, NEC)'를 추정하게 해 준다. 특히 생체내 NEC는 '무영향관찰농도(No Observed Effect Concentration, NOEC)'와 '영향농도(Effect concentration, EC)'처럼 분산분석이나 회귀분석모델과 같은 통계적 모델에 기반해서, 농도-반응관계만을 기술할 뿐인 기존 독성모델을 대체할 대안으로 최근에 OECD와 ISO에 의해서 추천되었다.

Key words : body residue approach, ecological risk, assessment, No Effect concentration

※ To whom correspondence should be addressed.
Tel: +82-2-863-4744; Fax: +82-2-863-4745
E-mail: jonghyeonlee@naver.com

INTRODUCTION

Current approach of aquatic toxicology for standard regulatory paradigm such as water quality criteria uses the environmental concentration as a surrogate for the concentration at the target site. This paradigm called as 'external concentration-based approach' is based on the premise that the toxicant concentration at the target site is proportion to the organism concentration, which is in turn proportional to the exposure concentration. Current aquatic toxicology has addressed numerous problems such as the interpretation of toxicity of contaminant mixtures, variable bioavailability of the chemicals in the complex media, the impact of intermittent exposures to biota, most of all, the significance of chemical residues in field-collected organisms exposed to various. These problems are related to using an external concentration as a surrogate dose for actual dose in site of toxic action. This approach was unavoidable since the involved toxicological processes, mainly dose-response relationship in target site (s), had been poorly understood.

Meanwhile 'body residue-based approach' opens a way to overcome the above problems in current aquatic toxicology (Landrum *et al.*, 1992; McCarty and Mackay, 1993; Sijm *et al.*, 1993). If effects can be expressed based on the body residue to produce the effect, one can get information of the intrinsic toxicity masked by the uncertainty regarding bioavailability and bioaccumulation. In addition, coupling of kinetic models with the body residue approach allows the prediction of toxic effects resulting from complex exposure scenarios (Landrum *et al.*, 1992).

In this review, current external concentration-based approach in aquatic toxicology are summarized, and then as an alternative approach on the current approach, body residue-based approach are introduced. In addition, newly developed method to estimate the Predicted No-Effect Concentration (PNEC) based on the body residue approach is introduced as an alternative of the traditional approaches such as No-Effect observed Concentration (NOEC) and Effect Concentration for 5% effect size (EC5) based on the external-concentration approach. Finally, further study needs for the effect analysis based on the body residue approach are addressed.

1. Current frame of aquatic toxicology: external concentration-based approach

1) Experimental design for the standard toxicity test

Toxicity represented as LC50 endpoint is a product of three types of factors-exposure duration, accumulation kinetics, and chemical potency (Rand *et al.*, 1995). Similarities or differences of the toxicity test results can be judged only when each set of experimental data is interpreted by quantifying the influence of parameters in each of the three component categories (Rand *et al.*, 1995). Current toxicity test results themselves (i.e., the numerical estimates of effect and no-effect concentration such as LC50 or No-Observable Effect Concentration, NOEC) are not the ultimate toxicological objectives; rather they are the basis for gaining toxicological insights, which can be used to make comparisons with other toxic agents and/or organisms (Rand *et al.*, 1995). For comparisons of toxicity among different agents and/or test organisms, it is assumed that a steady state is reached between the external chemical concentration and the concentrations of chemical at target sites in the organism during the short-term test period (Sprague, 1969). In the ideal situation, at the threshold exposure concentration where toxic effects have reached the incipient stage, the exposure water concentration should be a valid surrogate for the unknown amount of toxicant in the organism that is actually causing the effect. Once a threshold relationship is established, the potency and kinetic information obtained can be used to interpolate the time course prior to steady state.

Unfortunately, Sprague's admonishment to get steady-state toxicity test data by obtaining and reporting time-independent bioassay results, such LC50s

(Sprague, 1969), has been largely ignored. Lack of steady state simply means that more detailed toxicological investigation such as bioconcentration experiments is required because the underlying assumptions of the toxicity test design have been violated (Van Wezel *et al.*, 1995).

2) Prediction of chronic toxicity from acute toxicity

Chronic effects of toxicants are often inferred or estimated from observation made during short-term or 'acute' studies. Using acute lethality data to estimate chronic toxicity (lethality, growth, and reproduction) to test animals involves deriving an acute-to-chronic ratio (ACR, Kenaga, 1982). The ACR is used to estimate chronic NOECs for other species for which only acute toxicity data exist:

NOEC=LC50/ACR.

