WORKSHOP PROGRAMME

Defining the role of chemical activity in environmental risk assessment within the context of mode of action: Practical guidance and advice

29-30 October 2015
Snowbird Resort, Utah, USA

Jointly organised by

and

European Centre for Ecotoxicology and Toxicology of Chemicals

RIFM (Research Institute for Fragrance Materials)

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Contents

INTRODUCTION

AIM

Society is facing a variety of challenges in environmental risk assessment (ERA): growing concerns about the effects of multiple stressors (both chemical and non-chemical); risks associated with exposure to complex mixtures; and demands to quantify local site-specific risks. At the same time, risk assessors are seeking to provide a more efficient framework on which to address these emerging problems and questions in a manner that reduces cost and the use of laboratory animals.

This workshop will assess the applicability of using chemical activity in the interpretation of effects data within the context of environmental risk assessment, with an emphasis on the following key themes:

- To demonstrate the feasibility of using the chemical activity concept as an environmental risk assessment tool for neutral organic chemicals classified as baseline toxicants, including non polar and polar compounds.
- To determine the extent of chemical and toxicological domain for the use of the chemical activity concept as it is applied to polar and non-polar narcotics and to compounds with modes of action beyond narcosis and baseline toxicity for both acute and chronic ecotoxicological effects.
- To explore alternative methods for classifying the toxicological mode of action for chemicals, including the role of adverse outcome pathways in classification and to explore alternative dose metrics, and to assess the role of chemical activity as a potential complementary approach.
- To address issues of uncertainty and applicability domain with respect to physicochemical properties of organic chemicals, including miscible and ionizable organic chemicals, in applying the chemical activity concept to environmental risk assessment.

This Workshop was a recommendation of ECETOC Technical Report no. 120 and follows the work of Cefic LRI project ECO16.

BACKGROUND INFORMATION

1. Chemical activity and effect concentrations

The chemical activity concept has been shown to be a useful approach for relating exposure concentrations to acute toxicity endpoints[1-6], but can also be used to help understand the environmental fate and distribution of chemicals, analogous to the use of fugacity[7-10].

The most common approach to estimate chemical activity in the aqueous phase is as the fraction of the water solubility (liquid or sub-cooled liquid, if the substance is a solid at room temperature), i.e.

$$a = \frac{C_W}{S_W^L} \qquad (1)$$

where C_W is the concentration of the chemical in the aqueous phase (e.g., mg/L) and S_W^L is the water solubility (liquid or sub-cooled liquid). Equation 1 thus results in a unit less metric of between 0 and 1, which effectively provides a ratio of the energetic level in the aqueous phase observed in the environment/test system relative to the energetic level at the limit of solubility in water. Similarly, toxicity data (e.g., LC50s, EC50s) can be expressed in terms of chemical activity by replacing C_W with the selected endpoint concentration, i.e.

$$La_{50} = \frac{LC50}{S_W^L} \qquad (2)$$

Considerable effort has recently been invested towards defining the chemical activity domain of non-polar neutral organic chemicals that act as acute baseline toxicants, where La_{50} values are >0.01[10-12]. Fewer studies, however, have addressed chemicals with excess toxicity, La_{50} are <0.01[10-12]. Consequently, current understanding and application of the chemical activity concept imply that the tool could be readily used to assess the environmental risk of non-polar organic chemicals that act as baseline toxicants. Additionally, by estimating chemical activity using equation 2, based on data obtained from toxicity studies, it is also possible to assess the mode of action, differentiating between baseline and excess toxicity.

An advantage of the chemical activity concept is that it thus provides a more direct approach for relating external concentrations (i.e. in water, sediment, soil, air) with an effect concentration in an organism, which in the case of baseline toxicity has proved beneficial in reducing variability in effect concentration as a result of normalizing against the sub-cooled liquid water solubility of the chemical. The approach thus provides a method for comparing effect concentrations for non-polar neutral organics exhibiting baseline toxicity across (1) compounds; (2) species; and (3) environmental media[6,10]. Furthermore, given the additive nature associated with baseline toxicity, it is also possible to sum the chemical activities associated with mixtures of non-polar neutral organic chemicals to assess the potential risks associated with mixture exposure[13-14].

Whereas there are numerous examples that relate chemical activity to acute baseline toxicity, there are limited studies that have attempted to assess the relationship between chemical activity and excess toxicity and chronic effects. Additionally, the approach has also seen limited application to miscible and ionizable organic chemicals. These limitations were identified as important data gaps within the ECETOC task force report[15], and represent an important driver for initiating discussions aimed at addressing approaches for possibly expanding the applicability domain of chemical activity.

