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History of Wildlife Toxicology and the Interpretation of Contaminant Concentrations in Tissues

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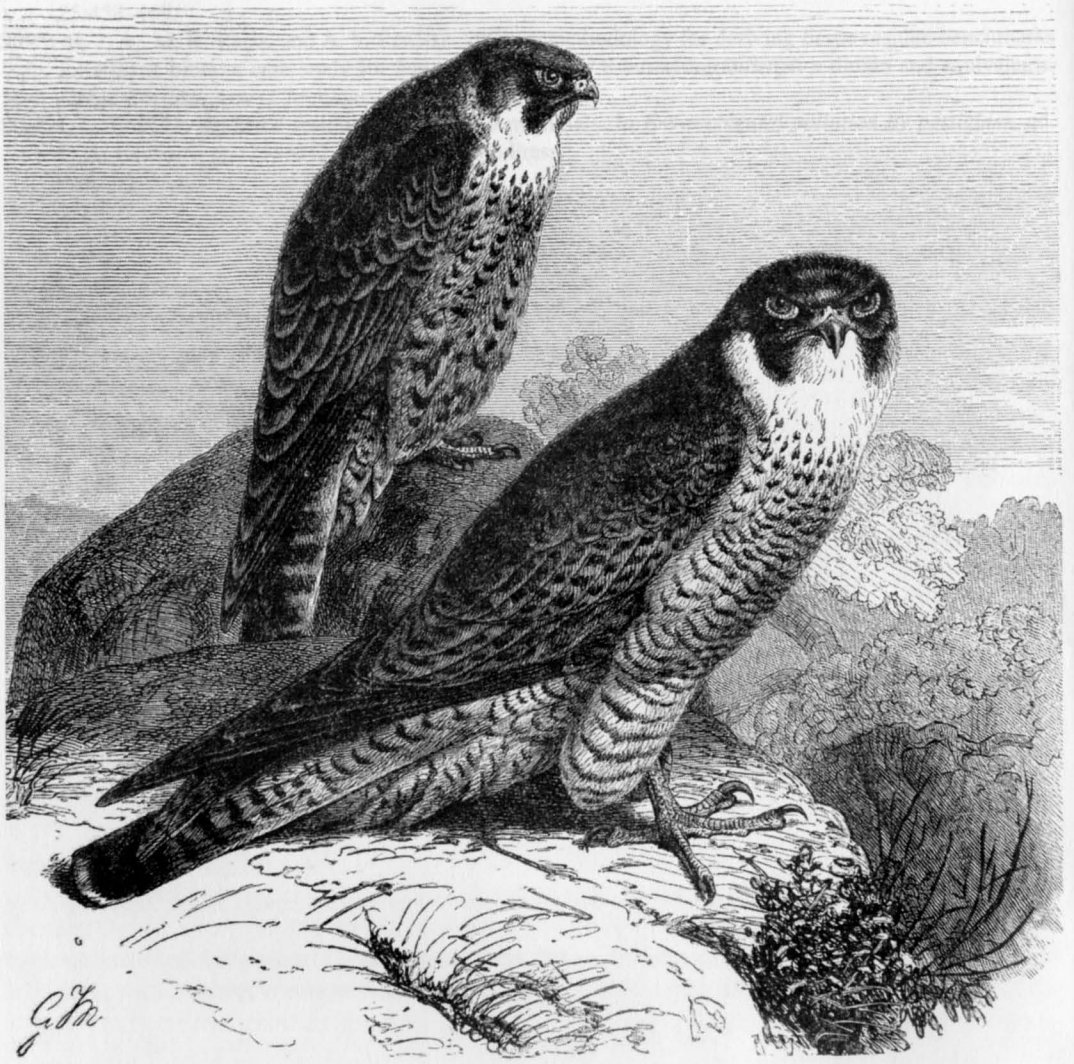

Peregrine Falcon

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

1 History of Wildlife Toxicology and the Interpretation of Contaminant Concentrations in Tissues

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1.1 INTRODUCTION

The detection and interpretation of contaminants in tissues of wildlife belongs to the field of toxicology, a scientific discipline with a long, intriguing, and illustrious history (reviewed by Hayes 1991, Gallo 2001, Gilbert and Hayes 2006, Wax 2006). We review its history briefly, to provide a context for understanding the use of tissue residues in toxicology, and to explain how their use has developed over time. Because so much work has been conducted on mercury, and dioxins and polychlorinated biphenyls (PCBs), separate case histories are included that describe the evolution of the use of tissue concentrations to assess exposure and effects of these two groups of contaminants in wildlife.

The roots of toxicology date back to early man, who used plant and animal extracts as poisons for hunting and warfare. The Ebers papyrus (Egypt ~1550 BC) contains formulations for hemlock, aconite (arrow poison), opium, and various metals used as poisons. Hippocrates (~400 BC) is sometimes credited with proposing the treatment of poisoning by decreasing absorption and using antidotes (Lane and Borzelleca 2007). Chanakya (350–283 BC), Indian advisor of the Maurya Emperor Chandragupta (340–293 BC), urged the use of food tasters as a precaution against poisoning, and

the Roman emperor Claudius may have even been poisoned by his taster Halotus in 54 AD. Moses ben Maimon (1135–1204), author of a treatise on poisoning, noted that dairy products could delay absorption of some poisons. Paracelsus (1493–1541) shaped the field of toxicology with his corollaries that experimentation is essential to examining the response, that therapeutic properties should be distinguished from toxic properties, that chemicals have specific modes of action, and that the dose makes the poison. The art of concocting and using poisons reached its "zenith" during the Italian Renaissance, eventually culminating in its commercialization by Catherine Deshayes (a.k.a., La Voisine, 1640–1680) in France.

One of the first to suggest a chemical method for the detection of a poison in modern times was Herman Boerhaave (1668–1738), a physician and botanist, who, according to Jurgen Thorwald (*The Century of the Detective*), placed the suspected poison on red-hot coals, and tested for odors. The Spanish physician Orfila (1787–1853) served in the French court, and was the first toxicologist to systematically use autopsy and chemical analysis to prove poisoning. He has been credited with developing and refining techniques to detect arsenic poisoning. Other historic accounts include extraction of alkaloids from postmortem specimens (Jean Servais Stas ~1851) as evidence in a nicotine poisoning case (Levine 2003). The chemical analysis of organs and tissues became the basis for establishing poisoning. Much of the early history of toxicology addressed whether someone had been poisoned and how to treat poisoning.

1.2 THE BEGINNINGS OF WILDLIFE TOXICOLOGY

Wildlife toxicology has generally dealt with environmental contamination and the unintentional poisoning of amphibians, reptiles, birds, and mammals (Rattner 2009). Concern over poisoning of wildlife began in the late nineteenth century, and initially focused more on identifying environmental problems than determining contaminant concentrations in tissues. Reports of pheasant (*Phasianus colchicus*) and waterfowl mortality related to ingestion of spent lead shot appeared in the popular literature (Calvert 1876, Grinell 1894). Once recognized, it was considered a common occurrence in waterfowl (Phillips and Lincoln 1930). Wetmore (1919) described postmortem signs of intoxication in waterfowl that contained shot in the gizzard and other portions of the digestive tract. Poisoning of waterfowl from lead mining wastes dumped into the Spring River in Kansas was described in 1923 (Phillips and Lincoln 1930). A report of arsenic-related mortality of fallow deer (*Dama dama*) near factories processing metal ores in Freiberg, Germany, made its way into the popular press in 1887 (Newman 1979). Controlled exposure studies with mercury, strychnine, and arsenic were conducted in domestic and wild fowl (Gallagher 1918, Whitehead 1934), including measurement of arsenic in tissues of dosed chickens (*Gallus gallus*) (Whitehead 1934). Alkali poisoning of thousands of eared grebes (*Podiceps nigricollis*) and shovelers (*Anas clypeata*) was documented in California in 1891 (Fisher 1893). Similar cases were subsequently described in many locations in the western United States, and alkali poisoning was even experimentally duplicated by Wetmore using captive birds, which were administered chlorides of calcium and magnesium (Phillips and Lincoln 1930). The hazard of ingested phosphorus from military munitions by waterfowl and swans was first recognized in 1923, and emerged as a problem on several occasions decades later (Phillips and Lincoln 1930). With the expansion of oil production and its use for marine propulsion after World War I, oiling of waterbirds and numerous die-offs occurred along the coast of the United States (over 35 incidents documented in Phillips and Lincoln 1930). In the aforementioned mortality incidents (i.e., lead shot, arsenic, alkali, phosphorus, and oil), the source and the presence of the toxicant were usually readily apparent (e.g., recovery of ingested shot, alkali salts or oil in or on birds).