However, this approach has some limitations (Mayer *et al.*, 1994).

(1) When one uses the ACR, the acute median lethal concentration (LC50) is compared with NOEC, often derived from an endpoint other than lethality. Although different degrees of response (acute 50% vs. chronic no-effect or 0%) could be used when response slopes were similar, the slopes could be different.

(2) The use of the ACR method does not take into consideration the progression of lethality through time that is observed in acute toxicity test. The progression of degree of response with duration of exposure should be essential when one predicts chronic lethality from acute toxicity data.

Assuming that concentration-response is a continuum in time, and the mode of toxic action for lethality is similar under acute and chronic exposures, Mayer *et al.* (1994) predicted successfully chronic lethality to fishes from acute toxicity data and demonstrated that growth effects can be predicted from the chronic lethality. But they did not succeed to estimate the chronic reproductive effects from acute lethality.

Roex *et al.* (2000) analyzed the variability in ACR values for various chemicals in relation to their mode of toxic action such as non-polar narcotics, polar narcotics, specifically acting compounds, which had been suggested by Verhaar *et al.* (1992). As an acute endpoint, the LC50 was used (invertebrate: 24-h or 48-h LC50 values, fish: 96-h LC50 values), as a chronic endpoint, the lowest test concentration at which the natural rate of population increase (r) is affected (LOEC (r)) was used. Non-polar narcotic chemicals demonstrate the smallest variation in ACRs, and acute tests can be used to derive chronic endpoints for this chemical class. For other classes, however, it is less reliable to predict chronic toxicity using the results of acute tests. In general, differences in species sensitivity rather than in mode of action for the chemical seem to determine differences in ACRs.

In the above studies, several endpoints that differ regarding time of exposure (acute and chronic) and level of organization (survival, growth, reproduction, and population growth rate) are compared. However, chronic toxicity data for toxicant with different modes of action can only be compared when a standardized parameter, which also has ecological relevance, is used (Forbes and Calow, 1999; Roex *et al.*, 2000). In addition, as acute endpoints, not a fixed exposure time LC50 values such as 24-or 48-h LC50 values, but the incipient LC50 values need to be used (Mayer *et al.*, 1994).

3) Bioavailability and multiple exposure pathways

Toxicity can vary with external factors such as temperature, pH, and ligand system in aquatic system such as salinity, concentration of dissolved or particulate organic matters, as well as intrinsic factors of a toxicant (Newman and Unger, 2003). Since total concentration of toxicant is not useful to predict the toxicity, a terminology of 'bioavailable fraction' was suggested to solve this problem (Hamelink *et al.*, 1994). In the case of metals, the free ionic activity model (FIAM) was suggested to predict the bioavailability fraction of a metal in aquatic system (Tessier

and Turner, 1995). According to the FIAM, the free ionic activity is the best dosimetry for the bioavailability and toxicity. In similar to metals, the freely dissolved form of organic compound represents the bioavailable fraction of organic compounds in aquatic system (Di Toro *et al.*, 1991). In addition, the FIAM was extended into predicting the sediment toxicity, where the sediment toxicity can be predicted by the free ionic activity or the freely dissolved concentration in the pore water between sediment particles. At the same time, according to the equilibrium partition (Eq-P) theory, the freely dissolved concentration for organic compounds can be predicted from organic carbon-normalized concentration in sediment.

Most of aquatic toxicity tests were conducted under single or multiple exposure conditions such as water-only exposure or sediment exposure without dietary uptake exposure. Results of the toxicity tests are summarized based on a concentration in water or sediment. This type of external concentration-based approach is based on the Eq-P theory among different phases such as water, organic matter, and biota. In contrary, in field situation, aquatic organisms are exposed to toxicants via water or sediment routes together with dietary uptake route at the same time. Therefore, external concentration-based approach cannot represent real exposure condition with the multiple exposure routes, but under-estimate the bioavailability because each exposure route additively contributes to the bioaccumulation of toxicant (Luoma *et al.*, 1992). Finally, the relative contribution of each exposure route, especially dietary exposure route is not generic, but specific to a local ecosystem (Luoma and Rainbow, 2005).