2. Modes of action in ecotoxicology and classification schemes

Numerous classes of compounds have specific modes of action[16]. Nowadays, several reporter gene assays are available to study specific mechanisms and modes of action, including for example genotoxicity, oxidative stress and hormonal effects[17,18]. Examples of experimental research in the area of ecotoxicology include: uncouplers of the oxidative phosphorylation[19], acetylcholine esterase inhibitors[20], alkylating agents (reactive compounds)[21]. Also polar narcosis is sometimes regarded as a mode of action different from “non-polar narcosis”[22]. Systematic studies into mode of action in in vivo fish toxicity studies are scarce. The early work of McKim and co-workers from the US EPA based in Duluth, Minnesota, is a good example of detailed and pioneering studies into modes of action[23].

Classifying compounds according to their mode of action is not a trivial exercise. An example of an attempt to develop a clear classification system is the approach proposed by the US EPA Duluth lab[24]. In their classification system a number of requirements for the assignment of a MOA to a specific compound are defined, including: (a) results from fish acute toxicity syndrome studies, (b) literature data on mechanistic studies, (c) joint toxicity data, (d) behaviour syndromes, (e) excess toxicity (Te)[1] and (f) similarity in chemical structure or chemical properties.

Most other classification systems adopt simpler approaches, which are typically based on items e) and f) from the list of requirements above. Structural alerts or rules are then applied to assign a MOA to a chemical[25,26]. Recently there has been considerable effort in developing an adverse outcome pathway (AOP) framework, related to developing greater mechanistic insight regarding specific modes of action by studying the chain of events that occur following a molecular initiating event (MIE) with a target up to the whole organism effect level[27,28]. It is believed that the chemical activity approach could provide a complementary approach towards an improved understanding of an AOP, as it has the potential to link exposure with the MIE in a single metric, but defining where and where

[1] Excess toxicity is defined as the ratio of the effect concentration that represent base line toxicity (using Kow) and the actual effect concentration.

it isn't useful would be very helpful in effectively illustrating the added value of chemical activity. Conversely, the concepts of AOP and MIE could be very useful in classification of chemicals, which could lead to improved ability to study relationships with chemical activity.

3. Modes of action, interactions, target sites

The target site for narcosis is the cell membrane. Also for specific acting compounds, the target can be located in the cell membrane (for example a specific protein). However, the location of the target site can also be in a more aqueous environment such as the cytosol (aqueous phase inside the cell) or blood. Differences in internal distribution may also lead to a shift in mode of action for chemicals within a certain class, for example a shift from a specific mode of action to narcosis[29]. Interaction of compounds with a target may vary from reversible van der Waals interactions, hydrogen bonding or covalent binding[16].

4. Dose metrics, dynamic aspects and modelling

As described above, chemical activity represents a measure for exposure, which can also be a useful metric in toxicokinetic studies. It is notable that, for specifically acting chemicals, the dynamic aspects (interaction with a target) are additional factors that can influence the final effect concentration. Consequently the influence of exposure time on effect concentrations is often related to a kinetic parameter, and represents a non-equilibrium scenario. For specifically acting chemicals, the effect of time may also be related to toxicodynamics, for instance, in the case of an irreversible interaction of a compound with its target[30]. A "simple" dose related parameter may thus represent an inappropriate metric for quantifying the response in a dose-response relationship, and exposure time may be needed as an additional parameter. A nice example is a study from Gülden where "area under the curve" was successfully applied in an analysis of cytotoxic potency of H_2O_2 in cell cultures[31]. Modelling of both the kinetic as well as the dynamic aspects will definitively lead to a better understanding of the effects of compounds with more specific modes of action and also of differences in species sensitivity[32-36]. It is anticipated that these modelling approaches can provide insight on appropriate dose parameters in ecotoxicology of compounds with modes of action other than baseline toxicity.

5. Uncertainty in key physicochemical property data

Although calculating chemical activity in the aqueous phase appears to be a relatively straight-forward exercise, it is important to recognize that uncertainty exists in both the toxicity data (e.g., LC50s) and the water solubility data. For chemicals which are solids at the system temperature, an additional consideration is that the sub-cooled liquid water solubility is estimated from the water solubility of the solid using the Fugacity Ratio (F):

$$S_W^L = \frac{S_W^S}{F} \tag{3}$$

A simplified approach to estimate the Fugacity Ratio (F) at 25 °C is as shown below.

$$\log F = -0.01(T_M - T) \tag{4}$$

where T_M is the melting point of the chemical and T is the system temperature. Implicit to this simplified approach is the applicability of Walden's Rule, which states that the entropy of melting (ΔS_M) is 56.5 J/K•mol. The equation for estimating the Fugacity Ratio in a more expanded form is as follows[1].

$$\log F = \frac{-\Delta S_M}{2.303RT}(T_M - T) \tag{5}$$

Consequently, an improved understanding related to the uncertainty surrounding the assumption of ΔS_M, as well as the propagation of error associated with uncertainty and variability in both the water solubility value used and the effect concentrations that have either been measured or are based on nominal concentrations, and the uncertainty associated with the melting point temperature of solids are required[37-45]. A greater appreciation of the influence of uncertainty is believed to be useful in helping to align chemical activity values to specific modes of action.