Qualitative and quantitative determination of presence of lead in stomach and caeca of waterfowl was described as early as 1919 (Wetmore 1919, Magath 1931). Traces of arsenic were reported in the liver of dead deer following application of calcium arsenate for forest insect control in 1926 (Danckwortt and Pfau cited by Keith 1996). In the detailed description of poisoning of nontarget

wildlife by thallium baits used to control ground squirrels, Linsdale (1931) mentioned the use of qualitative spectroscopic methods to detect thallium in tissues of dead geese, and quantitative methods to determine concentrations in edible tissues. Before 1940, the presence or actual concentrations principally served as evidence of exposure. Quantitative methods were used in analyzing lead-poisoned geese (*Branta canadensis*) in the early 1940s, and "some correlation" between the number of shot found in the gizzard with lead content of the liver and kidney (but not leg bone) was suggested (Adler 1944).

Environmental contaminant studies with captive waterfowl began at the Patuxent Research Refuge in the late 1940s. Through controlled exposure studies with captive birds, evidence of adverse effects (histopathological lesions, impaired reproduction, and lethality) on individuals began to be generated. In toxicity studies of white phosphorus used in military munitions, Coburn and coworkers (1950) found statistically significant changes in concentrations of elemental phosphorus in heart, liver, and kidney of mallards (*Anas platyrhynchos*) and black ducks (*Anas rubripes*) that were dosed with various quantities of white phosphorus. These data were then used to interpret phosphorus concentration in tissues of redhead ducks (*Aythya americana*) collected from northern Chesapeake Bay, which led to the conclusion that "it appears probable" that the birds had been killed from ingestion of elemental phosphorus (Coburn et al. 1950). In order to interpret quantities of lead that produce toxic signs in waterfowl, mallards were dosed with lead nitrate (soluble and readily absorbable form of lead) for several weeks (Coburn et al. 1951). Anemia, emaciation, and a number of pathological lesions were consistently noted, and lead concentration in bone and liver was 7 and 40 times greater than that found in control birds. The critical lead intake level was suggested to be between 6 and 8 mg/kg body weight/day, and it was stated that bone, liver, or soft tissues could be used to chemically verify lead poisoning in field samples.

1.3 SYNTHETIC PESTICIDES AND POISONING OF WILDLIFE

By the 1930s, a total of about 30 pesticides were in use in the United Kingdom, United States and elsewhere, including plant derivatives (e.g., pyrethrum and nicotine), inorganic compounds (e.g., calcium arsenate and lead), mercurial fungicides, and the synthetic weed killer dinitro-ortho cresol (Sheail 1985). Aerial application of pesticides became a common practice in the 1930s, and potential adverse effects of pesticides to wildlife were acknowledged at the Third North American Wildlife Conference (Strong 1938).

The discovery of the insecticidal properties of dichlorodiphenyltrichloroethane (DDT) in 1939, the development, production, and use of other organochlorine (e.g., hexachlorocyclohexane), organophosphorus pesticides (e.g., schradan), and rodenticides (e.g., Compound 1080), increased dramatically during and after World War II (Hayes 1991). Concerns about potential damaging effects of DDT on wildlife appeared in The Atlantic Monthly (Wigglesworth 1945), which prompted experimental studies. Field studies of DDT effects on wildlife were undertaken in Maryland, Pennsylvania, and Texas, and reduced numbers of some avian species and dead birds were noted at application concentrations of 4.4 and 5 pounds per acre (Hotchkiss and Pough 1946, George and Stickel 1949, Robbins and Stewart 1949). Parathion poisoning of geese attributed to spray drift was also reported at this time (Livingston 1952). In the United Kingdom, large numbers of wildlife poisonings (e.g., passerines, game birds, mammals) occurred in the early and mid-1950s related to the use of aldrin and dieldrin as seed dressings, and application of schradan for control of aphids (Sheail 1985). Many other organochlorine insecticides (e.g., chlordane, heptachlor, and toxaphene) came into use in agricultural and forest settings in the 1950s, and wildlife mortality was noted (Peterle 1991).

Reports of wildlife mortality from pesticide use were controversial, pitting scientists associated with agriculture and chemical companies against environmental scientists. Biologists relied on tissue analyses not just to understand environmental hazards associated with pesticides, but also to provide more definitive evidence of exposure and even adverse effect. This controversy also served

as an impetus to conduct controlled studies, which often relied on tissue concentrations as a measurement endpoint.

Data on concentrations of organic pesticides in tissues of wildlife began to appear in the early 1950s. Analysis of liver tissue from dead and intoxicated pheasants collected at pesticide-treated orchards revealed elevated concentrations of DDT (up to 326 μg/g), while parathion was detected in only a few birds (up to 5 μg/g) (Barnett 1950). Chronic dietary DDT and parathion feeding trials in pheasants demonstrated that the kinetics of the two pesticides were quite different (Barnett 1950). Substantial quantities of DDT were detected in fat (up to 8104 μg/g) and liver (up to 94 μg/g), but usually only trace amounts of parathion were found in liver. In a songbird study evaluating DDT (applied at 3 pounds per acre), Mitchell et al. (1953) found that whole body DDT concentrations in dead nestling songbirds were variable (up to 77 μg/g) and tended to be greater in dead nestlings in the sprayed area compared to the reference site. However, the overall songbird population was not affected (Mitchell et al. 1953). During this period, aldrin, dieldrin, and heptachlor were detected in tissues of dead birds and mammals following their field application (Post 1952, Clawson and Baker 1959, Scott et al. 1959, Rosene 1965). As aptly pointed out by Keith (1996), during this era investigators documented pesticide exposure in tissues of dead birds, but were often hesitant to conclude that the cause of death was pesticide-related.

Acute and chronic exposure studies were conducted using captive game birds that described signs of intoxication, lethality, and accumulation of residues of organochlorine pesticides in tissues (Dahlen and Haugen 1954, DeWitt 1955, 1956, DeWitt et al. 1955). The hazard of toxic chemicals to wildlife was frequently investigated using a combined laboratory-field approach (viz., determining the tissue concentrations of the compound and/or metabolites present in intoxicated or dead wild animals, and then comparing those values to concentrations in experimentally dosed animals exhibiting toxicological signs or effects) (Peakall 1992, Keith 1996). This approach worked well for organochlorine contaminants that readily bioaccumulated in tissues and exerted their lethal effects through neurotoxic mechanisms. For example, dietary feeding studies with captive quail and pheasants demonstrated that the concentrations of DDT in breast muscle were related to the severity of intoxication, with 34 μg/g in adult bobwhite (*Colinus virginianus*) and 22 μg/g in adult pheasants being associated with death (DeWitt et al. 1955). Barker (1958) reported brain concentrations of DDT and DDE (dichlorodiphenyldichloroethane) in robins (*Turdus migratorius*) and other passerines that succumbed following DDT application for Dutch elm disease. Based on this field study it was concluded that "the brain, being a suspected site of action, was considered to be best as an indicator of toxicity," with greater than 60 μg/g indicative of death in robins (Barker 1958). Other investigators made similar conclusions on the toxic concentration of DDT in brain tissue (>50 μg/g) in several species of birds, and extended findings by considering the sum of metabolites (Bernard 1963, Wurster et al. 1965, Stickel et al. 1966). This approach was used for many organochlorine compounds, including chlordane, heptachlor, dieldrin, and Aroclor 1254 (DeWitt et al. 1960, Stickel et al. 1969, 1984, and reviewed by Hoffman et al. 1996, Peakall 1996, Wiemeyer 1996). To improve diagnostic capabilities for free-ranging wildlife, the effects of body condition, lipid reserves, cessation of feeding, cold, and other stressors on tissue distribution and mobilization of organochlorines were examined in both controlled exposure and field studies (Harvey 1967, Stickel et al. 1970, Van Velzen et al. 1972, Heinz and Johnson 1981).

1.4 "SILENT SPRING" AND POPULATION LEVEL EFFECTS

With the publication of Rachel Carson's *Silent Spring* (1962), issues such as adverse effects of pesticides on nontarget organisms, ecological imbalances, chemical persistence, pesticide resistance, and human safety were publicized and debated not only among scientists, but also in all sectors of society. Eventually, some pesticides and environmental issues were addressed through testimony before government entities and courtroom litigation. This environmental movement sparked new legislation (e.g., in the United States, Resource Conservation and Recovery Act in 1965, National Environmental

Policy Act in 1970, and Toxic Substances Control Act in 1976; reviewed by Fairbrother 2009) and the establishment of distinct governmental agencies to deal with environmental pollution (e.g., U.S. Environmental Protection Agency in 1970). Research programs related to pesticides and industrial chemicals expanded in North America, Europe, and elsewhere. In the United Kingdom, Monks Wood Experimental Station was established to investigate effects of chemicals on animals and their supporting habitat. Chemical screening programs were initiated to examine toxicity, repellency and potential hazard of chemicals to birds and mammals (Heath et al. 1972, Schafer et al. 1983), and long-term environmental contaminant monitoring programs were established.