4) Toxicity under the time-varying exposure condition

USEPA (1998) stated on the possibilities to improve the current approach for regulation of water quality such as an approach that will better handle variable concentrations by use of a kinetic-based toxicity model coupled with a population response model. "A kinetic-based toxicity model considers the speed at which effects appear in different individuals and different concentrations. The kinetic-based toxicity model allows prediction of the toxicity of any series of time-variable concentrations. It can predict how often effects would occur, and what fraction of individuals in the species would be affected". A population response model is "to allow the toxic impact to be portrayed as the overall average reduction in the number of individuals in a species, both during lethal sublethal periods and during recovery periods, accounting for both partial lethality and partial recovery" (USEPA, 1998).

Current kinetic models for invertebrates are thermodynamic relations to empirically predict steady state, i.e., the relation between the bioconcentration factor (*BCF*) for non-polar organic compounds and the octanol-water partition coefficient (K_{OW}) (McCarty *et al.*, 1992; Di Toro *et al.*, 2000). Current efforts for kinetic-based toxicity model allow prediction of effects for non-polar organics acting by a narcotic mechanism based on body residue and should be predictable from toxicokinetic models (McCarty *et al.*, 1989; Mackay *et al.*, 1992; McCarty and Mackay, 1993; Rand *et al.*, 1995; Di Toro *et al.*, 2000).

Usually, kinetic models were developed to describe and predict processes that alter exposure regimes and the toxicokinetic factors that result in toxicologically significant accumulation of chemicals on or in the body of exposed organisms (Landrum *et al.*, 1994). Once such factors are understood, it may then be possible to modify exposure regimes or avoid circumstances that create exposures so that adverse effects do not occur. This represents the essence of the current approach for the application of sound scientific principles to the development of external concentration-based regulatory criteria for environmental protection (Landrum *et al.*, 1994). Until now, few studies applied the kinetic-based toxicity model to the toxicity of any series of time-variable concentrations (Hickie *et al.*, 1995; Reinert *et al.*, 2002). The population response model to derive the allowable frequency of excursion above the criterion has

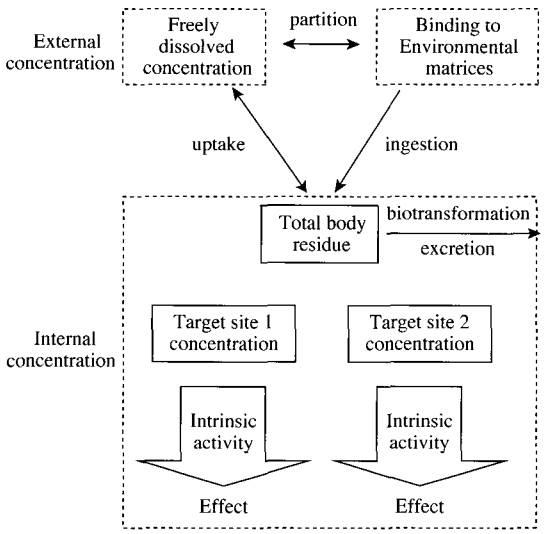

Fig. 1. Relationship between external concentration, toxicokinetics, internal concentration, target site concentration, and biological effect (modified from Escher and Hermens, 2002).

seldom been studied coupled with the time-variable exposure conditions (Barnthouse, 2003).

2. Body residue-based approach as an alternative of current frame in aquatic toxicology

The current frame in aquatic toxicology results in the difficulties in determining the bioavailabe fraction of the environmental concentration, multiple uptake routes, pulsed doses, non-steady-state situations (e.g., short exposure times), and toxicant biotransformation (Fig. 1). However, if effects were based on the body residue required to produce the effect, complications arising from the uncertainty regarding bioavailability and accumulation would essentially be eliminated (Landrum *et al.*, 1992).

1) Advantage of body residue approach

The link between environmental exposure or internal dose and adverse biological responses, whether it is laboratory-based toxicity endpoints or field-based ecological effects, is currently the most poorly understood aspect. However, shifting form comparison between ambient water concentrations and water concentrations known to cause toxic effects ('external concentration-based approach') to comparison between organisms concentration and internal critical body residue known to cause toxic effects ('body residue-based approach') has several advantages (McCarty and Mackay, 1993; Sijm *et al.*, 1993; Van Wezel *et al.*, 1995).

(1) Body residue-based approach gives more information on the concentration of the chemical at the site of the toxic action and then may help to distinguish and understand various modes of toxic action.

(2) Difference of sensitivity between species can be assessed. Species differences in the LC50 values for a compound may reflect a bioconcentration behavior and/or a different intrinsic toxicity, while species differences in lethal body residue reflect only the intrinsic toxicity of the compound.

