2011

Introduction to "Environmental Contaminants in Biota, 2nd edition"

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Published in *Environmental Contaminants in Biota: Interpreting Tissue Concentrations, 2nd edition,* ed. W. Nelson Beyer & James P. Meador (Boca Raton: CRC, 2011).

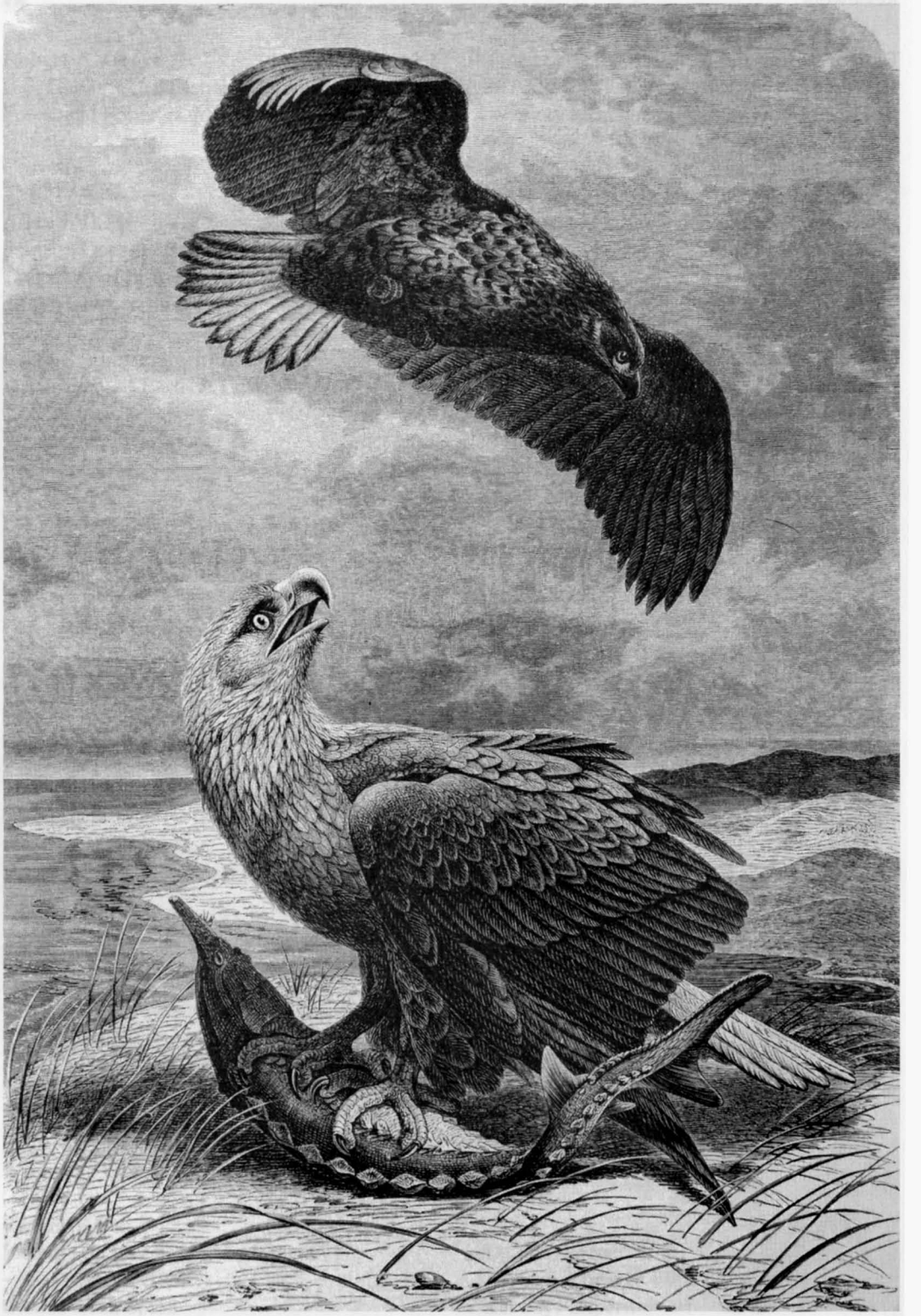
SECOND EDITION

ENVIRONMENTAL CONTAMINANTS IN BIOTA

Interpreting Tissue Concentrations

Edited by
W. Nelson Beyer
James P. Meador

CRC Press
Taylor & Francis Group



White-Tailed Sea Eagles

By G. Mutzel, from *The Royal Natural History,* edited by Richard Lydekker, Frederick Warne & Co., London, 1893–94.

Introduction

W. Nelson Beyer and James P. Meador

Ecotoxicology is the study of the movement of environmental contaminants through ecosystems and their effects on plants and animals. Examining tissue residues of these contaminants in biota is basic to ecotoxicology, both for understanding the movement of contaminants within organisms and through food chains, and for understanding and quantifying injuries to organisms and their communities. This book provides guidance on interpreting tissue concentrations of environmental contaminants.