Population declines observed in many species of fish-eating and raptorial birds were of great concern to biologists. Following the discovery of an increased frequency of broken peregrine falcon (*Falco peregrinus*) eggs in England, Moore and Ratcliffe (1962) and many other investigators (reviewed in Sheail 1985 and Keith 1996) detected organochlorine pesticide residues (e.g., DDE, dieldrin, and lindane) in eggs. In a classic paper, Ratcliffe (1967) reported that weights of raptor eggshells fell markedly and rapidly after DDT use was instituted, and Hickey and Anderson (1968) used correlation analysis to demonstrate that shell thickness was inversely related to the concentration of DDE in eggs. Controlled exposure studies followed that proved DDE caused eggshell thinning and impaired reproduction (Heath et al. 1969). Similar relationships have been demonstrated in a number of predatory avian species (Hickey and Anderson 1968, Blus et al. 1972, Blus 1996), although some species are considerably more sensitive (e.g., brown pelican, *Pelecanus occidentalis*) than others. Concerns over the effects of moisture loss related to incubation stage, particularly in addled eggs, resulted in the development of concentration correction factors (Stickel et al. 1973). Adverse effects of organochlorine pesticides were also described in wild mammals, most notably bats (reviewed in Clark and Shore 2001), and the first reports of organochlorine contaminants and mercury appeared in marine mammals in the 1960s (reviewed in O'Shea and Tanabe 2003). The use of tissue residues has evolved from merely explaining the cause of local wildlife die-offs to its use in the investigation of the status of wildlife populations, and in some cases the possible fate of species.

Advances in chemical analysis and instrumentation enhanced detection capabilities and revealed some unsuspected problems. In 1966, Swedish scientist Soren Jensen reported several unknown peaks in a gas chromatogram that interfered with the quantification of DDT in environmental samples (Jensen 1966). These unknown peaks were subsequently identified as PCBs, which raised the possibility that previously reported DDT and metabolite values may have been falsely elevated by these interfering peaks. It was quickly recognized that PCBs were present in biota on a global scale, with perhaps the highest concentrations in fish-eating birds (up to 14,000 μg/g) (Risebrough et al. 1968, Wasserman et al. 1979). Quantification of these complex mixtures was based in part on matching chlorinated biphenyl patterns to the commercial Aroclor formulations, classified on the percentage of chlorination of the biphenyl. In the environment, these complex mixtures changed substantially due to natural weathering and biological processes, and Aroclor pattern recognition techniques were used to quantify total PCB concentrations in free-ranging wildlife. Toxicity studies of PCBs were undertaken in birds and mammals. It was realized that poor reproduction in ranch mink (*Mustela vison*) was due to the presence of PCBs in their food source, Great Lakes coho salmon (*Oncorhynchus kistutch*) (Aulerich and Ringer 1977). In the 1970s, studies focused on commercial mixtures (e.g., Aroclor 1254, Clophen A60), and concentration thresholds associated with lethality and embryotoxicity (e.g., <10 μg/g in eggs; reviewed by Hoffman et al. 1996). Concentrations of PCBs in liver and whole bodies were found to be indicative of exposure, but of limited diagnostic value in explaining mortality events (i.e., extremely high concentrations of PCBs are necessary to evoke mortality in adult birds).

Studies in the 1960s indicating a possible link between contaminant exposure (mainly organochlorines) and reproductive dysfunction in Great Lakes colonial nesting waterbirds (Hickey et al. 1966, Keith 1966, Gilbertson 1974, 1975, Gilman et al. 1977) led to a long-term research and monitoring program (Peakall and Fox 1987) using herring gulls (*Larus argentatis*) as bioindicators.

This herring gull monitoring program still continues today as an integral part of a multifacetted bi-national program to evaluate Great Lakes ecosystem health (Shear et al. 2003).

The toxicity of metals during this era focused primarily on mercury and lead. By the late 1950s, waterfowl poisoning by ingestion of spent lead shot, and effects on populations were further characterized (Bellrose 1959). Studies with captive Canada geese (Cook and Trainer 1966) and mallards (Locke et al. 1966, Barrett and Karstad 1971) dosed with lead shot reported concentrations of lead in liver and blood, associated pathological lesions, signs of intoxication, and death. However, in a lead study by Longcore and coworkers (1974) ranges indicative of exposure were proposed (>3 μg/g wet weight in brain, 6–20 μg/g in liver or kidney, and 10 μg/g in blood), that when combined with necropsy findings (presence of lead fragments in digestive tract), case history and histopathological lesions, could be used to make a definitive diagnosis of lead poisoning. In time and with the acquisition of additional data, these ranges became a more formalized criteria, including categories of lead exposure (e.g., background), and levels of injury or effect (e.g., subclinical, clinical, and severe poisoning) (Friend 1985, Franson 1996, Pain 1996).

1.5 ADVANCES IN MEASUREMENT ENDPOINTS OF CONTAMINANT EXPOSURE

By the 1970s, restrictions were placed on the use of some organochlorine compounds, including DDT and PCBs, although to some scientists the decision on DDT was misguised (Roberts et al. 2010). Controlled exposure studies in wild birds and mammals began to focus on sublethal biochemical, physiological, and behavioral effects of organic compounds and metals.

Use of organophosphorus and carbamate pesticides for farm crops, mosquito abatement, and for control of forest insect pests (e.g., spruce budworm in Canada described as "The Thirty Years' War," Burnett 1999) increased dramatically. Although these anticholinesterase pesticides had short environmental half-lives, they were not without adverse effects to birds and other nontarget organisms (Mineau 1991, Kendall and Lacher 1994, Grue et al. 1997). Because these compounds are rapidly metabolized, laboratory studies focused on enzymatic indicators (cholinesterase and other esterases) in blood and tissues of exposed birds (Bunyan et al. 1968a, 1968b, Ludke et al. 1975). Detection of organophosphate poisoning in wildlife quickly evolved to include the combination of inhibition of cholinesterase activity in brain tissue (~50%) along with the presence of organophosphorus or carbamate parent compounds or metabolites in tissues or ingesta (Hill and Fleming 1982). Many direct poisoning cases, and intriguing incidents involving secondary poisoning, are described in the peer-reviewed literature (Henny et al. 1985, Mineau et al. 1999). Refinements over time included the development of extensive libraries of reference values for unexposed animals and cholinesterase reactivation assays (Fairbrother et al. 1991). The combination of reduced cholinesterase activity and detection of residues or metabolites in tissues for diagnosis of poisoning has remained steadfast (Hill 2003).

Although a longstanding problem, major petroleum spills resulting in large bird kills (e.g., *Torrey Canyon* in 1967, Union Oil drilling platform in 1969, *Arrow* tanker in 1970) heightened public awareness and concern. From both an historical (Phillips and Lincoln 1930) and modern day perspective, evidence of exposure of wildlife following major oil spills is usually apparent by visual inspection and petroleum odor of the integument (feathers or fur) of suspect animals. In the 1960s and 1970s, numerous controlled exposure studies were undertaken that focused on characterizing the effects of crude petroleum oil and refined petroleum products on wildlife (Holmes 1984, Jessup and Leighton 1996). Despite the development of analytical methods (e.g., Gay et al. 1980), tissue concentrations and related measures (e.g., total resolved hydrocarbons; presence of aromatic, high molecular weight hydrocarbons and odd-numbered hydrocarbons; and ratios of pristine to n-C17 and phytane to n-C18; Hall and Coon 1988) are only occasionally measured in wildlife following oil spill events. In time it became recognized that (1) the composition of crude and refined petroleum varies considerably, (2) the chemical and physical properties of petroleum change through weathering and volatilization following a spill, (3) ingested petroleum compounds

are often rapidly metabolized, and (4) there are substantial differences in toxicity following external exposure and ingestion of various crude or refined petroleum products (Jessup and Leighton 1996, Albers 2003). Accordingly, tissue concentrations of aliphatic and aromatic components of petroleum oil that are associated with adverse effects have not been developed. Instead, measurements are used to document exposure, most commonly for purposes of natural resource damage assessments following a spill event. However, confirmation of the presence of petroleum oil on the integument does not necessarily indicate that oil was the cause of death (Jessup and Leighton 1996). In the 1980s, enzyme-linked immunosorbent assays for detection of oil, and detailed fingerprinting for matching oil on exposed animals with its source were developed, and are now commonly used (Peters et al. 2005).