(3) If the lethal body residue for a compound of a species is known, the amount necessary for killing the species will be known. In this case, previous exposition of the compound can be taken into account in toxicity assessment.

(4) Mixture toxicity may be easily described. If different chemicals have the same model of toxic action, e.g. narcosis, the lethal body residue that causes narcosis may be derived from the sum of the body residues of the individual compounds. Each compound therefore equivalently contributes to their toxicity.

(5) The lethal body residue is assumed to be less dependent on exposure conditions such as difference of exposure media (water-only or sediment exposure, dietary uptake, etc) and attainment of equilibrium conditions. Therefore, metabolism, multiple uptake pathway, limited bioavailability and changing exposure concentrations are not confounding factors in interpreting the body residue, because the concentration inside the organism is measured.

For these reasons the comparison of field and laboratory data can be facilitated.

2) Critical body residue interpretation of environmental hazard in aquatic biomonitoring species

Biomonitoring studies have generated a wealth of information describing contaminant loads in living organisms collected from contaminated sites. Living organisms act as integration of environmental exposure and, depending on the feeding habits and mode of interaction with environmental media, particular species will take up more or less of a given contaminant. Thus, biomonitoring body residue data can establish that a contaminant is present in the ecosystem but cannot by itself, define the hazard posed by its presence. Therefore, the meaning of variable residue levels between species as well as the biological impact of harboring a given residue needs to be interpreted and established.

The Critical Body Residue (CBR) required to produce a statistically significant toxicological response for a given endpoint, e.g. mortality, may significantly improve interpretation of biomonitoring data (McCarty and Mackay, 1993). Importantly, CBRs incorporate information about all possible routes of exposure, accumulation kinetics and bioavailability thus eliminating variability caused by these phenomena. Thus, most of the problems with biomonitoring studies can be avoided. In addition, existing biomonitoring data can be made more useful by establishing the relationship between body residue of contaminant and the biological effect that will result for both acute and chronic endpoints.

Use of environmental or organism concentrations are, in fact, surrogates for the target site concentration in the organism necessary to cause an observed effect or CBR. While the environmental concentration of contaminant necessary to depending upon the hydrophobicity of the chemical, the nature of the medium in which the contaminant residues, and the type and amount of interaction that biomonitor has with the contaminated medium, the CBR of a chemical in an organism needed to be produce that response varies little. In fish, the concentration of narcotic chemicals necessary to produce acute toxicity varies from 2 to 8 mmol/kg wet weight (van Hoogen and Opperhuizen, 1988; McCarty and Mackay, 1993; Sijm *et al.*, 1993).

Importantly, a few researches investigated the CBR used as biomonitors (van Hoogen and Opperhuize, 1989; Sijm *et al.*, 1993; Landrum *et al.*, 1994; van Wazel *et al.*, 1995; Kane Driscoll *et al.*, 1997a, b; Fisher *et al.*, 1999; Yu *et al.*, 1999), but nor has a relationship between sub-lethal effects and body residue for any organism been established (Arthur and Dixon, 1993; Mortimer and Connell, 1995). If CBRs can be established for several different biomonitoring organisms for several types of effects ranging from acute toxicity to chronic sub-lethal effects, aquatic risk assessment will be dramatically improved (Jarvinen and Ankley, 1999). However, several operational definitions for the empirical measurement and theoretical estimation of CBR value have been suggested and confused implementing the CBR concept into the toxicity assessment (Lee *et al.*, 2002; Landrum *et al.*, 2005). Barron *et al.* (2002) stated that the uncertainty of the CBR approach was similar to the external concentration-based approach such as LC50, because the CBR value depended upon the same sources of variability associated with aqueous exposure such as the aqueous dosing regime, chemical structure, individual species sensitivity, biotransformation processes, and lipid content, etc. These uncertainties are partially due to the different measurement methods for the time dependency of CBR.

3) Time-dependence of critical body residue (CBR)