6. Estimating chemical activity in non-aqueous media (i.e. biota)

Because toxicity data may be reported in terms of internal concentration (i.e., body burden) and non-equilibrium conditions may necessitate the estimation of internal concentrations and chemical activity in biota, the reliability of methods to calculate chemical activity in non-aqueous phases also requires careful consideration. Mackay et al.[1] suggest that chemical activity in non-aqueous phases can be calculated in an analogous fashion to aqueous phases, i.e.,

$$La_{50} = \frac{CBR}{S_{\mathbf{B}}^{L}} \qquad (6)$$

where CBR is the Critical Body Residue (i.e., internal LC_{50}) and S_B^L is the solubility of the chemical in the organism, which is estimated as:

$$S_B^L = K_{BW} S_W^L$$

where K_{BW} is the biota-water partition coefficient. Adding to the uncertainty discussed above, are thus the challenges associated with assessing the uncertainties aligned with equation 6. Alternatively, the internal LC_{50} can also be estimated from external LC_{50} using toxicokinetic (TK) models. Given the various methods that can be used in obtaining chemical activity, guidance is thus needed if the concept is to be routinely and transparently applied within a risk assessment framework.

7. Feasibility of applying the chemical activity concept to miscible organic chemicals (MOCs)

Whereas the concept of chemical activity has been widely applied to non-polar neutral organics, a key challenge is assessing how to apply the concept to very hydrophilic chemicals (i.e., miscibles organic chemicals). In the instance of MOCs there is no quantifiable limit to the solubility of the chemical in water. 'Empirical' water solubilities of miscible chemicals (e.g., methanol, ethanol, acetone), however, may still be reported, for instance, as 10^6 mg/L in the EPISUITE database.

For neutral organic chemicals, it is possible to calculate chemical activity using the following alternative expression:

$$a = x_i \gamma_W \qquad (7)$$

where x_i is the concentration of the chemical in the aqueous phase expressed as a mole fraction and γ_W is the (dimensionless) activity coefficient of the chemical in water (at the given mole fraction).

γ_W for neutral organic chemicals span multiple orders of magnitude, which follows from the inverse relationship between the activity coefficient and water solubility. For example, the activity coefficients at infinite dilution for 1-butanol and benzo(a)pyrene are 50 and 10^8 respectively[46]. For more hydrophobic chemicals, γ_W in dilute solution and at saturation are typically within 30% and any concentration-dependence of the activity coefficient can be ignored[46]. For more hydrophilic (miscible) compounds, γ_W will exhibit a stronger concentration-dependence. However, as per the definition of γ_W, γ_W tends towards a value of 1 as the mole fraction of the chemical in aqueous solution increases.

There are numerous experimental techniques available for estimating γ_W at infinite dilution and empirical data are available for some miscible chemicals e.g., γ_W = 1.6, 3.7 and 7.0 for methanol, ethanol and acetone respectively[46]. As both the upper bound (γ_W at infinite dilution) and lower bound (γ_W = 1) is known for these miscible chemicals, LC50s can be expressed using chemical activity (i.e., converted to Ea_{50}s), at least as a bounded first approximation, i.e.,

$$Ea_{50} = x_i(LC50) \rightarrow x_i(LC50)\gamma_{W,\mathrm{inf}} \quad (8)$$

where x_i(LC50) is the LC50 expressed as a mole fraction. Equation 8 thus represents a possible approach to enable an estimate of chemical activity in relation to an effect concentration. Further assessment, however, is required to better understand the feasibility of the approach and to quantify uncertainties and define potential limitations[38,40,46-50].