By the end of the 1980s, the use of lead shot for hunting waterfowl and coots was banned in the United States, and restrictions were placed on the use of lead fishing tackle in the United Kingdom due to the unintentional poisoning of mute swans (*Cygnus olor*) (Pattee and Pain 2003). Investigations on effects of heavy metals (e.g., lead, cadmium, and zinc) at industrial, mining, and hazardous waste sites examined exposure and responses at the individual and population levels of biological organization. Selenium became a significant environmental issue in the early 1980s when dramatic effects, including death and embryonic deformity of birds, were observed at the Kesterson National Wildlife Refuge in California (Ohlendorf and Hothem 1995, Ohlendorf 2003). In response to findings of selenosis and waterbird death at the Kesterson Reservoir, numerous field and feeding studies of birds were undertaken to establish toxicity thresholds. Using various statistical models (logit, probit, Weibull functions), much emphasis was placed on determining the toxicity of selenium in bird eggs. The probability of teratogenesis in black-necked stilts (*Himantopus mexicanus*) increased when selenium concentrations exceeded 37 μg/g dry weight (i.e., EC10, estimate of concentration affecting 10% of the population), while the EC10 for teratogenesis in mallards and in American avocets (*Recurvirostra americana*) was estimated to be 23 and 74 μg/g, respectively (Skorupa 1998a, 1998b). The threshold for reduced egg hatchability, a more sensitive measure of selenosis, was estimated to be 6–7 μg/g in stilt eggs, but avocets were found to be considerably more tolerant with hatchability effects at 60 μg/g. There has been considerable debate on the selenium threshold concentration for impaired hatchability in waterfowl, with an EC10 ranging from 12.5 to 16 μg/g.

The development and use of biomarkers of contaminant exposure and adverse effect expanded dramatically in the 1990s (McCarthy and Shugart 1990, Huggett et al. 1992, Peakall and Shugart 1993). The impetus was multifold. Organic contaminant and elemental analysis of tissues was, and continues to be, highly quantitative but costly and time consuming. Some biochemical measurements were amenable to rapid screening of samples, and a few were rather specific for certain contaminants and linked to the mechanism of toxicity (e.g., δ-aminolevunic acid dehydratase inhibition and protoporphyrin accumulation in blood of lead-poisoned birds and mammals). In some instances, rapid metabolism does not permit detection of parent compounds or metabolites in tissues, and thus enzymatic and other biochemical assays are utilized in place of tradition analytical methods (e.g., neurotoxic esterase activity for organophosphorus-induced delayed neuropathy caused by tri-*o*-tolyl phosphate and leptophos; Ecobichon 1996). It was quickly recognized that other biochemical measurements (e.g., changes in plasma transaminase and lactate dehydrogenase activities) were sensitive generalized responses that were precursors or indicators of cellular damage, although such measurements lack toxicant specificity. In time, other biomarkers (cytochrome P450, metallothionein, heat stress proteins, DNA damage, and measures of oxidative stress) were utilized as indicators of exposure and/or adverse effects in wildlife, and several exhibited dose-response relationships. Endpoint measurements were characterized for sensitivity, specificity, variability, clarity of interpretation, validity, and applicability to field sampling (McCarthy and Shugart 1990, Huggett et al. 1992, Peakall and Shugart 1993). Although biochemical markers are of tremendous value in ecotoxicology, only a few have gained widespread acceptance for risk assessments and natural resource damage assessments. Often these endpoints are most valuable as ancillary measures used in combination with contaminant concentration and other endpoints.

1.6 INTERPRETING EXPOSURE USING NEW MOLECULAR AND MODELING TECHNIQUES

On a grand scale, high prevalence of embryonic deformity was observed in some populations of colonial nesting fish-eating birds in the Great Lakes (Great Lakes Embryo Mortality, Edema, and Deformities Syndrome; Gilbertson et al. 1991). Such epidemic-like events and catastrophes including the Chernobyl nuclear reactor meltdown, and the Exxon Valdez and Gulf War oil spills, greatly expanded ecotoxicological research worldwide. Exposure studies with captive wild birds and mammals, in parallel with modeling efforts, were used to estimate no adverse effect level (NOAEL) and lowest observable adverse effect level (LOAEL) for PCBs in diets and drinking water (e.g., Heaton et al. 1995, U.S. EPA 1995, Forsyth 2001). Perhaps more germane to this text, the tissue concentrations of PCBs that correspond to the dietary NOAEL and LOAEL were also estimated (Heaton et al. 1995, Forsyth 2001). The realization of extreme toxicity of dioxin and dioxin-like coplanar PCB congeners in laboratory rodents (Poland and Knutson 1982), chicken eggs, and cell culture systems (Safe 1984, 1990) led to measurement (Kubiak et al. 1989) and toxicity testing (reviewed by Hoffman et al. 1996) of individual congeners in wildlife. The use of mammalian toxic equivalency factors to estimate dioxin equivalents of coplanar PCB congeners was applied to wild bird eggs. Potency estimates for dioxin-like PCB congeners (toxic equivalents, TEQs) were subsequently compiled (reviewed in Hoffman et al. 1996), and along with dioxins and dibenzofurans were eventually formalized at a World Health Organization workshop in 1997 (Van den Berg et al. 1998).

The use of nondestructive and minimally or noninvasive sampling techniques became more common in the 1990s. The rationale arose from the desire to use samples that did not entail the sacrifice of animals for ethical or scientific reasons (species status as threatened or endangered) and the sampling of animals repeatedly at a site where only a few individuals were found (Fossi and Leonzio 1994). Much of the analysis of such samples has focused on biochemical endpoints. Concentrations of organochlorine pesticides and metabolites, PCBs, and metals (lead, mercury, cadmium, and vanadium) in blood, milk, feathers, hair, and excreta are often correlated with levels found in historically used tissues (e.g., liver and kidney), and thus critical concentration values associated with harm were developed for some contaminants in these matrices (Fossi and Leonzio 1994).

Pesticide hazards to migratory species were highlighted by the death of some 20,000 Swainson's hawks (*Buteo swainsoni*) from monocrotophos poisoning during their winter migration to Argentina (Hooper et al. 2003). Monitoring and forensic studies documented anticoagulant rodenticide exposure and secondary poisoning in raptors (e.g., Stone et al. 1999, 2003), and restrictions were placed on the use of some of these compounds (US EPA 2008). Investigation of wildlife die-offs at industrial and mining sites continued (e.g., Hill and Henry 1996, Henny 2003), and in some instances metal concentration thresholds in tissues associated with toxicity were established (e.g., vanadium, Rattner et al. 2006). Studies of forest birds exposed to the organic-arsenical pesticide MSMA (monosodium methanearsonate) used for suppression of the mountain pine beetle in British Columbia revealed a significant hazard to woodpeckers (*Picoides* spp.), and findings led to the removal of MSMA from the marketplace (Morrissey et al. 2007, Albert et al. 2008). With reports of feminization of alligators (*Alligator mississippiensis*) in Lake Apopka, Florida (Guillette et al. 1994) and the publication of *Our Stolen Future* (Colborn et al. 1996), laboratory and field investigations were launched that focused on endocrine-disruptive effects of pollutants on wildlife. Despite extensive research, widespread effects of pollutants on endocrine function of free-ranging wildlife have been difficult to demonstrate; however, effects on the gonadal subsystem of wild fish seem to be pronounced (Jobling et al. 1998). Ecotoxicological research and monitoring of amphibians greatly expanded in response to worldwide declines of their populations, and the realization that some pesticides might be responsible for limb and other structural deformities (Sparling et al. 2000).

Emerging contaminant issues in the twenty-first century have included the global detection of perfluoroalkyl surfactants in wildlife (Giesy and Kannon 2001), and the dramatic increase in

concentrations of polybrominated diphenyl ether (PBDE) flame retardants in eggs and tissues of birds (Norstrom et al. 2002). The population crash of *Gyps* vultures in the Indian subcontinent resulted in a remarkable forensic investigation documenting secondary poisoning (renal failure) of vultures that fed on carcasses of cattle that had been treated with the nonsteroidal anti-inflammatory drug diclofenac (Oaks et al. 2004). Old World vultures were found to be quite sensitive to diclofenac (LD50 of 0.1 to 0.2 mg/kg body weight), with concentrations in kidney and liver of affected birds being <1 μg/g wet weight (Oaks et al. 2004, Shultz et al. 2004, Swan et al. 2006). This catastrophic event was the first time that a veterinary drug resulted in species endangerment. Notably, New World vultures do not seem to be sensitive to diclofenac (Rattner et al. 2008).

The use of stable isotopes to identify the environmental source of a metal is a recent development in the field of wildlife toxicology. In a study of California condors (*Gymnogyps californianus*), lead concentrations and stable isotope ratios demonstrated that the source of exposure was a combination of background environmental lead, and ingested spent lead ammunition that has a distinctly lower ^{207}Pb to ^{206}Pb ratio (Church et al. 2006).