Body residue approach is a common assumption for a toxicokinetic-toxicodynamic model as well as an application method of a constant CBR to interpret biomonitoring data. In many types of toxicokinetic-toxicodynamic model, toxic effect depends upon the body residue. The first attempt of the body residue approach was to establish the body residue basis for toxicity. The critical body residue (CBR) for a wide range of non-polar narcotic organics known as most

common environmental toxicant was relatively constant from 2 to 8 mmol kg^{-1} wet weight (McCarty and Mackay, 1993). In this attempt only toxicokinetic process was considered to be a time-limiting step and then assumed constant threshold (CBR) with exposure time. Meanwhile, in the case of other organics with different mode of toxic action (reactive compound or receptor-mediated toxicant), the CBR values decreased even after body residue attain the steady state (Verhaar *et al.*, 1999; Legierse *et al.*, 1999). Therefore, the real challenge is the toxicodynamics of a compound to investigate the time course of toxicity. Considerable research has been requested to determine the minimum data sets required to establish threshold body residue (CBR) for the major environmental toxicants (Landrum *et al.*, 1992). Further more, the time-dependence of threshold body residue for a compound needs to be investigated related to its mode of toxic action, because our concerns are not only to determine the threshold concentration, but also 'to predict how often effects would occur, and what fraction of individuals in the species would be affected (USEPA, 1998)'.

3. Application of body residue approach to estimate the Predicted No-Effect Concentration (PNEC) in ecological risk assessment

One of the final product of the effect analysis in ecological risk assessment is a measure of the Predicted No-Effect Concentration (PNEC) such as No-Observed Effect Concentration (NOEC)/the Lowest Observed Effect Concentration (LOEC), or the Effect Concentration for 10% effect size (EC10), etc. The PNEC is not a time-dependent measure, but an essentially time-independent toxicity threshold, whereas the above measures for the PNEC are determined at an arbitrary chosen exposure time for a test species, e.g., 4 days or 21 days for *daphnia magna*. In addition, these measures are determined experimentally and estimated using specific statistical methods such as ANOVA for NOEC/LOEC or time-independent regression analysis for the concentration-response modeling such as EC10. It is, however, noticeable that a statistically non-significant effect does not imply that biologically significant effects are absent (Kooijman and Bedaux, 1996). A truly time-independent PNEC cannot be determined experimentally, but estimated only by a toxicokinetic-toxicodynamic model, which is a systematic application method of the body residue approach for the quantitative effect assessment.

1) ANOVA approach: NOEC/LOEC

In standard toxicity test, the mean response at each concentration is compared with the untreated mean in the control using the analysis of variance (ANOVA). The highest concentration that is not significantly different from the untreated is then designated as the No Observed Effect Concentration, or NOEC. The "No-Effect" concept in PNEC is easily associated with the NOEC. So the NOEC was the main summary parameters of aquatic ecotoxicity tests. Actually, in the regulatory guidelines for environmental quality in many countries, the NOEC has played an important role. The US-EPA used the NOEC in order to derive the final chronic value for the aquatic ecosystem.

Meanwhile, many researchers have commented severe statistical problem in the NOEC approach. Pack (1993) summarized the disadvantages of the NOEC as follows

"(1) the NOEC must be one of the test concentrations and therefore depends on No-Effect concentrations the choice of the test concentrations; (2) no precision statements are possible with the NOEC; (3) because of the variability in an experiment the NOEC may correspond to large effects; (4) the NOEC approach gives no information on the slope of the concentration-effect curve, i.e. the range of the sensitivity of the chemical." (de Bruijin and van Leeuwen, 1996).

Chapman *et al.* (1996) stated as follows

"(a) the NOEC is not a good estimate of the NEC, (b) NOECs are highly variable between tests and can lead to contradictory results, (c) relatively subtle

differences in the way an analysis is carried out can also lead to quite different results, (d) EC50s or other point estimates are more consistent, more reliable and less variable than NOECs and can be compared between tests, and (e) using different taxa interchangeably in tests will increase variability" (de Bruijin and van Leeuwen, 1996).

In OECD workshop, it was concluded that the NOEC is inappropriate and should therefore be phased out. Finally, OECD was recommended to move towards a regression-based estimation procedure and initiate a study of the available time-dependent regression model (both mechanistic and empirical) to incorporate the time course of toxicity into the data analysis procedure.

2) Time-independent regression approach: Effect Concentration estimation (EC)

An "effective concentration" (EC) is defined as the concentration that produces a specified size of effect relative to an untreated control. A regression model is fitted to the data and, through a process known as inverse estimation, a concentration corresponding to a specified percent effect relative to the control is estimated. Confidence intervals for the EC can, and should always be, estimated. The curve fitted will usually be empirical in nature and will not have any particular biological justification.

There are many methods to estimate EC_0, which includes threshold model, hormesis model, and benchmark concentration. The benchmark concentration is defined as the statistical lower confidence limit on a concentration, which produces some predetermined increase in response rate compared to the untreated control. In other words, it is the lower confidence limit on an EC estimate. If EC estimation is to replace the NOEC, then the size of effect of interest needs to be decided upon. USEPA is using the benchmark concentration with benchmark response of 5% or 10% in order to estimate the reference dose (RfD) or to replace the NOEC. The benchmark approach has been proposed as an alternative procedure that can be used until biologically motivated approaches are available for some or all effects (USEPA, 2000).

