From bioavailability science to regulation of organic chemicals


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The bioavailability of organic chemicals in soil and sediment is an important area of scientific investigation for environmental scientists, although this area of study remains only partially recognized by regulators and industries working in the environmental sector. Regulators have recently started to consider bioavailability within retrospective risk assessment frameworks for organic chemicals; by doing so, realistic decision-making with regard to polluted environments can be achieved, rather than relying on the traditional approach of using total-extractable concentrations. However, implementation remains difficult because scientific developments on bioavailability are not always translated into ready-to-use approaches for regulators. Similarly, bioavailability remains largely unexplored within prospective regulatory frameworks that address the approval and regulation of organic chemicals. This article discusses bioavailability concepts and methods, as well as possible pathways for the implementation of bioavailability into risk assessment and regulation; in addition, this article offers a simple, pragmatic and justifiable approach for use within retrospective and prospective risk assessment.

**INTRODUCTION**

Straightforward approaches are required to assess the risks associated with contaminated sites and chemicals that require regulation. However, realistic assessments must also include the consideration of bioavailability. To enable regulatory decisions, the fraction of a chemical present in soil or sediment that is available for uptake, and for causing adverse effects to biota within a given time span, should be explicitly considered. Moreover, such decisions must rely on measurements made using established and, preferably, standardized methods. In this paper, we summarize the current state of knowledge on bioavailability science and translate this knowledge into a simple, pragmatic and justifiable approach for use in prospective and retrospective assessment and management of risk.

A recent search of articles published since 1996, carried out using the Web of Science database and the search-terms "bioavailability/organic/pollutant", identified 2028 papers with 59,776 citations. Despite this, the application of "bioavailability" in the risk assessment (RA) of soil and sediments remains very limited, and assessments are routinely based on the total extractable chemical concentrations alone, even if it...
can be shown that most of the chemical burden is either nonmobile or nonbioavailable. At the moment, risk characterization, which is based on total contaminant loading, is an overly protective, conservative approach that minimizes liability should something go wrong and transfers cost to the owners of the contaminated sites. In spite of the recent shift to a more risk-based assessment strategy, the implementation of bioavailability knowledge for the production of a more pragmatic, site-specific approach is still uncommon.

Retrospective RA targets the identification and evaluation of the potential negative effects of chemical substances (e.g., from contaminated soil and water) and is implemented through national legislation on soil contamination. In contrast, prospective RA is carried out in the context of the market authorizations of chemicals. In Europe, the latter is implemented at the legislative level mainly by means of regulations (e.g., REACH Regulation, Plant Protection Products Regulation, and Biocidal Products Regulation). At present, total extractable concentrations are used for both forms of regulatory RA. However, over the past few years there has been growing acknowledgment of the need to include bioavailability in risk assessment frameworks. Methods that consider bioavailability have also been promoted for the purpose of water and sediment monitoring. This has led to the inclusion of a bioavailability-specific method (passive sampling, see below) in the guidance provided under the Water Framework Directive. However, this approach is only included as a complementary method. Similarly, the guidance of regulatory frameworks based on prospective RA highlights the relevance of bioavailability. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) has recently proposed chemical-residue extraction approaches for use in soil/sediment degradation studies that fractionate the total residue on the basis of biological relevance rather than on the basis of extraction efficiency alone. These approaches are designed to differentiate the concentration of the residue that is bioavailable and hence relevant from that which is nonbioavailable and hence not relevant in the RA.

As the knowledge base of bioavailability science continues to grow, new possibilities and refinements may be identified, expanding the potential for implementation. To facilitate the inclusion of bioavailability within RA frameworks, agreement between scientists, regulators and industry is required regarding the incorporation of bioavailability knowledge into existing structures, to obtain a more realistic estimation of risk. One major question remains: are we ready for this? In a brief but unconstrained presentation of the most established scientific knowledge on bioavailability, this article aims to bridge the gap between the scientific and regulatory community.