New models have been developed to estimate tissue concentration and distribution of legacy and emerging contaminants in wildlife. For example, a toxicokinetic model in the developing herring gull embryo predicts lipid mass balance and distribution of PCBs between the embryo, and yolk and albumen compartment (Drouillard et al. 2003). The model predicts that greatest PCB concentrations in the embryo occur during pipping, or shortly thereafter, when yolk lipids have been completely absorbed into the embryo, which is consistent with empirical data. Retention and elimination half-lives have also been modeled for numerous PCB and PBDE congeners in juvenile and adult American kestrels (*Falco sparverius*) (Drouillard et al. 2001, 2007). A bioenergetic-based model for tree swallow (*Tachycineta bicolor*) nestlings has been used to quantitatively examine factors (weight-normalized food consumption) and processes (growth dilution) that influence PCB bioaccumulation (Nichols et al. 1995, 2004). Several kinetic models have been developed for mercury in birds, and one such model with a bioenergetics-based component has been used to predict blood mercury concentration as a function of food intake, food mercury content, body mass, and mercury absorption and elimination in common loon (*Gavia immer*) chicks (Karasov et al. 2007). Work has been initiated on physiological-based pharmacokinetic models for some chlorinated hydrocarbons, methylmercury, and anticoagulant rodenticides in wild birds. Such models permit calculation of tissue concentrations (internal dose) of contaminants for a variety of administered doses, and support interspecific extrapolations for risk assessments. Application of uncertainty factors in estimating toxicity reference values have become well-accepted, and are now used to estimate adverse effect concentrations for toxicant intake (e.g., milligrams per kilogram body weight per day), concentrations in media, and tissue-based toxicant concentrations (micrograms per day) (USACHPPM 2000). Using this approach, predicted no effect concentrations for perfluorooctane sulfonate (PFOS) in the diet (i.e., 0.013 mg PFOS/kg body weight/day) and in the liver, serum, and egg yolk (0.08 μg PFOS/g wet weight, 0.15 μg PFOS/mL, and 1 μg PFOS/mL, respectively) of a generic female top-level avian predatory species have been generated (Newsted et al. 2005). Statistical techniques are now being used to derive tissue concentrations associated with toxicological benchmarks. Buekers et al. (2009) have recently calculated the fifth percentile hazard concentration (HC5) of blood lead levels associated with a no observed effect concentration (NOEC) in bird and mammals. Theoretically, at blood lead concentrations below the HC5, 95% of all higher vertebrates will be protected. As these examples illustrate, tissue concentrations are being used to answer increasingly more complex questions. Although tissue concentrations are still used to examine the fate of a particular organism, they are also used to elucidate contaminant hazards to populations and to ecosystems.

1.7 CASE HISTORY: MERCURY IN WILD BIRDS

Mercury (Hg) exposure has long been considered a potentially serious threat to the health of both humans and wildlife. The ecotoxicological literature on Hg is substantial, having evolved over many

years, and serves to illustrate some of the problems faced by ecotoxicologists when trying to evaluate injury based on tissue contaminant concentrations. The fate of Hg in the environment is complex. For example, Hg originates from both natural sources and industrial processes; it may be released into the environment in a number of different chemical forms; it may be chemically interconverted within the abiotic environment; and it may be metabolized by microorganisms to form either methyl Hg or inorganic Hg, which differ considerably in dietary absorption, tissue distribution, and toxicity in exposed wildlife. Furthermore, the chemical forms of Hg may be changed within some organs (e.g., demethylation by liver), further complicating interpretation of wildlife tissue concentrations. The principles learned from the literature on Hg are applicable to other less well-studied environmental contaminants.

Mercury first received attention as a toxicological issue for wildlife in the 1950s and 1960s when elevated Hg concentrations and poisonings were reported in a wide variety of seed-eating birds and small mammals, and their predators. In these cases, the ultimate source of Hg exposure in small granivores was the consumption of agricultural seeds (mainly wheat, barley, and oats) coated with alkyl Hg fungicide compounds (commonly methylmercury dicyandiamide). Predators, including raptorial birds and various carnivorous mammals, were in turn poisoned after feeding on Hg-poisoned prey. Although poisoning of wildlife from this Hg source occurred in a number of different countries, the most comprehensive report of the phenomenon is probably that of Borg et al. (1969) who described the Swedish experience and concluded that the extent of Hg poisoning was great enough to have caused population reductions of some affected species. Although Borg et al. (1969) did not indicate specific threshold tissue concentrations for assessing Hg poisoning in wildlife, they were among the first to suggest that tissue-Hg (or alkyl Hg) concentrations, together with supporting evidence such as behavioral signs and/or characteristic histopathology, were the primary criteria for diagnosing Hg poisoning in wildlife.

In the 1960s, Hg poisoning of scavenging and fish-eating birds in Japan was related to the industrial release of methyl Hg, the most notable effects occurring in Minamata Bay (Doi et al. 1984). Other major point-sources of Hg to the environment during the 1960s and 1970s were effluents from pulp mills and chloralkali plants. Aquatic wildlife, especially fish-eating species, sampled from environments affected by these industrial emissions, commonly demonstrated elevated tissue-Hg concentrations (e.g., Fimreite 1974). Occasionally, overt intoxication and mortality of fish-eating wildlife (e.g., wild mink, Wobeser and Swift 1976; and wild otter, *Lutra canadensis,* Wren 1985) were attributed to Hg exposure from such sources. In addition, reproductive impairment in wild fish-eating birds was linked to elevated Hg exposure in such environments (Fimreite 1974, Barr 1986). These early studies examined mainly gross toxicological endpoints such as overt neurotoxicity, reproductive failure, and outright mortality, but sometimes also included histopathological examination for lesions at the cellular level (Tejning 1967, Borg et al. 1969, 1970, Fimreite 1971, Fimreite and Karstad 1971, Aulerich et al. 1974, Heinz 1974, Pass et al. 1975, Heinz and Locke 1976, Wobeser et al. 1976, Finley and Stendell 1978, Finley et al. 1979, Heinz 1979).

A combination of field studies of methyl Hg-exposed animals, and controlled dosing studies using captive animals, helped elucidate tissue and dietary levels of methyl Hg that were associated with overt toxicity or reproductive impairment (reviewed by Wren et al. 1986, Eisler 1987, Scheuhammer 1987, and more recent reviews by Heinz 1996, Thompson 1996, Burger and Gochfeld 1997, Wolfe et al. 1998). In these studies, it was common to measure and report only total Hg concentrations in tissues, with the implicit assumption that because exposure was known to be primarily to methyl Hg, tissue levels of total Hg and methyl Hg would be essentially identical. This assumption was probably valid for most field and lab studies conducted in the 1960s and 1970s because dietary methyl Hg exposures in these studies tended to be high, and the duration of exposure was generally fairly brief, certainly not more than a few months. However, the assumption is not valid for scenarios involving chronic, lower-level dietary methyl Hg exposure. A review of Hg concentrations in liver and kidney tissue of wildlife that died from Hg poisoning during the methyl

Hg-treated grains era, indicated that total Hg concentrations >20 μg/g wet weight represent potentially lethal exposures. But in other unrelated studies, much higher concentrations of total Hg (in some cases, several hundred μg/g) in liver of apparently healthy wild animals were reported (e.g., ringed seal, *Pusa hispida* and bearded seal, *Erignathus barbatus,* Smith and Armstrong 1975; striped dolphins, *Stenella coeruleoalba,* Itano et al. 1984; polar bears, *Ursus maritimus,* Norstrom et al. 1986). An apparently healthy wandering albatross (*Diomedea exulans*) had liver concentrations >1000 μg Hg/g dry weight (Thompson and Furness 1989). How could such dramatically elevated Hg concentrations fail to be accompanied by signs of severe toxicity? When studied further, Hg in livers of these and other species was shown to contain variable proportions of organic (methyl) and inorganic forms, with a generally decreasing organic fraction as total Hg concentrations increased. After absorption from the diet, some methyl Hg is apparently demethylated in certain tissues in response to increasing methyl Hg accumulation. Thompson and Furness (1989) demonstrated this phenomenon in a number of seabird species, suggesting that long-lived species with relatively slow molt cycles might be slow to eliminate methyl Hg through new feather growth and that, therefore, demethylation of methyl Hg might be an important additional mechanism to reduce the body burden of toxic methyl Hg. More recent studies have addressed apparent species differences in demethylation efficiency among different wild avian species (e.g., Scheuhammer et al. 2008, Eagles-Smith et al. 2009). Taken together, these studies demonstrated that Hg in liver cannot be assumed to be present primarily as methyl Hg, even though wildlife are exposed primarily to dietary methyl Hg in fish and other prey. Inorganic Hg resulting from demethylation in liver is often found in close association with selenium (Se), especially at higher Hg concentrations (e.g., Koeman et al. 1975, Thompson and Furness 1989, Dietz et al. 1990, Scheuhammer et al. 1998a). Further discussion of the biological Hg–Se relationship may be found in accompanying chapters by O'Hara et al. (Chapter 10 of this volume) and Shore et al. (Chapter 18 of this volume).