Tissue concentrations have long been used both to identify the cause of toxicity in animals and as a measure of the severity of toxicity. More recently, they have been incorporated into environmental models, tying together exposure, kinetics, and toxic effects. Measuring tissue concentrations is basic to studies on the kinetics of contaminants, which entails characterizing the rates of uptake and elimination in organisms, as well as redistribution (organs, lipid, and plasma) within them. Tissue concentrations are also used in ecological studies examining the movement of contaminants between organisms and within biological communities.

In monitoring programs, tissue concentrations tell us about the geographical distribution of contaminants and how they change through time. Measuring contaminants in tissue can also be important for defining the background, or the uncontaminated condition, as well as identification of hot spots and gradients from point sources. Although analyses of soils and sediments also provide information on the distribution of contaminants, analyses of tissues provide information that is more meaningful to ecotoxicologists. In some instances, chemical analyses of tissues gave the first hint of the global dispersion of chemicals. The environmental importance of polychlorinated biphenyls, tributyltin, and perfluorooctanesulfonic acid was not recognized until these compounds were found in tissues of widely distributed animals. Sometimes knowing simply that a contaminant is present in an organism is useful. For example, if an avian die-off has occurred and brain tissue shows greatly reduced activity of cholinesterase, then documenting the presence of an organophosphate or carbamate pesticide in the carcasses may be all that is required to find the cause of that die-off (Mineau and Tucker 2002). When pathologists examine toxicological cases, tissue analyses are usually essential to making a diagnosis. For the most part, however, this book provides guidance on relating tissue concentrations quantitatively to injury, which lies at the core of ecotoxicology. Thousands of research papers reporting tissue concentrations are published each year, and their value depends on ecotoxicologists being able to interpret the toxicological consequences of those concentrations.

The logic for relying on tissue residues in wildlife toxicology was put forth by Bill and Lucille Stickel (1973), who explained how tissue concentrations may best be used in diagnosing poisoning of birds by organochlorine pesticides. Biologists had suspected that birds were being poisoned by applications of pesticides, but differences among species, the physiological condition of the birds, and extraneous factors made it difficult to establish the cause of death. Analyzing the contents of the digestive tract for the presence of a pesticide, the usual means of diagnosing poisoning in humans, failed because all of the birds in a sprayed area had some exposure to the pesticide. Live birds collected at the site often had whole-body concentrations of pesticides that exceeded those of birds found dead. In a series of controlled studies on birds dosed with various organochlorine pesticides, the Stickels and colleagues demonstrated that because the lipids that store the pesticides are metabolized when a bird stops feeding (due to sickness caused by exposure to these pesticides), those

pesticides in the body may be mobilized and then rapidly become lethal. Although various organs could be used to indicate sublethal exposure to pesticides, analyzing the brain was key to identifying those birds that had lethal residues. Unlike concentrations in other organs, lethal concentrations in the brain were remarkably consistent, even in different species and in birds with different exposures. The brain is the logical organ to analyze because the organochlorine pesticides were neurotoxic, but the decision to rely on brain residues was a practical one. The reader is referred to Keith (1996) and to the following chapter in this book for a history of the use of tissue residues in evaluating hazards of contaminants to wildlife.

Aquatic toxicologists also rely on tissue concentrations when interpreting hazards, although much of this research has been relatively recent. The underpinnings of tissue residue toxicity were considered in the early 1900s by Meyer and Overton, who addressed the narcotic effect of organic compounds (Lipnick 1995) and by researchers who measured pesticides and metals in fish (Ferguson 1939, McCarty et al. in press). As these sporadic papers touted the virtues of using tissue residues to assess toxic responses, they were largely ignored by aquatic toxicologists, who emphasized exposure to contaminants in water and sediment. It was not until the early 1990s that a more in-depth analysis of tissue residue toxicity for a variety of chemicals and modes of action was considered (McCarty 1991, McCarty and Mackay 1993). After that, a flurry of research papers explored this topic in greater detail. These include published works on PAHs and other compounds at narcotic concentrations (Di Toro et al. 2000), chlorophenols (Kukkonen 2002), PCBs in salmonids (Meador et al. 2002a), tributyltin (Meador 2000, Meador et al. 2002b), mercury and DDT in fish (Beckvar et al. 2005), dioxins in fish (Steevens et al. 2005), and general reviews from Barron et al. (2002), Meador (2006), and Meador et al. (2008). At a Pellston workshop in 2007, 40 of the world's leading experts conducted a critical review of the tissue residue approach for toxicity assessment (see Integrated Environmental Assessment and Monitoring Jan. 2011).