Disadvantages of EC estimation as an alternative the NOEC approach are as follows

"(1) The estimate usually depends upon the choice of model. The confidence interval for small effect size is relatively large. Precision of EC estimates depends upon the number of test concentrations and their values. Therefore, it is needed to determine optimum selection of test concentrations. This may need to be done separately for each model. (2) For the benchmark concentration not only do the model and the effect size need to be chosen but also the confidence level used in estimating the confidence interval. Both threshold and hormesis models requires at least one extra parameters compared with a normal sigmoid model such as a logistic model. This makes it more difficult to fit the model. Experience suggests that confidence intervals around NEC estimates from threshold and hormesis models tend to be very wide" (Chapman, 1998).

3) Time-dependent regression approach : Internal No-Effect Concentration (NEC)

Kooijman and Bedaux (1996) developed the Dynamic Energy Budget toxicity (DEB-tox) model as a time-dependent regression approach to estimate the PNEC. The DEB-tox model can be used to estimate the No-Effect Concentration (NEC) as a model parameter from data from several aquatic toxicity tests.

Recently, in an ISO/OECD report (Magaud, 2003), the DEB-tox model was suggested for the ecotoxicity data analysis as an alternative for traditional measures for PNEC such as NOEC/LOEC or LC_x /EC_x. Assuming that toxicological parameters such as hazard rate are proportional to the body residue that exceed the internal NEC, the DEB-tox model can make it possible to estimate the internal NEC as a time-independent toxicity threshold.

Essential difference between the DEB-tox model and other traditional measures for PNEC is that the DEB-tox model is process-based. This makes it

possible to extrapolate the results from laboratory bioassay into the field conditions such as time-varying exposure concentration. In addition, extrapolations from one chemical into other chemicals, from one species into other species, from individual response into population consequences make it easier to apply the bioassay results to the ecological risk assessment.

Effects of toxicants were modeled by a change in the parameters of the dynamic energy budget of an organism, as a function of the body residue of the toxicant. In addition, with the help of eco-physiological model such as the dynamic energy budget model, the NEC concept was successfully applied to analyze sub-lethal effect such as growth, reproduction, and population growth as well as mortality data.

FURTHER STUDY NEEDS

As a long-term alternative for the external concentration-based approach, not the body residue-based approach, but the dose-based approach was suggested (Reiley *et al.*, 2003). The external concentration-based approach assumed that the rate of uptake of the chemicals is the same in both the toxicity test and the field. However, in field condition, multiple pathway exposure via food uptake and sediment ingestion can violate the uptake equality assumption. Instead, body residue-based approach assumes that the concentration-response relationship is independent of uptake route (Reiley *et al.*, 2003). The dose-based approach can be extended to estimate the fate of the absorbed dose and the accumulation of injury. Such an extension has the potential to overcome the assumption that toxicity is independent of the route of uptake.

ACKNOWLEDGEMENT

Thanks are due to Dr. P. Landrum for his advice in Great Lake Environmental Research Laboratory (GLERL)/National Oceanographic and Atmospheric Administration (NOAA) in USA.

REFERENCES

Arthur AD and Dixon DG. Effects of rearing density on the growth response of juvenile fathead minnow (*Pimephales promelas*) under toxicant-induced stress, Can J Fish Aquat Sci 1993; 51: 365-371.

Barnthouse LW. Quantifying population recovery rates for ecological risk assessment, Environ Toxicol Chem 2003; 23(2): 500-508.

Barron MG, Hansen JA, Lipton J. Association between contaminant tissue residues and effects in aquatic organisms, Rev Environ Contam T 2002; 173: 1-37.

Chapman PM, Caldwell RS and Chapman PF. A warning: NOECs are inappropriate for regulatory use. Environ Toxicol Chem 1996; 15: 77-79.

Chapman PM. Alternatives to the NOEC based on regression analysis. In Report of the OECD Workshop on Statistical Analysis of Aquatic Toxicity Data., volume 10 of OECD Environmental Health and Safety Publications, pp. 59-63. OECD, 1998.

De Bruijin JHM and van Leeuwen CJ, No-effect concentrations in environmental policy. In Kooijman and Bedaux eds, The analysis of aquatic toxicity data. VU University Press, 1996.