A major lesson for wildlife toxicologists from the published literature on apparent demethylation of methyl Hg and accumulation of relatively nontoxic Hg–Se complexes is that toxicological assessments should not rely solely on total Hg concentration measurements in typically analyzed tissues such as liver. This is especially true for long-lived piscivores and other aquatic predators for which years of chronic low-level dietary methyl Hg exposure may be occurring. In such cases, a high proportion of liver Hg may be present as inorganic Hg bound with Se. Scheuhammer et al. (1998a) suggested that total Hg, organic (methyl) Hg, and Se should be analyzed rather than total Hg alone, when using liver, kidney, and/or brain tissue for toxicological assessments. Wiener et al. (2003) recommended that, when only total Hg measurements were available, Hg in skeletal muscle should be analyzed in addition to liver, as almost all of the Hg in muscle remains methylated. Total Hg concentrations in liver are not by themselves sufficiently informative to make confident toxicological judgments.

By the 1980s, the use of mercurial seed dressings had been abandoned, and releases of Hg from the chloralkali and pulp industries had been eliminated or drastically curtailed. At least in North America, some other sources of previously significant environmental Hg releases (e.g., its use in gold mining) had already been phased out by the early 1900s (Eisler 2000). However, some of these older sources of environmental Hg contamination can still cause substantial exposure in wildlife today. For example, waterbirds nesting in the Carson River basin, contaminated with Hg from gold refining operations during the late 1800s, continue to be exposed to substantially elevated dietary methyl Hg concentrations that are of toxicological concern, especially with respect to egg hatchability and health of young (Henny et al. 2002, Hill et al. 2008). Similarly, predatory fish and fish-eating wildlife such as bald eagles (*Haliaeetus leucocephalus*) continue to experience elevated Hg exposure near a former Hg mine in central British Columbia, Canada (Weech et al. 2004, 2006). However, in addition to locations experiencing continued Hg contamination from past point-source emissions, a growing recognition evolved during the 1980s that environments remote from such releases could also contain fish (and consequently fish-eating wildlife) with elevated Hg concentrations. Predominant among such remote "Hg-sensitive" environments were acid-impacted lakes

(Björklund et al. 1984, Scheuhammer 1991, Spry and Wiener 1991, Scheuhammer and Blancher 1994), and reservoirs and lakes created by flooding of vegetated land where environmental Hg methylation and food chain transfer of Hg are enhanced (Bodaly et al. 1984, Johnson et al. 1991, Hall et al. 2005). Furthermore, in some very remote environments, temporal investigations indicated that Hg levels in wildlife were increasing near the end of the twentieth century (Monteiro and Furness 1997, Braune et al. 2005), whereas levels were declining in some more industrialized areas (Koster et al. 1996).

In response to the recognition of elevated Hg concentrations in food chains of certain remote ecosystems, studies of the effects of environmental Hg exposure in wildlife continued through the 1990s and beyond. A number of field studies sought to characterize exposure and effects in fish-eating wildlife in Hg-sensitive habitats, and to better understand the relation between elevated Hg in wildlife and their prey (Wren et al. 1987a, 1987b, Meyer et al. 1995, DesGranges et al. 1998, Evers et al. 1998, 2003, Scheuhammer et al. 1998b, 2001, Burgess et al. 2005, Champoux et al. 2006). In more recent toxicological studies, emphasis has been placed on clarifying the effects of environmentally realistic dietary methyl Hg exposures at the molecular (Spalding et al. 2000, Heath and Frederick 2005, Basu et al. 2005, 2006, 2007, 2009, Kenow et al. 2008, Scheuhammer et al. 2008), organismal (reproductive endpoints) (Wren et al. 1987a, 1987b, Heinz and Hoffman 1998, 2003, Dansereau et al. 1999, Albers et al. 2007), and population (Meyer et al. 1998, Moore et al. 1999, Sample and Suter 1999, Evers et al. 2005, 2008, Burgess and Meyer 2008) levels of organization in wild birds and mammals. In addition, species differences in methyl Hg toxicity *in ovo* have begun to be explicitly addressed through avian egg injection studies (Heinz et al. 2006, 2009). Contemporary reviews of the ecological impacts and toxicology of methyl Hg in wildlife have explicitly recognized that current levels of Hg exposure for some wildlife species in some environments are sufficiently high to be of toxicological concern (Wiener et al. 2003, Scheuhammer et al. 2007, Wolfe et al. 2007). In addition, tissue-Hg concentrations recognized to be harmful have gradually decreased as increasingly sensitive cellular and biochemical effects have been identified. For example, significant correlations between brain Hg concentrations and the density of some neurotransmitter receptors in mink have been observed well below the previously estimated lowest observable effect concentration (LOEC) for Hg in mink or otter brain (Scheuhammer et al. 2007). Shore et al. (2010), using species sensitivity distributions, have established egg-Hg concentrations that are protective of 95% (HC5) of avian species.

Although fish-eating wildlife generally exhibit substantially higher exposure to dietary methyl Hg than terrestrial animals, recent research has identified certain terrestrial food chains in forest habitats that appear to concentrate methyl Hg. Some forest songbird species feeding in such food chains can experience dietary methyl Hg exposure at least as high as fish-eating birds. For example, blood Hg concentrations exceeding 4 μg/mL were reported in red-eyed vireos (*Vireo olivaceus*) and Carolina wrens (*Thryothorus ludovicianus*) (Cristol et al. 2008); these levels exceed the estimated threshold for reproductive impairment in common loons (2.87 μg/mL in breeding females; Scheuhammer et al. 2007). Spiders (order Araneae), which had methyl Hg concentrations similar to fish preyed upon by belted kingfishers (*Megaceryle alcyon*), were found to be a major dietary source of methyl Hg for these terrestrial birds (Cristol et al. 2008). Additional studies are required to better understand the environmental conditions that lead to elevated methyl Hg concentrations in these terrestrial food webs, and to determine if reproductive or other impairments accompany elevated Hg exposure in the most at-risk wildlife species.

In summary, Hg in wildlife has been studied for more than 50 years, and much has been learned regarding its food chain transfer, accumulation, and toxic effects. Recent studies have begun to document subtle, yet important effects of Hg on behavior, neurochemistry, and endocrine function in wildlife at currently relevant levels of environmental exposure. Insofar as substantial global anthropogenic Hg emissions will likely continue into the foreseeable future, there will undoubtedly be a need for continued research on ecotoxicology of Hg, and a revisiting of tissue concentration effect thresholds, well into the twenty-first century.

1.8 CASE HISTORY: DIOXINS AND PCBs IN WILD BIRDS

PCBs, polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) are structurally similar, persistent, and lipophilic chemicals, which have widely contaminated environmental media, where they have the potential to cause toxicological effects in wild birds. PCBs are anthropogenic in origin and were manufactured and widely used until the latter decades of the twentieth century. PCDDs and PCDFs were produced as by-products of industrial processes and combustion, especially of plastic wastes. The chemistry, environmental fate, and toxicology of these chemicals are complex, and hence controversial.

The word "dioxin" became known to the scientific community, and eventually part of the public lexicon, as a result of the death of millions of broiler chickens during the 1950s in parts of the eastern and southwestern United States. The condition was labeled "chick edema disease" as it was characterized by excessive fluid in the pericardial sac and abdominal cavity, subcutaneous edema, liver necrosis, and death beginning at about 3 weeks of age (Friedman et al. 1959). Investigators quickly traced the source to toxic factors present in fatty acid feed supplements obtained from "fleshing greases" produced as a by-product of the hide tanning industry (Wootton and Alexander 1959). Several years of toxicological and chemical research eventually implicated the use of chlorophenolic biocides as hide preservatives, and the identification of PCDDs, particularly 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin as the main chick edema factor (Higginbotham et al. 1968, Firestone 1973). Verrett, Flick and coworkers dosed both chicks and chick embryos with individual PCDDs and PCDFs providing the first data of potential value for interpreting tissue concentrations (Verrett 1970, Flick et al. 1973).

Concerned over PCDD contaminants in chlorophenolic pesticides, some researchers began to investigate food chain contamination in areas of intensive use. During the 1960s, an estimated 400 kg of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) was sprayed by the United States military onto the forests of Indochina as a contaminant in the 20 million kg of the herbicide 2,4,5-T, a component of Agent Orange, used as a chemical warfare agent (Huff and Wassom 1974). A 1970 survey of Vietnamese rivers found that whole body samples of catfish (Siluridae), for example, from the Dong Nai River had mean 2,3,7,8-TCDD concentrations of 810 pg/g wet weight (Baughman and Meselson 1973). There appears to have been no published attempt to extrapolate that finding to wildlife; however, assuming that the reported concentrations in fish were accurate within an order of magnitude, and using the biomagnification factor from fish to fish-eating birds for 2,3,7,8-TCDD of 32 (Braune and Norstrom 1989), aquatic birds feeding in that system would have accumulated sufficient TCDD alone to cause overt toxicity, even in less sensitive species.