8. Feasibility of applying the chemical activity concept to ionizable organic chemicals (IOCs)

The applicability of the chemical activity concept to ionizable organic chemicals (IOCs) represents an additional challenge. Firstly, the water solubility of IOCs is a function of the intrinsic solubility of the compound and the degree of ionization[51,52], where the degree of ionisation is a function of pH and pK_a. The type and concentration of counterion(s) present in solution are also considerations for determining the apparent solubility limit[53,54]. Even if the apparent water solubility can be estimated, the appropriateness of using this estimate in chemical activity calculations (such as Equation 1) has not yet been fully addressed. While methods to estimate activity coefficients for IOCs have been proposed (REF Mami), it is unclear if these approaches are congruent with the methods for neutral organic chemicals and hence can be used in the same manner (i.e. Equation 7). IOCs also exhibit different partitioning behaviour compared to neutral organic chemicals[55-58], complicating the estimation of the biota-water partition coefficient (or more appropriately, the biota-water distribution ratio, D_{BW}). Furthermore, in addition to challenges associated with estimating a chemical activity for IOCs, is the complexity associated with aligning a derived chemical activity to an effect concentration. The key challenge here is that IOCs, examples of which include active pharmaceutical ingredients and pesticides, are unlikely to act strictly as baseline toxicants, but will have a specific mode of action.

WORKSHOP STRUCTURE

We propose a 2-day workshop, using a series of key questions to focus discussion before and during the workshop. The workshop is structured around three Working Groups. Activities will include an introductory session, substantial group discussion and writing periods, accompanied by regular plenaries that serve to update participants on progress and changes that occur in topic development. A detailed schedule for the workshop is provided in the following sections.

Briefly, the introductory session will serve to stimulate participant understanding of chemical activity through presentation of material, covering the fundamental thermodynamic principles that form the basis of the concept, as well as a brief introduction of the outline of each work group's topic. Initial refinement and expansion of work group questions will result from this introductory session.

It is anticipated that between 10-14 experts will be assigned to each specific Working Group, where they will discuss issues, prepare draft written materials, and refine those drafts into a coherent manuscript or workshop report chapter. Workshop participants will be invited based on their expertise in areas such as environmental toxicology, environmental chemistry, and environmental risk assessment. We estimate approximately 40 individuals will participate, representing academia, government, and industry. Output from the workshop is expected to first take the form of an ECETOC workshop report, followed by a series of papers prepared for a journal agreed by participants to be appropriate, and which ensures cost-effective and timely release of workshop findings.

The workshop will be held prior to the SETAC North America meeting in Salt Lake City, 29-30 October, 2015, at the Snowbird Resort in Utah. The resort is located near to Salt Lake City, and will provide transport from Salt Lake City International Airport upon arrival to the workshop venue, as well as transport to a designated location near the Salt Palace Convention Centre following the workshop. Additional details regarding the facilities provided at the Snowbird Resort can be found at: http://www.snowbirdmeetings.com/. Funding for travel and accommodation for workshop participants is also available.

PROGRAMME DAY 1: THURSDAY 29 OCTOBER 2015

08:00 –08:30	*Registration and coffee*	
08:30 - 08:50	**Welcome and introductory remarks**	**Malyka Galay Burgos** ECETOC, Belgium
08:50 - 09:20	**Foundational aspects of the concept of chemical activity**	**Philipp Mayer** Technical University of Denmark
09:20 - 9:40	**Application of the "chemical activity" concept**	**Frank Gobas** Simon Fraser University, Canada
9:40 - 10:00	**General information about mode of actions in ecotoxicology**	**Joop Hermens** University of Utrecht, Netherlands
10:00 - 10:20	**Challenges and potential limitations – physicochemical properties**	**Todd Gouin** Unilever, UK
10:20 - 11:00	*Coffee break*	
11:00–12:30	**Breakout into workgroups** ➢ Workgroup 1: "Full utilisation of the chemical activity concept for non-polar organic chemicals (Log K_{ow} ≥ 2)" ➢ Workgroup 2: "Classification of chemicals according to MOA and chemical activity or other dose metrics for chemicals with specific mode of action" ➢ Workgroup 3: "Challenges and potential limitations to the application of the chemical activity concept for ecological risk assessment – Physicochemical properties & partitioning"	
12:30 - 13:30	*Lunch*	
13:30 –15:30	**Workgroups (continued)** ➢ Workgroup 1: "Full utilisation of the chemical activity concept for non-polar organic chemicals (Log Kow ≥ 2)" ➢ Workgroup 2: "Classification of chemicals according to MOA and chemical activity or other dose metrics for chemicals with specific mode of action" ➢ Workgroup 3: "Challenges and potential limitations to the application of the chemical activity concept for ecological risk assessment – Physicochemical properties & partitioning"	
15:30 - 16:00	*Coffee break*	
16:00 - 17:00	**Plenary: feedback & discussion with panel** *Breakouts report back (5-10 minutes each)* *Identify key points, consensus and research needs*	
19:30	*Dinner*	