THE STATE-OF-THE-ART IN BIOAVAILABILITY SCIENCE

For bioavailability to be accepted by environmental regulators and incorporated into RA frameworks, two questions must be addressed: (1) what is meant by “bioavailability”, and (2) how should it be measured? Over the last 30 years, numerous publications have discussed the concepts and definitions of bioavailability. These are illustrated in Figure 1. However, the discussions have not always considered how these definitions might be used to provide relevant and measurable data to support RA and remediation. This uncertainty has fuelled the reluctance of the regulatory/RA community to include
“bioavailability” within RA and management procedures. For example, a survey conducted in the UK on the applicability of bioavailability in risk-based regulation contacted 375 local authorities, with the results revealing that 70% of the respondents thought bioavailability would be useful in supporting decision making. However, 78% expressed concern that the lack of statutory guidelines was hampering the application of bioavailability to the RA and management of contaminated land.

Depending on the scientific approach, different definitions of bioavailability have been developed. Figure 1 shows several of the definitions accepted by scientists. The main schools of thought consider bioavailability (focusing on the aqueous or dissolved contaminant), bioaccessibility (incorporating the rapidly desorbing contaminant in the exposure), and chemical activity (determining the potential of the dissolved contaminant for biological effects). Ehlers and Luthy (2003) summarized the findings, for retrospective situations, of the NRC Committee on Bioavailability of Contaminants in Soil and Sediments, in which “bioavailability” was not defined; rather, the merits of “bioavailability processes” in assessing contaminated soils and sediments were discussed. The concept of bioavailability was further discussed by Semple et al., who identified and defined the “bioaccessible” and “bioavailable” fractions: after a certain exposure time, bioaccessibility extends beyond bioavailability, encapsulating what is bioavailable, as well as potentially bioavailable (rapidly desorbing contaminant), which may be determined using chemical methods. With the development of passive samplers, Reichenberg and Mayer applied the concepts of chemical activity and bioaccessibility to the description of bioavailability. Similarly, the International Organization for Standardization (ISO) perceived bioavailability as a relevant issue by highlighting that exposure time is important, particularly with regard to the choice of method.

For prospective situations, the regulatory approval of chemicals, particularly pesticides, has involved the use of 14C-labeled chemicals in well-defined systems. For most chemicals, persistent, residual 14C-activity often remains in the soil, even after the most aggressive solvent extractions have been performed. This residual 14C-activity is defined as the nonextractable residue (NER). NERs can usually be quantified only if 14C-labeled (and also 13C-labeled) chemicals are used, and they are not a measurable parameter in retrospectively contaminated soil or sediments. NERs may be defined as the chemical itself associated with mineral and/or organic matter fractions. However, if care is not applied, NERs may also describe the transformation products of 14C within microbial biomass (biochemical components), or even 14C-carbonates, and undefined 14C-transformation products. These assimilated residues (known as biogenic NERs) are of no ecotoxicological concern. Thus, in prospective RA, it is important that the potential for the extensive formation of such residues is taken into account when considering the significance of NER and bound residues.

In this section, four key concepts have been introduced: bioavailability, bioaccessibility, chemical activity, and NERs. Bioaccessibility, chemical activity and NERs are well-known terms within the research community but are less commonly used or understood in the public/regulatory domains, compared with bioavailability. Therefore, it is important to be aware of the differences between scientific and regulatory perception; these differences serve as key motivation for this paper. In regulatory decision-making scenarios, a greater degree of clarity, predictability, and perhaps, greater simplicity are required than in science. In addition to characterizing the risks, an estimation of the uncertainties of the methods is required for robust and pragmatic regulatory decision making. However, other factors may influence the decision-making process. For example, who is responsible, what are the costs, and for what purpose will the land be used? The complexities of the science
Bioavailability should not make decision making more complex or uncertain. To implement bioavailability within RA and management, decisions must be clearly articulated and well-justified, so that they can be understood by nonexperts and incorporated into existing frameworks.