The wide assortment of terms used in the field illustrates how researchers have evolved different ways of thinking about tissue concentrations. We begin this discussion with terms based on a mechanistic approach, originally defined by a work group on metals (Norberg 1976), although applicable to other contaminants as well. Several definitions are relevant here. The work group defines the "critical concentration" for a cell as the concentration at which undesirable functional changes, reversible or irreversible, occur in the cell. The "critical organ concentration" is defined as the mean concentration in the organ at the time any of its cells reaches critical concentration. The "critical organ" is that organ that first attains the critical concentration of a metal under specified circumstances of exposure and for a given population (Nordberg 1976). This approach is precise, assuming cause and effect. Cadmium's well-known effect on renal function seems to fit well into this framework. In practice, however, this approach does not work well for many environmental contaminants. A toxicant, such as lead, may affect many organs and systems simultaneously, and the signs and lesions observed among lead-poisoned individuals may vary substantially. Because organochlorine compounds are stored in lipids, throughout the body, they are not associated with a single organ. Nor is identifying "that organ that first attains the critical concentration" as simple as it sounds. A histopathologist using electron microscopy may detect lesions not visible using light microscopy. Drawing on more sensitive measures, such as those used in genomics, a toxicologist may detect alterations at lower tissue concentrations and exacerbate the difficulty in differentiating a harmless response from an adverse response. Risk assessors try to select endpoints that they consider meaningful to an assessment, which is not always the same as selecting the most sensitive endpoint.

The expression "critical concentration" is often useful when generalizing about tissue concentrations applicable to a taxon, as long as the effect and the circumstances are made clear. For example, based on studies conducted on several species ingesting lead shot, we might identify a critical concentration in livers of waterfowl expected to be associated with death. The term "threshold" means the concentration at which an effect is first observable.

The terminology of tissue concentrations used commonly by aquatic toxicologists is based on the traditional toxicological expressions of exposure—LCp or LDp (lethal) and ECp or EDp (sublethal)

values, where C is the external concentration, D is the administered dose, and p is the percentage responding. In many cases aquatic toxicologists use LRp or ERp, where "R" denotes tissue residue (Meador 1997). There is a distinction between toxicity metrics that are expressed in terms of the amount of a toxicant that is delivered or administered to the organism and the actual tissue concentrations associated with the response. The dose is generally expressed as μg or μmol toxicant/gram body weight/day or as single-dose μg/g or μmol/g and is usually administered by feeding, injection, gavage, or bolus to determine the LD50 or other measures of toxicity. The acquired dose (tissue residue) is used to characterize adverse effects as a function of the measured or predicted tissue concentration, such as an LR50. The administered dose, as it is metabolized and excreted, may be very different from the tissue concentration associated with toxicity (Meador 2006). For aquatic toxicologists, "critical body residue" (CBR) is a general term often implying a whole-body concentration that is related to an adverse effect. A CBR can be characterized by any one of a number of toxicity metrics (e.g., LR50, ER10, or LOER) depending on the application. These values are best expressed as a molar concentration, especially when comparing among toxicants.

The terms "diagnosis" and "diagnostic" have well-established uses in veterinary science, and these terms can be applied in some instances to aquatic and wildlife toxicological studies. A diagnosis is a determination of the cause of an illness from its signs and lesions, through an examination by a trained diagnostician or pathologist. Making a diagnosis implies not only identifying a cause but also ruling out other potential causes of the observed signs and lesions. Consequently, ecotoxicologists may determine that the probable cause of death is a contaminant, but they are not making a "diagnosis" unless other causes are ruled out. A diagnostic residue is a concentration in tissue that supports a diagnosis of poisoning if the signs and lesions observed in the animal are consistent with the poison in question. A diagnostician starts with observed effects and reasons back to a cause, establishing the diagnosis, whereas an ecotoxicologist usually starts with an exposure or tissue concentration and tries to deduce possible toxic effects.

The need for screening values in ecological risk assessment has led to the use of "hazardous concentrations." For example, Aldenberg and Slob (1993) described a statistical method to calculate the lower confidence limit based on a percentile of a distribution of no-effect or lowest effect levels measured in different species within a taxonomic group. When calculated at the fifth percentile, the value is meant to be protective for 95% of the species or focal group. This threshold, or protection value, is lower than those derived from central tendency values (e.g., mean or median) that will protect far fewer organisms. The calculation of the HC_5 usually requires a large database from comparable studies.