Close of first day

PROGRAMME DAY 2: FRIDAY 30 OCTOBER 2015	
08:30–10:30	**Workgroups (continued)** ➢ Workgroup 1: "Full utilisation of the chemical activity concept for non-polar organic chemicals (Log Kow ≥ 2)" ➢ Workgroup 2: "Classification of chemicals according to MOA and chemical activity or other dose metrics for chemicals with specific mode of action" ➢ Workgroup 3: "Challenges and potential limitations to the application of the chemical activity concept for ecological risk assessment. Physicochemical properties & partitioning"
10:30 - 11.00	*Coffee break*
11:00 - 12:00	**Plenary feedback & discussion with panel** *Breakouts report back (5-10 minutes each)* *Identify key points, consensus and research needs*
12:00 - 13:00	*Lunch*
13:00–15:30	**Breakout into workgroups** ➢ Workgroup 1: "Full utilisation of the chemical activity concept for non-polar organic chemicals (Log Kow ≥ 2)" ➢ Workgroup 2: "Classification of chemicals according to MOA and chemical activity or other dose metrics for chemicals with specific mode of action" ➢ Workgroup 3: "Challenges and potential limitations to the application of the chemical activity concept for ecological risk assessment – Physicochemical properties & partitioning"
15:30 - 16:00	*Coffee break*
16:00 - 17:00	**Breakout into workgroups** ➢ Workgroup 1: "Full utilisation of the chemical activity concept for non-polar organic chemicals (Log Kow ≥ 2)" ➢ Workgroup 2: "Classification of chemicals according to MOA and chemical activity or other dose metrics for chemicals with specific mode of action". ➢ Workgroup 3: "Challenges and potential limitations to the application of the chemical activity concept for ecological risk assessment – Physicochemical properties & partitioning"
17:00 - 18:00	**Plenary: feedback & discussion with panel** Breakouts report back (5-10 minutes each) Identify key points, consensus and research needs
19:30	*Dinner*

Close of Workshop

WORKGROUP 1: "FULL UTILISATION OF THE CHEMICAL ACTIVITY CONCEPT FOR NON-POLAR ORGANIC CHEMICALS (LOG KOW ≥ 2)"

1. Can 0.01 (i.e. 1% of liquid solubility) be used as a chemical activity benchmark to distinguish baseline toxicity and excess toxicity?
2. Could the observation of non-toxicity at chemical activity of 1 (i.e. 100% of liquid solubility) be used for categorising a chemical as being non-toxic?
3. Is it possible and meaningful to set a general predicted no-effect activity (PNEA) for baseline toxicity?
4. Is it possible and meaningful to set a general predicted no-effect activity (PNEA) for mixture constituents with regards to baseline toxicity?
5. Is it scientifically correct to assess the sorptive capacity or "solubility" of neutral hydrophobic organic chemicals in non-aqueous phases as the product of the non-aqueous-water partition coefficient and the aqueous solubility?
6. What are the inherent assumptions in a comparison of activities of neutral organic chemicals among various environmental media?
7. Is it possible to include an activity framework in AOP analysis?

First Name	Name	Role
Philipp Frank	Mayer & Gobas	Moderator
Annika	Jahnke	*Rapporteur*
Tim	Bowmer	
William	Doucette	
Tala	Henry	
Dries	Knapen	
Lynn	McCarty	
Tom	Parkerton	
Stine	Schmidt	
Foppe	Smedes	
Jay	Tunkel	
Dik	van de Meent	

WORKGROUP 2: "CLASSIFICATION OF CHEMICALS ACCORDING TO MOA AND CHEMICAL ACTIVITY OR OTHER DOSE METRICS FOR CHEMICALS WITH SPECIFIC MODE OF ACTION"

1. *Chemical activity and effect concentrations*

- Can chemical activity help us to identify compounds with modes of action other than non-polar narcosis?
- Can chemical activity be useful to interpret differences in effect concentrations of non-polar versus polar narcosis compounds?
- Are there enough data to estimate the range in chemical activity of compounds with a certain mode of action?
- How big is the variation in chemical activity for chemicals with a certain mode of action.
- Are there enough data to estimate the range in chemical activity of compounds with diverse specific modes of action?
- Is there an advantage of applying a chemical activity concept to compounds with specific modes of action and if so, what are these advantages?

2. *Modes of action in ecotoxicology, classification scheme sand adverse outcome pathways*

- How can we classify compounds according to their mode of action? What kind of systems are available and how reliable are they?
- How does the adverse outcome pathway approach relate to, and be useful in, classification into modes of action?