In our proposal, the concept of bioavailability considers the importance of an organism’s cell membrane (Figure 2). Only the molecules of the chemical that can interact with or pass across a biological membrane are considered to be bioavailable. Of course, this is dependent on the morphological and physiological properties of the organism, the soil/sediment-contaminant contact time, the physicochemical characteristics of the chemical(s) and the properties of the soil or sediment, as well as the properties of other phase materials, such as tar, oil or black carbon. To have bioavailability included within the RA and management of contaminated systems, the following should be understood by interested parties: (1) organic chemicals are sorbed to soil/sediment and sorption becomes stronger with time (aging); (2) desorption and remobilization from these sites will take more time and, therefore, putative toxicity will decline; and (3) only the rapidly desorbing and the aqeuosly dissolved molecules of the chemical are bioavailable, as illustrated in Figure 2. The assessments of soil/sediment and the target chemical should be based on two measurable values: the total extractable concentration measured with a suitable method, and the bioavailable concentration as measured with a well-defined and explainable chemical method (desorption extraction, passive sampling or aqueous extraction) or the effect of the bioavailable concentration on an organism (biological tests). In our model, we consider slowly desorbing chemicals not to be bioavailable. We understand that this is a simplification, in scientific terms. However, this simplification is powerful because it enables the regulator to discriminate risks. Maintaining this distinction will facilitate the substitution of our proposed model for the old model, which is based on total concentrations.

**Chemical Methods for Measuring Bioavailability**

The pioneering work on bioavailability originally used mild extraction, passive sampling or aqueous extraction. These methods later evolved into mechanistically based approaches to determine bioavailability, providing data suitable for use in fate models. During the recent development of the ISO guideline on bioavailability, it was decided that these methods should be standardized. For organic chemicals, two possible approaches were identified: (1) methods based on the desorption of the target chemicals from soil or sediment by an extractant operating as an infinite sink, and (2) methods that measure the chemical concentration freely dissolved solely in the aqueous phase.

The results of infinite sink methods using Tenax28–33 and cyclodextrin34–38 extraction during approximately 20 h are currently used to predict toxicity and biodegradation, and are in the process of being standardized.39 The results of these methods represent and define what is referred to as the rapidly desorbing fraction. The second complementary approach is the use of passive sampling to determine the freely dissolved concentration as a measure of the chemical activity of organic chemicals in soils and sediments.16 This approach proposes that chemical activity drives bioavailability (Figure 1). Passive sampling has been performed with different systems in which chemicals partition between the dissolved phase and a solid or liquid sampling phase without significantly affecting the soil-water or sediment–water equilibrium. Different materials have been tested for nonpolar chemicals and polymers such as polyoxymethylene, polydimethylsiloxane and polyethylene, and are routinely used.40 Polar organic chemical integrative samplers and solid phase microextraction with materials such as polyacrylate are used for the passive sampling of polar chemicals.34,42 Using these methods, the measured concentrations of the freely dissolved chemicals are orders of magnitude lower than those calculated using the distribution coefficients ($K_{oc}$) of the chemicals, and therefore, their bioavailability can be considered to be lower than predicted.33

**Biological Methods for Measuring Bioavailability**

Protecting an organism from a toxic chemical means that the bioavailability of the chemical for that organism should be known. There is only one way to ensure that a chemical method is representative for the actual exposure (and, potentially, the effects) suffered by an organism, that is, showing that such chemical measurements are closely linked to the biological process driven by exposure. As ISO 17402 states, this can be directly accomplished by using that organism to measure the effect, accumulation or degradation of a given chemical.18 Several (mostly standardized by ISO and OECD) ecotoxicological test methods are available to determine bioavailability in the soil and sediment compartments.44 These methods were developed in the context of prospective RA, but they are also applicable in retrospective RA. They focus primarily on invertebrates and, to a lesser degree, on plants or microorganisms (the latter, only in soil). The bioavailability of a wide range of specific chemicals for these biological groups is relatively well studied. Examples include polycyclic aromatic hydrocarbons (PAHs), pentachlorophenol,45 and pesticides in general.47 It is obvious that, because of the high number of organic chemicals (which may end up in soils), the large range in soil properties (which may influence the availability of these chemicals) and the taxonomic, physiological and behavioral diversity of soil biota (which may react quite differently to chemical pollution), there is no single test method that can be used. Therefore, a battery of tests, which consists of methods that reflect the various combinations of chemicals, soils and organisms, as well as the different putative exposure pathways, is necessary.44