Di Toro DM, Zarba CS, Hansen DJ, Berry WJ, Swartz RC, Cowan CE, Pavlou SP, Allen HE, Thomas NA, Paquin PR. Technical basis for the equilibrium partitioning method for establishing sediment quality criteria. Environ Toxicol Chem 1991; 11: 1541-1583.

Di Toro DM, McGrath JA and Hansen DJ. Technical basis for narcotic chemicals and polycyclic aromatic hydrocarbon criteria. I. Water and tissue, Environ Toxicol Chem 2000; 19: 1951-1970.

Escher BI and Hermens JLM. Modes of action in ecotoxicology: their role in body burdens, species sensitivity, QSARs, and mixture effects, Environ Sci Technol 2002; 36: 4201-4217.

Fisher SW, Chordas III SW and Landrum PF. Lethal and sublethal body residues for PCB intoxication in the oligochaete, *Lumbriculus variegates*, Aquat Toxicol 1999; 45: 115-126.

Forbes VE and Calow P, Is the per capita rate of increase a good measure of population-level effects in ecotoxi-

cology?, Environ Toxicol Chem 1999; 18: 1544-1556.

Hamelink JL, Landrum PF, Bergman HL, Benson WH. Bioavailability: Physical, Chemical, and Biological Interactions , Lewis Publishers, Boca Raton, 1994.

Hickie BE, McCarty LS and Dixon DG. A residue-based toxicokinetic model for pulse-exposure toxicity in aquatic systems, Environ Toxicol Chem 1995; 14: 2187-2197.

Jarvinen AW and Ankley GT. Linkage of Effects to Tissue Residues: Development of a Comprehensive Database for Aquatic Organisms Exposed to Inorganic and Organic Chemicals. SETAC Press, Pensacola, FL. 1999.

Kane Driscoll S, Harkey GA and Landrum PF. Accumulation and toxicokinetics of fluoranthene in sediment bioassays with freshwater amphipods, Environ Toxicol Chem 1997a; 16: 742-753.

Kane Driscoll S, Harkey GA and Landrum PF. Accumulation and toxicokinetics of fluoranthene in water-only exposure with freshwater amphipods, Environ Toxicol Chem 1997b; 16: 754-761.

Kenaga EE. Predictability of chronic toxicity from acute toxicity of chemicals in fish aquatic invertebrates, Environ Toxicol Chem 1982; 1: 347-358.

Kooijman SALM and Bedaux JJM. The analysis of Aquatic Toxicity Data: VU University Press. Amsterdam, 1996.

Landrum PF, Dupuls WS and Kukkonen J. Toxicokinetics and toxicity of sediment-associated pyrene and phenanthrene in *Diporeia* spp.: examination of equilibrium-partitioning theory and residue-based effect for assessing hazard, Environ Toxicol Chem 1994; 13: 1769-1780

Landrum PF, Eadie BJ, Faust WR. Variation in the bioavailability of polycyclic aromatic hydrocarbons to the amphipod Diporeia (spp.) with sediment aging, Environ Toxicol Chem 1992; 11: 1197-1208.

Landrum PF, Steevens JA, McElroy M, Gossiaux DC, Lewis JS and Robinson SD. Time-dependent toxicity of dichlorodiphenyldichloroethylene to *Hyalella azteca*, Environ Toxicol Chem 2005; 24: 211-218.

Lee J-H, Landrum PF and Koh C-H. Prediction of time-dependent PAH toxicity in *Hyalella azteca* using a damage assessment model, Environ Sci Technol 2002; 36: 3131-3138.

Legierse KCHM, Verhaar HJM, Vaes WHJ, Wouter HJ, De Bruijn JHM and Hermens JLM. Analysis of the time-dependent acute aquatic toxicity of organophosphorus pesticides: the critical target occupation model, Environ Sci Tehchol 1999; 33: 917-925.

Luoma SN and Rainbow PS. Why is metal bioaccumulation so variable? Biodynamics as a unifying concept, Environ Sci Technol 2005; 39: 1921-1931.

Luoma SN, Jones C, Fisher NS, Steinberg NA, Oremland RS, Reinfelder J. Determination of selenium bioavailability to a benthic bivalve from particulate and solute pathways. Environ Sci Technol 1992; 26: 485-491.

Luoma SN and Rainbow PS. Why is metal bioaccumulation so variable? Biodynamics as a unifying concept, Environ Sci Technol 2005; 39: 1921-1931.