3. *Modes of action, interactions and target sites*

- Chemical activity is estimated from concentration and solubility. Can the concept be applied to all kind of "target site environments"?
- Are there certain mechanisms of action for which the chemical activity concept offers a promising tool / are there certain mechanisms of action for which the chemical activity concept is not really useful.

4. *Dose metrics, dynamic aspects and modelling*

- What can we learn from toxicokinetic and toxicodynamic modelling?
- Chemical activity is a useful dose metric for narcosis, but is it also for compounds with specific modes of action or do we need other dose parameters?
- How can we handle the dynamic aspects in dose response relationships?

First Name	Name	Role
Joop Rolf	Hermens & Altenburger	Moderators
Dan	Salvito	*Rapporteur*
Mark	Cronin	
Scott	Dyer	
Malyka	Galay-Burgos	
Nynke	Kramer	
Victoria	Otton	
Erwin	Roex	
Paul	Thomas	
Lucia	Vergauwen	
Dan	Villeneuve	

WORKGROUP 3: "CHALLENGES AND POTENTIAL LIMITATIONS TO THE APPLICATION OF THE CHEMICAL ACTIVITY CONCEPT FOR ECOLOGICAL RISK ASSESSMENT – PHYSICAL-CHEMICAL PROPERTIES & PARTITIONING"

1. *Uncertainty in key physical-chemical property data*

- How reliable are available water solubility data? How reliable are current approaches for estimating water solubility in the absence of empirical data?
- How reliable are available melting point data? How reliable are current approaches for estimating melting points in the absence of empirical data?
- How reliable is Walden's Rule given the wide range of chemical structures for which the chemical activity concept may be applied to?
- How reliable are available methods to estimate the entropy of melting (ΔSM) from chemical structure?
- Taken together, what is the expected uncertainty in chemical activity calculations for 'data poor' chemicals?

2. *Calculation of chemical activity in non-aqueous phases (biota)*

- Is the octanol-water (KOW) paradigm sufficiently accurate for estimating KBW? When is it necessary to consider more sophisticated approaches (e.g., ppLFERs) for estimating KBW?

3. *Application of the chemical activity concept to miscible organic chemicals (MOCs)*

- To what extent are empirically-based chemical activity coefficients available for miscible chemicals and how reliable are these data?
- How reliable are computational approaches (e.g., UNIFAC, COSMOTherm, SPARC) for estimating chemical activity coefficients for miscible chemicals?
- Case Study: Are the chemical activities corresponding to LC50s for 'narcotic miscibles' calculated using Equation 7 consistent with expectations (i.e., Ea50s ~ 0.01)?
- Given the (relatively) low affinity for lipids and other non-lipid organic matter, what modifications to the approach for estimating KBW (see above) are necessary?

4. *Application of the chemical activity concept to miscible organic chemicals (MOCs)*

- To what extent can approaches to calculate chemical activity for neutral organic chemicals be expanded/modified to IOCs? Are methods for estimating the activity coefficients of electrolytes (e.g., DeBye-Huckey approach) (REF Mami) compatible with methods for neutral organic chemicals?
- Case Study: Can the intrinsic water solubility (i.e., water solubility of the neutral form) and fraction of chemical in neutral form in solution be used to calculate chemical activity from LC50s?

First Name	Name	Role
Todd	Gouin	Moderators
James	Armitage	*Rapporteur*
Jennifer	Apell	
Jon	Arnot	
Robert	Burgess	
Meara	Crawford	
Karen	Eisenreich	
Fabian	Fischer	
Robert	Hoke	
Mark	Parnis	
Michael	Roberts	

Abstract

Foundational aspects of the concept of chemical activity

Philipp Mayer
DTU-Environment, Technical University of Denmark, Denmark

The chemical activity of an organic chemical quantifies its potential for spontaneous physicochemical processes, such as diffusion, sorption, and partitioning. For instance, the chemical activity of a sediment contaminant determines its equilibrium partitioning concentration in sediment-dwelling organisms and differences in chemical activity determine the direction and extent of diffusion between environmental compartments [1,2]. This makes chemical activity a meaningfull and well-defined exposure parameter that is closely linked to fugacity and freely dissolved concentration [2]. Classical toxicological studies have provided the first indication that narcosis occurs within a relatively narrow band of chemical activity [3-5], and during the last 10 years several studies have confirmed this for the „baseline toxicity“ of non-polar organic chemicals and their mixtures [6-8].