For a critical concentration to be credible, it must be based on substantial evidence. Well-designed, controlled toxicological studies establish a cause-and-effect relation between the administration of a poison and an effect. Some controlled studies also establish a cause-and-effect relation between whole-body or specific tissue concentrations and an effect on an organism or that specific tissue. More often, however, the relation between a tissue concentration and an effect is a correlation. If an observed relationship between tissue concentration and injury holds true in other experiments and is consistent with observations in the field, then the correlation becomes credible and useful. In some instances the relation cannot possibly be based on cause and effect. For example, in the classic toxicological example in which researchers related DDE residues in raptor eggs to eggshell thinning, the DDE that caused the eggshell thinning was in the female that laid the egg. The DDE in the egg could not have caused the thinning. The important point is that the relation was found to be consistently reliable and was based on well-designed studies conducted under both controlled and field conditions. Because the DDE in the egg was correlated at some level to DDE in the adult, the concentration in egg became a useful surrogate. In some cases such as these where the mechanism is known, ancillary correlations may be useful as surrogate measures for the actual biologically effective dose at the receptor.

The more evidence collected under variant conditions, the more credible the argument. Critical concentrations are least reliable when based on few data, when they are applied to species that are

not closely related, and when the timing or route of exposure is different from the conditions in the study used as a reference. Whenever animals are dosed under experimental conditions, concentrations in many organs will increase and be correlated with each other and with effects, but most of those correlations will fail to be robust. Critical concentrations may be derived from field studies, but will be in error if an observed effect is incorrectly attributed to the contaminant or if the animals were subjected to additional stressors, lowering their sensitivity. Extrapolating from tissue concentrations to effects on populations or ecosystems is especially tenuous. To establish a credible relation between a contaminant and a population requires extensive work on several populations, as described by Ohlendorf and Heinz in Chapter 21 on selenium in this book.

Tissue concentrations of some contaminants are especially challenging to interpret. Concentrations of polycyclic aromatic hydrocarbons (PAHs), for example, are difficult to interpret in higher animals because they tend to be rapidly metabolized and excreted (Eisler 2000). However, a recent study correlated the administered dietary dose of PAHs with biliary metabolites in fish (Meador et al. 2008). Even though the biliary metabolites are not tissue concentrations, these values do represent an internal dose that can be correlated to toxic effects and measured in field collected animals in a similar fashion to assess harm. Further, elements that are homeostatically regulated in an organism pose another difficulty. Sometimes a target organ, however, may be identified that does show a sharp increase in tissue concentrations as toxicity is approached, even though concentrations are still regulated in most tissues. For some other elements, such as mercury, the total concentration of the element may be misleading, because the element's toxicity is so dependent on its chemical form.

The large number of poorly studied manufactured and natural chemicals is daunting. These industrial compounds, elements, pharmaceuticals, personal care products, pesticides, and others, are often best considered as chemical classes because of their overwhelming numbers. As shown for many toxicants, grouping chemicals by class and mode of action often results in similar toxicity metrics among several species and higher taxa, which is immensely helpful in our quest to characterize toxicity and quantify the concentrations likely to result in adverse responses. The authors of the book chapters adeptly address the challenges. With patience, the relations between tissue concentrations and toxicity are becoming better understood and their use in ecotoxicology gradually refined.

The study of tissue concentrations rests entirely on the validity of the chemical analyses supporting them. In general, the ability of today's analytical chemists to provide reliable analyses of most important environmental contaminants surpasses the ability of ecotoxicologists to interpret those concentrations. There is a perception that some poisons leave no traces, especially among mystery readers. Consider, for instance: "*I am assured that there are many poisons known only to a few chemists in the world, a single grain of which is sufficient to destroy the strongest man and leave not the slightest trace behind. If the poisoner be sufficiently accomplished he can pursue his calling without the faintest risk of detection.*" *Mr. Sabin sipped his wine thoughtfully* (from E. Phillips Oppenheim, 1903, *The Yellow Crayon*). Now, however, concentrations of almost all important contaminants or their metabolites may be detected in wine and in tissues, and, most importantly, they may be interpreted. Although uncovering the relation between concentration and effect requires considerable research and careful interpretation, the results are worthy, as the chapters of this book prove.

We are excited to present this second edition. Many of the chapters in this book address chemical classes that were explored in the first edition, which the authors have painstakingly updated with current data and, in some cases, with new ways of analyzing those data. We are also fortunate to have chapters that address tissue concentrations of some toxicants that have not been considered previously. Lastly, our second edition is illustrated with eighteenth-century engravings of fish, wildlife, and invertebrates, to remind us of what ecotoxicology is about. They are taken from *The Royal Natural History*, edited by British naturalist Richard Lydekker, and published in six volumes by Frederick Warne, 1893–1894.

ACKNOWLEDGMENTS

We thank Randy Brehm, Jennifer Smith, David Fausel, and Soniya Ashok of Taylor & Francis for their expert help in publishing this book. Mary Beyer of the Patuxent Wildlife Research Center provided editorial assistance and Jaime Rodríguez Estival of the Instituto de Investigación en Recursos Cinegéticos, Ciudad Real, Spain, prepared the figures of the engravings.

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