Magaud. Guidance document on the statistical interpretation of ecotoxicity tests., volume TC 147/ SC 5/ WG 10/ N 0390. ISO and OECD, Paris, 2003.

Mayer FL, Krause GF, Buckler DR, Ellersieck MR and Lee G. Predicting chronic lethality of chemicals to fishes from acute toxicity test data: concepts and linear regression analysis, Environ Toxicol Chem 1994; 13: 671-678.

McCarty LS and Mackay D. Enhancing ecotoxicological modeling and assessment, Environ Sci Tehchol 1993; 27: 1719-1728.

McCarty LS, Ozburn GW, Smith AD, Bharath A, Orr D and Dixon DG. Hypothesis formulation and testing in aquatic bioassays: a deterministic model approach, Hydrobiologia 1989; 188/189: 533-542.

McCarty LS, Mackay D, Smith AD, Ozburn GW and Dixon DG. Residue-based interpretation of toxicity and bioconcentration QSARs from aquatic bioassays: neutral narcotic organics, Environ Tox Chem 1992; 11: 917-930.

Mortimer MR and Connell DW. Effect of exposure to chlorobenzenes on growth-rates of the crab P*ortunus pelagicus* (L), Environ Sci Technol 1995; 29: 1881-1886.

Newman MC and Unger MA. Fundamental of Ecotoxicology. Lewis Publishers, 2003.

Pack S. A Review of Statistical Data Analyses and Experimental Design in OECD Aquatic Toxicology Test Guidelines. Shell research Ltd. Sittingbourne, Kent, UK. 1993.

Rand GM, Wells PG and McCarty LS. Introduction to aquatic toxicology. In Fundermentals of Aquatic Toxicology 2nd edition, ed, Rand GM, Taylor and Francis, Washington DC, pp. 3-67, 1995.

Reiley MC, Stubblefield WA, Adams WJ, Di Toro DM, Hodson PV, Erickson RJ and Keating Jr FJ. Reevaluation of the State of the Science for Water-qaulity Criteria Development; Society of Environmental Toxicology and Chemistry (SETAC); Pensacola. FL. USA. 2003.

Reinert KH, Giddings JM and Judd L. Effect analysis of time-varying or repeated exposures in aquatic ecological risk assessment of agrochemicals, Environ Toxicol Chem 2002; 21: 1977-1992.

Roex EWM, van Giestel CAM, van Wezel AP and van Straalen NM. Ratios between acute aquatic toxicity and effects on polulation growth rates in relation to toxicant mode of action, Environ Toxicol Chem 2000; 19: 685-693.

Sijm DTHM, Schipper M and Opperhuizen A. Toxicokinetics of halogenated benezens in fish: lethal body burden as a toxicological end point, Environ Toxicol Chem 1993; 12: 1117-1127.

Spargue JB. Measurement of pollutant toxicity to fish. 1. Bioassay methods for acute toxicity, Water Res 1969; 3: 793-821.

Tessier A and Turner DR. Metal Speciation and Bioavailability in Aquatic Systems. John Wiley & Sons, 1995.

US Environmental Protection Agency. Water quality standards regulation; proposed rule, Federal register, 1998; 63: 36742-36806.

US Environmental Protection Agency. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. Office of Water and Office of Science and Technology, EPA-822-B-00-004. 2000.

van Hoogen G and Opperhuizen M. Toxicokinetic of chlorobenzenes in fish, Environ Toxicol Chem 1988; 7: 213-219.

Van Wazel AP, De Vries DAM, Kostense S, Sijm DTHM and Opperhuizen A. The relevance of aquatic organisms' lipid content to the toxicity of lipophillic chemicals: toxicity of lindane to different fish species, Ecotoxicol Environ Safe 1995; 28: 53-70.

Verhaar HJM, de Wolf W, Dyer S, Legierse KCHM, Seinen W and Hermens JLM. An LC50 vs time model for the aquatic toxicity of reactive and receptor-mediated compounds. Consequences for bioconcentration kinetics and resk assessment, Environ Sci Tehchol 1999; 33: 758-763.

Verhaar HJM, van Leeuwen CJ and Hermens JLM. Classifying environmental pollutants. Structure-activity relationships for prediction of aquatic toxicity, Chemosphere 1992; 25: 471-491.

Yu Q, Chaisuksant Y and Connell DW. A model for non-specific toxicity with aquatic organisms over relatively long periods of exposure time, Chemosphere 1999; 38: 909-918.