The first aim of this presentation will be to emphasize the physical meaning of chemical activity, basically suggesting that „mass concentration“ and „chemical activity“ are two complemtary dimensions for chemicals in the environment, exactly like we know from other areas (heat content versus temperature; water content versus water activity). The second aim will be to present how chemical activity can be measured and controlled in environmental research and testing, since this has the very important implication that chemical activity goes beyond modelling and re-calculations of mass based data. The final aim will be to initiate the discussion of why and how „chemical activity“ can help (1) to link exposure between media, (2) to compare sensitivities between species, (3) to assess (excess) toxicity of chemicals and (4) to add up the exposure for mixtures?

References.

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Philipp Mayer

Professor Philipp Mayer was born in 1968 and studied at the Technical University of Denmark (M.Sc, 1995), the University of Wisconsin, Milwaukee (Fullbright, 1994-1995) and the University of Utrecht (Ph.D., 2000). He was then Study Director (GLP) and Product Manager for Environmental Toxicology at TNO (NL, 2001-2002), before he moved back to Denmark for a position at the National Environmental Research Institute (2001-2013), today part of Aarhus University (DK). Since 2013, Philipp Mayer is Professor for Applied Environmental Chemistry at the Technical University of Denmark, Lyngby, Denmark.

The research focus of his group is on partitioning based analytical technology and the fate, exposure and effects of organic contaminants in the environment: (1) Partitioning Based Analytical Technology to determine the available exposure of organic contaminants. (2) Exposure Assessment: Exploring the potential of chemical activity as new exposure parameter. (3) Effect Assessment: Toxicity research of hydrophobic organic substances. Introducing "Passive Dosing" for the improved exposure control of laboratory experiments."

Abstract

Modes of action in ecotoxicology: classification, chemical activity and dose metrics

Joop Hermens
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Utrecht University, the Netherlands

The chemical activity concept is a promising approach in the understanding and prediction of ecotoxicological effect concentrations of organic contaminants. This concept has successfully been applied to compounds that are known to act via non-polar narcosis. Application of this concept to compounds beyond non-polar narcosis is not yet explored. It is believed that the chemical activity approach could provide a complementary approach towards an improved understanding of an Adverse Outcome Pathway (AOP), as it has the potential to link exposure with the Molecular Initiating Event (MIE) in a single metric.

This presentation is an introduction into further workgroup discussion. The following topics will be briefly introduced with a few examples using literature data. (i) application of the chemical activity approach to compounds with more specific modes of action, and (ii) to compounds with multiple modes of action; (iii) classification into mode of action (MOA) and the potential role of adverse outcome pathways (AOP) in classification; (iv) the potential link between chemical activity and AOP in predicting the effects on whole organism level (quantitative AOP). Initial data analyses show that chemical activities are very useful to interpret and predict effects of chemicals with a MOA beyond narcosis.

Joop Hermens

Joop Hermens is associate professor at the Institute for Risk Assessment Sciences, Utrecht University and leads the Environmental Toxicology and Chemistry group at IRAS.

Research in this group is directed towards a better understanding of the exposure of contaminants in the environment in relation to effects on ecosystems and on human health. Within this line of research, new technologies have been developed for the estimation of the bioavailable and internal concentrations of organic contaminants in both aquatic and terrestrial organisms and compartments (soil and sediment). In a broader perspective, the group is interested in dynamic aspects of exchange processes at a micro scale (from cells to clay minerals). More recent research topics include exposure assessment in in vitro studies with a focus on classical contaminants as well as ionized compounds such as pharmaceuticals, biocides and surfactants.

Abstract

Challenges and potential limitations to the application of the chemical activity concept for ecological risk assessment – Physical-chemical properties & partitioning

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The chemical activity concept has recently been promoted as a useful approach for assessing and evaluating the potential risks posed by chemicals in the environment. To date the use of chemical activity has been largely applied to neutral organic chemicals, with a focus on chemicals that are classified as baseline narcotics. The calculation of chemical activity in the aqueous phase is seemingly trivial, being simply the ratio of the concentration of the chemical in water divided by the water solubility (or sub-cooled liquid water solubility if the chemical is a solid at ambient temperature). LC50 or EC50 data can be converted to chemical activities (i.e., La50s, Ea50s) in the same way. The apparent simplicity of this ratio masks the potentially large uncertainties in these calculations, driven by uncertainties in the underlying property values. These uncertainties/errors are particularly relevant for solid chemicals for which chemical activity calculations require data on melting point (MP) and entropy of fusion at the melting point (ΔSM). Non-equilibrium conditions between biota and the aqueous phase (driven for e.g., by biotransformation in vivo) may necessitate the estimation of chemical activity in biota itself, which requires additional partitioning data (e.g., lipid-water partition coefficients). The main objective of WG3 is to evaluate the current state of the science with respect to uncertainties in key physical-chemical properties and the corresponding uncertainty/error in chemical activity calculations and interpretation of toxicity data. For example, the extent to which uncertainty/error in property values can explain deviations in the lethal chemical activities (La50s) of baseline narcotics from expected values (La50 = 0.01–0.1) will be assessed. The applicability of the chemical activity concept to miscible organic chemicals (MOCs) and ionisable organic chemicals (IOCs) will also be probed through theoretical considerations and case studies. The main deliverables from the WG3 discussions will be guidance on the potential pitfalls in applying the chemical activity concept to diverse sets of chemicals and practical advice for addressing key uncertainties in chemical activity calculations in different situations.