The European (prospective) regulation on plant-protection products48 already uses a suite of tests, including an earthworm reproduction test,9 collembolan reproduction test,30 predatory mite reproduction test,51 plant seedling emergence test,52 and plant vegetative vigor test.53 These tests include the two main biotic groups that must be protected in soils (invertebrates and plants) and consider the different putative exposure pathways,
that is, via pore water and soil (earthworms and Collembola), via food (mites), and via pore water and air (plants). Different taxonomic groups (e.g., Arthropoda, Oligochaeta) and morphological/physiological (i.e., hard- and soft-bodied) groups are also included. Comparable requirements also exist for pharmaceuticals.54 Other standardized tests (e.g., Enchytraeidae, Nematoda) might be needed to establish robust relationships between bioavailable fractions and to conduct assessments for other groups of chemicals. In some cases, test methods that have not yet been standardized may be helpful (e.g., with Isopoda).55

Information on the potential for the biodegradation of chemicals is relevant for both prospective RA and retrospective RA, and this process may also be affected by bioavailability. The OECD biodegradation guidelines are the most widely used for regulatory purposes and are the basis for the biodegradation testing demanded in the U.S. and E.U.4,36,57 Methods for assessing biodegradability in soil (OECD 304) using 14C-labeled chemicals are suitable for studying the kinetics of biodegradation and the transformation pathways. As mentioned above, the results of these biodegradability tests are very comparable with those of the infinite sink chemical methods; therefore, biodegradability tests are suitable biological methods for estimating the bioavailability of biodegradable chemicals.30,33,35,59 If both measurements are made, the more conservative result (corresponding to the higher amount of the chemical released, and therefore bioavailable) can be used as the indicator of risk.

APPLICATIONS OF BIOAVAILABILITY IN RETROSPECTIVE RISK ASSESSMENT

Retrospective management of contaminated soil has been commonly practiced in the industrialized world since the 1970s. Measurements of the (total) concentrations of contaminants, such as metals, PAHs, polychlorinated biphenyls (PCBs), and pesticides, made it clear that a large number of sites have been contaminated. In many countries, quantifying the total, maximum allowable and background concentrations of chemicals in soil and sediments has made it possible to identify contaminated sites. However, the risks tend to be overestimated when total extractable concentrations have been used, resulting in the remediation of potentially contaminated sites that did not pose significant risk to receptors. Although bioavailability is not commonly used, there are a relatively small number of examples in which such measurements have been considered in the management of contaminated sites. Examples from two countries, (1) The Netherlands, with a focus on risk-related values, and (2) Australia, where the focus was on remediation, are presented.

In The Netherlands, the list of maximum allowable concentrations addresses specific land uses, such as natural areas, agriculture, living, playgrounds, and industrial sites. The values are defined for a standard soil having 10% organic matter (OM) and measured values are required to be corrected by the actual % OM of the soil to accommodate different soil types. Although this was not the explicit intention when developing the system, the correction factor in practice turned out to be a first attempt to apply standard values on the basis of the bioavailable fractions, and in combination with land use, they are more risk based. Sequestering and strong specific binding are not accounted for by this correction, and the corrected value does not always explain the bioavailability and risks. As a step toward the implementation of bioavailability in this model, a general protocol for considering bioavailability in a higher-tier risk evaluation was agreed upon by experts in The Netherlands2 and has been applied to specific sites with contaminated sediments (including harbors) and a large area (450 ha) of diffuse contaminated soil using desorption extraction and/or passive sampling methods as described in this paper. The sites were contaminated mainly with hydrophobic persistent chemicals like PAHs, PCBs and/or mineral oil. The proposal for the inclusion of bioavailability in the generic regulation in retrospective RA has not yet been implemented.