While a number of laboratories were investigating environmental contamination by dioxins, in 1966 during gas chromatographic analysis for DDT, Jensen identified a series of PCB compounds (Jensen 1966, Jensen et al. 1969). Risebrough and coworkers (1968) soon reported that birds from the remotest areas of the globe were contaminated by PCBs. Studies of PCB toxicity to birds, particularly chickens, soon followed (Chapter 14 of this volume, reviewed by Eisler 1986, Bosveld and Van den Berg 1994, Barron et al. 1995). Compared to many of the organochlorine insecticides in wide use at that time, acute toxicity of PCBs was low and also varied according to the degree of chlorination of the Aroclor mixture (Hill et al. 1975). In cases of experimentally caused mortality, the brain was the most reliable diagnostic tissue for determining lethal concentrations of PCBs (e.g., brain: 300–400 μg/g wet weight in pheasants, Dahlgren et al. 1972; 76–445 μg/g in fish-eating birds, Koeman et al. 1973; and 310 μg/g in passerines, Stickel et al. 1984; liver: 70–697 μg/g in Bengalese finch, *Lonchura striata*, Prestt et al. 1970). A study of lethal effects on the great cormorant (*Phalacrocorax carbo*) reported a lower brain threshold, and attempted to determine if that species was more sensitive or whether results were confounded by furan contamination from the Clophen A60 dosing mixture (Koeman et al. 1973). Mortality and residue analyses of ring-billed gulls (*Larus dalawarensis*) in the early 1970s on the Great Lakes also implicated PCBs as a possible causative factor (Sileo et al. 1977).

During the late 1960s, scientists began to assess the effects of PCB mixtures on avian reproduction, principally focusing on chickens, but also including other galliform and nongalliform species. It soon became evident that, as with dioxins, chickens were more sensitive than other tested species. Some researchers employed the egg injection technique, and findings varied according to factors such as the Aroclor mixture, injection site, and dosing vehicle. For example, 5 μg/g of Aroclor 1242 injected into chicken eggs on day zero of incubation caused a variety of malformations in embryos, and other effects in hatched chicks (Carlson and Duby 1973). Peakall and Peakall (1973) conducted a feeding study with Aroclor 1254 in the ring dove (*Streptopelia risoria*), and showed that embryonic mortality increased with egg concentrations. In subsequent experiments with artificially incubated eggs, they found that the embryonic mortality was caused by altered parental behavior, specifically reduced nest attentiveness.

By the late 1970s, surveys of PCB contamination revealed, not surprisingly, that wildlife in heavily industrialized ecosystems, such as the North American Great Lakes and the Baltic region, were particularly contaminated, and thus those regions became foci for investigating the effects of environmental contaminants on birds (Gilman et al. 1977, Falandysz 1980) (Table 1.1). As early as 1970, colonies of gulls (*Larus* spp.) and terns (*Sterna* spp.) nesting on Lakes Ontario and Michigan, were exhibiting high rates of nest failure associated with embryotoxicity and various deformities among hatched birds (Gilbertson 1974, 1975). Mean PCB concentrations (as Aroclor 1254:1260) in herring gull eggs were 142 μg/g wet weight at a colony in Lake Ontario and 92 μg/g at a Lake Michigan colony (Gilman et al. 1977). There were extensive field and laboratory investigations of the Great Lakes avifauna; however, establishing cause–effect linkages, and thus critical concentrations of specific compounds proved problematic. During the period when signs of toxicity were overt, fish-eating bird eggs contained elevated concentrations of a complex mixture of halogenated aromatic contaminants in addition to PCBs, including DDTs, mirex, hexachlorobenzene, and TCDD (Peakall and Fox 1987).

The early research and monitoring of wildlife contamination by PCBs and dioxins was hindered by limitations in analytical chemistry. PCB quantification was based on one or two peaks resolved by packed column gas chromatography (GC), ineffective at separating most individual congeners. With the introduction and widespread use of fused-silica capillary GC columns, greater resolution of compounds was possible, but identification of many peaks remained problematic. In the early 1980s, Mullin et al. (1984) reported the synthesis and relative retention times of all 209 PCB congeners, which allowed researchers to comprehensively assess the patterns of PCB congeners present in various environmental media. By comparing patterns of congener peaks among sediment, forage fish, and birds, Norstrom (1988) showed which congeners were more resistant to metabolic degradation and therefore, tended to bioaccumulate, and he suggested some general structural properties governing bioaccumulation in birds.

Given the findings of widespread embryotoxicity, including deformities, during the late 1960s and early 1970s, the presence of 2,3,7,8-TCDD in the Great Lakes food chain had been hypothesized, but could not be established with analytical methods employed at that time (Bowes et al. 1973). By the early 1980s, the availability of high resolution mass spectrometry (MS) combined with GC/MS enabled the quantification of PCDDs and PCDFs in tissue samples at <10 pg/g. A new GC/MS analytical method was developed and applied to a spatial survey of the Great Lakes, and to a temporal survey made possible by retrospective analysis of herring gull egg samples archived in the Canadian Wildlife Service National Specimen Bank (Elliott et al. 1988). The results showed that eggs from a colony in Lake Ontario contained mean concentrations of 2, 3, 7, 8-TCDD that were greater than 1000 pg/g in 1971, and which had decreased to about 100 pg/g by 1980 (Stalling et al. 1985). The GC/MS method enabled examination of PCDD and PCDF patterns in environmental media and biota, demonstrating that chlorine substitution at the 2, 3, 7, and 8 carbon positions conferred resistance to metabolic breakdown, indicating therefore that those compounds tended to bioaccumulate (Stalling et al. 1985).

TABLE 1.1
Some Representative Studies of PCBs and Dioxins in Wild Birds

Species	Location	Contaminants	Study Type	Reference
Western grebe, *Aechmophorus occidentalis*	British Columbia	PCBs, PCDDs, PCDFs, OCs	Monitoring	Elliott and Martin 1998
Black-footed albatross, *Phoebastria nigripes*	North Pacific	PCBs, OCs	Monitoring	Auman et al. 1996
Northern gannet, *Morus bassanus*	Eastern Canada	PCBs, DDE, OCs	Poor reproductive success	Elliott et al. 1988
Great cormorant, *Phalacrocorax carbo*	Netherlands, Japan	PCBs	Reports of mortality, monitoring	Koeman et al. 1973, Guruge and Tanabe 1994
Double-crested cormorant, *Phalacrocorax auritus*	Great Lakes	PCBs, OCs	Deformities, variable reproductive success	Larson et al. 1996, Powell et al. 1998, Custer et al. 1999
Black-crowned night heron, *Nycticorax nycticorax*	Eastern U.S.	PCBs, OCs, PCDDs, PCDFs	Monitoring study	Rattner et al. 1997, 2000, 2001
Great blue heron, *Ardea herodias*	British Columbia	PCDDs, PCDFs	Reproductive failure	Elliott et al. 1989, 2001a, Bellward et al. 1990
Wood duck, *Aix sponsa*	Arkansas	TCDD, TCDF	Poor reproductive success, egg injection	White and Seginak 1994, Augspurger et al. 2008
Herring gull, *Larus argentatus*	Great Lakes	PCBs, OCs	Poor reproductive success	Gilman et al. 1977
Glaucous gull, *Larus hyperboreus*	Norway	PCBs, OCs	Monitoring study	Bustnes et al. 2001
Common tern, *Sterna hirundo*	Great Lakes, Netherlands	PCBs, PCDDs, PCDFs	Deformities, poor reproductive success	Gilbertson et al. 1976, Bosveld et al. 1995
Forster's tern, *Sterna forsteri*	Great Lakes	PCBs, TCDD	Reproductive problems	Kubiak et al. 1989, Harris et al. 1993
Caspian tern, *Hydroprogne caspia*	Great Lakes	PCBs, OCs	Monitoring	Struger and Weseloh 1985
Atlantic puffin, *Fratercula arctica*	Great Britain	PCBs	Toxicological field experiment	Harris and Osborne 1981
White-tailed sea-eagle, *Haliaeetus albicilla*	Sweden	PCBs, PCDDs, PCDFs, OCs	Poor reproductive success	Helander et al. 2002
Bald eagle, *Haliaeetus leucocephalus*	United States, British Columbia	PCBs, OCs, PCDDs, PCDFs	Poor reproductive success	Wiemeyer et al. 1993, Elliott and Harris 2001
Osprey, *Pandion haliaetus*	Pacific Northwest, Wisconsin, Ontario	PCBs, PCDDs, PCDFs	Monitoring, industrial site assessment	Elliott et al. 2001a, Henny et al. 2009, Woodford et al. 1998, DeSolla and Martin 2009
American kestrel, *Falco sparverius*	Lab study	CB-126, CB-77, Aroclor mixture	Egg injection study, feeding study	Hoffman et al. 1998, Fernie et al. 2001, 2003

continued

TABLE 1.1 (continued)
Some Representative Studies of PCBs and Dioxins in Wild Birds