Short C.V.

Todd Gouin

Todd Gouin is an environmental fate modeller, based at the Safety & Environmental Assurance Centre at Unilever, in the UK, where he has been employed since June, 2009. Prior to joining Unilever, Todd spent two years as an assistant professor of environmental & analytical chemistry at the University of Alaska Fairbanks. Todd received his PhD under the supervision of Dr. Don Mackay at Trent University in Canada in 2005, followed by a NSERC government-funded post-doctoral fellowship with Dr. Frank Wania at the University of Toronto Scarborough. He has authored over 50 scientific articles, book chapters, and reports on topics related to the environmental fate and transport of organic pollutants. He is currently the chair of the SETAC Exposure Modelling Advisory Group, where he has a strong interest in ensuring that developments in exposure science are well communicated both within and outside of SETAC, and that advances in tools for assessing exposure are appropriately adopted towards methods used in chemical risk assessment in the 21st Century.

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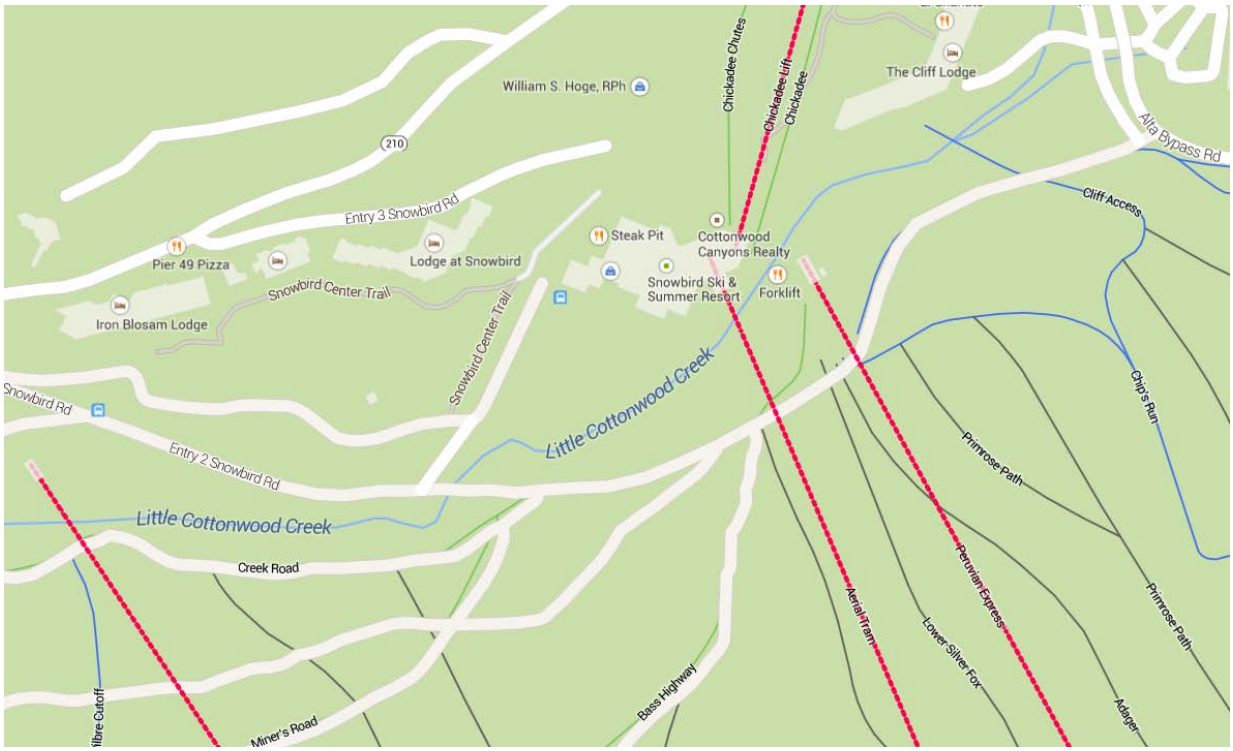

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