Australia is an example of pioneering work on the introduction of bioavailability in full-scale land management given the recent introduction of bioavailability and in particular metal and metalloid bioavailability in its National Environment Protection Measure (NEPM). While organic contaminant bioavailability is yet to be incorporated in the Assessment of Site Contamination (ACS) at the NEPM, it is nevertheless included in contaminated site risk characterization.60,61 Research toward the development of standard operating procedures is the focus of Australian studies with a view to inclusion of bioavailability in the next revision of the ACS-NEPM. Indeed, up to 60% of contaminated sites, with the majority in the urban environment, are likely to include organic contaminants. Despite an expenditure for remediation exceeding three billion Australian dollars per annum, less than 10% of the sites have been remediated over the past 20 years, with most of the remediation carried out through excavation and disposal in landfills. It has also been recognized that some remediated sites were most likely otherwise safe from an exposure perspective. Therefore, it was necessary to change the governing policies. One important tool was the explanation of bioavailability to regulators using the concepts given in this paper, which made it possible to design new remediation methods. If organic chemicals are immobilized, the flux from the soil to the pore water is low, usually too low for the contaminant to pose risks. The underlying basis for this approach is to demonstrate to regulators using appropriate indicators, that the toxic contaminant, once immobilized, will not be bioavailable over time and hence poses no risk to receptors.62 Jurisdiction in Australia now recognizes that the process of aging can be accelerated via chemically induced immobilization, which results in a rapid decline in bioavailability. An example of successful immobilization-based remediation using a modified clay sorbent in Australian soils has been documented for pollution by perfluorooctanesulfonate, a highly recalcitrant contaminant.63 After treatment, the bioavailable concentration of the chemical, measured as the concentration in the water phase, remained below the detection limit, and no toxicity to earthworms was observed. Another example is the successful immobilization of DDT in soil by a modified clay.64 Activated carbon has also been used in Australia, as is the case in the U.S. and E.U.,55,66 to decrease the bioavailability of PCBs and PAHs in soils and sediments.62

The global exchange of experience will be important for future developments. Guidelines are necessary for further applications of remediation in which modifying bioavailability has a central role. A good example of such a guideline is the so-called TRIAD approach (only recently completed as an ISO standard).67 The tiered approach described in this standard is also an important part of our proposal.

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Applications of Bioavailability in Prospective Risk Assessment

Legislation addressing the prospective RA of chemicals usually requires companies to provide data on basic substance properties (e.g., vapor pressure, log $K_{ow}$ and solubility), basic fate properties (e.g., hydrolysis, degradation, bioaccumulation) and information on (eco)toxicity and exposure, which are then used to assess the risks that a chemical may pose for human health or the environment. For example, under the European REACH regulation companies are responsible for providing information throughout the supply chain regarding the hazards, exposure, risks, and safe use of chemical substances that they manufacture or import. The follow-up regulatory action is then the responsibility of public authorities, with obligations and responsibilities of the companies in some processes. Usually, RA approaches start with simplified, worst-case assumptions that do not require significant amounts of detailed information, for example, the use of total concentrations as a first estimation of exposure. Higher-tier, more realistic RA might be necessary if there is a clear need.

Many of the regulatory frameworks on chemicals allow for weight-of-evidence approaches or the use of several lines of evidence, which may include the determination of bioavailability. For example, REACH allows for such substance-specific approaches to be used by registrants by adapting the standard information requirements to their substance. Similarly, bioavailability can play a role in other regulatory frameworks, for example, in the assessment of chemicals leading to restrictions. Such adaptations must be scientifically valid, well-documented and justified, with the uncertainties described and addressed. Furthermore, when a substance falls under different regulatory regimes because it is used as a pesticide, a biocide or a veterinary medicine, different exposure scenarios may exist and must be taken into account.

The Plant Protection Products Regulation and related guidance documents do not currently take bioavailability into account in their calculations of potential exposure. An EFSA scientific opinion on the comparative usefulness of total soil and pore water concentrations concluded that for soft-bodied soil organisms and plants, pore-water-mediated uptake was mainly responsible for the effects caused. The opinion also acknowledged the limitation of the use of total soil concentrations based on publications demonstrating reduced toxicity with time, even though soil residues remained constant. A software tool (PERSAM) was subsequently developed to calculate the total soil and pore-water exposure values. This tool relies on the use of soil/water equilibrium-partitioning values to calculate pore-water concentrations even after many years of aging. This is a reasonable first-tier approach, but the option to use aged sorption values or desorption measurements would be a straightforward way to improve the realism of the predicted exposure values by introducing elements of bioavailability. However, extrapolations of approaches from other regulatory frameworks may not always be possible, or may be complex. For example, the EU sets rules for the sustainable use of pesticides to reduce the risks and impacts of pesticide use on human and environmental health. Including bioavailability in the RA of these different regulatory frameworks could add to the complexity of the RA. Therefore, a clear explanation of the steps to be taken when including bioavailability in the RA is required.
THE WAY FORWARD: INTELLIGENT AND PRAGMATIC APPROACHES FOR RISK ASSESSMENT

For regulatory purposes, it is necessary to use a straightforward approach to assess contaminated sites, to inform the development of new chemicals, and to determine the risks to human and environmental health posed by chemicals. The present retrospective risk assessment uses total concentrations and has been the standard for over 30 years, despite being overly conservative and overly protective, especially when decisions on the remediation of soil and its reuse are required.

Depending on the case, an appropriate selection of the methods and test organisms must be made for retrospective and prospective risk assessments. The data used for decision-making must be clearly and understandably connected to the presence of organic chemicals in the soil or sediment environment (Figure 2). As with chemical methods, there should be a restricted number of bioassays used, and where possible, these should be validated and preferably standardized in combination with proper quality assurance and control procedures. In this context, it is important that transparent criteria, commonly defined beforehand by risk assessors and stakeholders alike, are used when selecting the most appropriate biological test methods. These criteria include the possible pathways, site-specific conditions, ease of application, sensitivity, costs of the tests, and interpretation of the results by non-ecotoxicologists.

To include the results of tests on bioavailability in decision making a weight-of-evidence approach should be used. To date, the TRIAD approach, which consists of three lines of evidence, namely, environmental chemistry, (eco)toxicology and ecology, represents the most enlightened approach. It has been used extensively and successfully in sediment ecotoxicology for approximately 30 years and is currently being standardized by the ISO. In a tiered approach, it is neither practical nor economically feasible to use all of the available methods. Therefore, a stepwise, tiered, approach, similar to that used for metals, is proposed. A decision is made after each tier on whether further investigation is necessary (Figure 3). According to this scheme, bioavailability can be included at a higher tier to provide additional site-specific data. Under the regime proposed in this paper, bioavailability will be part of a second-tier of assessment. This new proposal provides an opportunity for the inclusion of a more detailed interrogative assessment procedure in which bioavailability plays a role and that will potentially lead to more realistic RA.

So, are we ready for this new approach? Our conclusion is yes. The system we propose is simple and is limited to measuring the totally extractable chemical, as well as the bioavailable concentration, which is represented by the freely dissolved concentration and the fraction that rapidly desorbs and moves into the water phase. Under normal circumstances, NERs would not be considered within this proposed RA framework because the risk comes from the extractable fractions in the soils and sediments. Measurement means the application of validated and preferably standardized chemical and biological methods. In the authors’ opinion, the knowledge already provided by science supports the proposed simplification.

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Notes

The views and opinions expressed in this article represent exclusively the personal ideas of the authors and do not represent the official position of the European Chemicals Agency (C.A. and B.V.), nor of the European Commission and its Directorate General for Internal Market, Industry, Entrepreneurship and SMEs (G.S.). The authors declare no competing financial interest.

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(full details can be found at http://sesss10.setac.eu/programme/about_the_speakers/)

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(1) Search performed at Web of Science (Thompson Reuters, New York), on 27th July of 2015.