Species	Location	Contaminants	Study Type	Reference
Northern bobwhite, *Colinus virginianus*	Lab study	CB-126, CB-77	Egg injection study	Hoffman et al. 1998
Ring-necked pheasant, *Phasianus colchicus*	Lab study	2,3,7,8-TCDD	Feeding study, egg injection	Nosek et al. 1992, 1993
Great horned owl, *Bubo virginianus*	Kalamazoo River, Michigan	PCBs	Contaminated site assessment	Strause et al. 2007a, 2007b
Tree swallow, *Tachycineta bicolor*	New York, Massachusetts, Rhode Island	PCBs, TCDD	Contaminated site assessment	McCarty and Secord 1999a, 1999b, Custer et al. 2003, 2005
Eastern bluebird, *Sialia sialis*	Wisconsin, Michigan	TCDD	Lab study, contaminated site assessment	Thiel et al. 1988, Neigh et al. 2007
American robin, *Turdus migratorius*	Massachusetts	PCBs	Contaminated site assessment	Henning et al. 2003
Eurasian dipper, *Cinclus cinclus*	Wales	PCBs	Point source assessment	Ormerod et al. 2000
American dipper, *Cinclus mexicanus*	British Columbia coastal watershed	PCBs, OCs	Source determination	Morrissey et al. 2005
Starling, *Sturnus vulgaris*	Illinois	PCBs	Contaminated site assessment	Arenal et al. 2004

Availability of a full range of compounds for toxicity testing advanced understanding of the structure–activity relationships of the 17 various 2,3,7,8-substituted PCDDs and PCDFs and the structurally similar non-*ortho* and mono-*ortho* PCB congeners. That similarity in structure and effects furthered the theory that there was a common mechanism of action that hinged on the binding to the cytosolic aryl hydrocarbon (Ah) receptor protein, translocation into the nucleus and induction of gene transcription and corresponding proteins (Poland and Knutson 1982). Ranking of potencies for individual congeners relative to 2,3,7,8-TCCD resulted in development of the toxic equivalence factor (TEF) scheme, whereby the toxicity of complex mixtures could be estimated by multiplying each congener concentration in a given sample by its TEF and summing the results of the multiple congeners to obtain the TCDD TEQ concentration of the sample (Safe 1984, 1990). An expert panel recommended avian-specific TEFs, now in wide usage (Van den Berg et al. 1998); however, recent experiments have reported that 2,3,7,8-TCDF may be more toxic than 2,3,7,8-TCDD in some bird species, while 2,3,4,7,8-pentaCDF may be tenfold or more toxic to Japanese quail (*Coturnix japonica*), than TCDD, requiring a reassessment of avian TEFs (Cohen-Barnhouse et al. 2008).

Brunström and coworkers (Brunström 1988, 1990, Brunström and Andersson 1988, Brunström and Lund 1988) conducted a series of egg injection experiments using chickens and other avian species. Those and other studies provided avian-specific data on the relative potencies of various PCB congeners, and further demonstrated that the chicken was in a class of its own in relative sensitivity to dioxin-like compounds, while the pheasant and the turkey (*Melleagris gallopavo*) were intermediate in sensitivity, with other species such as ducks and gulls being much less sensitive. Meanwhile, Nosek et al. (1992, 1993) studied the toxicology of TCDD in more depth using the pheasant as a model species.

Congener-specific analytical techniques were employed in field and laboratory investigations of ongoing health problems including poor reproductive success of bird populations in the Great Lakes. Given the similarity between the apparent syndrome in that region and chick edema disease,

Gilbertson and coworkers (1983, 1991) developed the concept of the Great Lakes Embryo Mortality, Edema and Deformities Syndrome (GLEMEDS). By the late 1980s, the non-*ortho* PCBs were suggested as the likely causative factor, because of their wide distribution, greater environmental concentrations, and dioxin-like toxicity. Kubiak et al. (1989) investigated a Forster's tern (*Sterna forsteri*) colony in the Green Bay region of Lake Michigan that was exhibiting what was later considered GLEMEDS-type signs of toxicity. Their egg-swap studies in particular pointed toward a parental behavioral mechanism to explain lower productivity, rather than embryotoxicity. A subsequent study of those birds suggested NOAELs for PCBs and for hatching success (Harris et al. 1993). Studies of common terns (*Sterna hirundo*) in North America (e.g., Hoffman et al. 1993), and in Europe (Becker et al. 1993, Bosveld et al. 2000), reported some sublethal effects on chick growth and development, but no clear evidence of PCB effects on hatching success. Reproduction and contaminants, particularly elevated PCB concentrations were investigated by Struger and Weseloh (1985) in Great Lakes Caspian terns (*Sterna caspia*), and despite relatively high concentrations of PCBs, there were no apparent effects on productivity.

Of particular concern to many researchers were the continued reports during the early 1990s of deformed nestlings in the Great Lakes, considered by some to be a clear diagnostic of poor fitness in wildlife. Clustered incidences of bill deformities among double-crested cormorants (*Phalacrocorax auritus*) nesting at Lake Michigan colonies were regularly reported. Ludwig et al. (1996) and Giesy et al. (1994) considered that the correlative evidence was sufficient to implicate PCBs as a chemical driver of deformities in Great Lakes cormorants. It has, however, proven difficult to conclusively establish cause and effect between the observed deformities and PCB concentrations in the field, given inconsistency in laboratory results, and potential confounding factors such as disease and genetics, which are discussed more thoroughly in Chapter 14.

In the mid-1980s, eggs of aquatic birds from the Pacific coast of Canada were found with high concentrations and an unusual pattern of PCDDs and PCDFs (Elliott et al. 1989). Work with great blue herons (*Ardea herodias*) explored possible links between colony failures and increasing PCDD and PCDF contamination from forest industry sources. Throughout the 1990s, field work was conducted on a variety of potentially vulnerable species, including herons, cormorants, bald eagles, osprey (*Pandion haliaetus*), tree swallows, and various waterfowl species, which described spatial and temporal patterns in contamination, and successfully established linkages with specific forest industry sources (Elliott and Martin 1994, Elliott et al. 1996a, 2001a, Harris and Elliott 2000, Harris et al. 2003). A complementary series of laboratory studies employing artificial incubation and egg injection explored the toxicological aspects in more depth, and generated data useful for recommending criteria for interpreting tissue concentrations of PCDDs in a number of avian species (Bellward et al. 1990, Sanderson et al. 1994a, 1994b, Sanderson and Bellward 1995, Elliott et al. 1996b, 2001b, Janz and Bellward 1996). The contamination and potential effects of PCDDs and PCDFs from the pulp and paper industry were also studied in fish-eating and insectivorous birds from other locations in North America (Champoux 1996, Wayland et al. 1998, Woodford et al. 1998, Custer et al. 2002).

Given its conservation status until the mid-1990s as federally endangered in the United States and in some Canadian provinces, and its position as a top predator, the role of contaminants in the decline of the bald eagle was widely investigated. Nests in many regions of North America were visited regularly to document reproduction and to salvage unhatched eggs for contaminant analysis. Statistically significant negative associations were found between productivity and various contaminants, including PCBs, while DDE effects on shell quality was identified as the main determinant (Wiemeyer et al. 1993). In the Great Lakes region, Best et al. (2010) reported that associations continued between PCBs and productivity into at least the late 1990s. To improve the quantity of data obtained, the salvaged egg metric was enhanced by measuring contaminant burdens in blood samples from nestling bald eagles (Bowerman et al. 1995, 1998), an approach also applied in Sweden to the white-tailed sea-eagle (*Haliaeetus albicilla*). Meanwhile, improved analytical techniques also made it possible to measure PCDDs, PCDFs, and non-*ortho* PCBs in eagle nestlings (Elliott

and Norstrom 1998). Tentative critical concentrations for PCBs and DDE in nestling eagle blood samples were derived (Elliott and Norstrom 1998) based on regressions between nestling blood and egg samples, which were later modified by Elliott and Harris (2001) and Strause et al. (2007a). As exposure to legacy contaminants such as PCBs was declining in many jurisdictions during the 1990s, some researchers began to directly investigate ecological factors, particularly the relative role of food supply and weather that may interact with contaminant exposure and effects (Elliott et al. 1998, 2005, Dykstra et al. 1998, Gill and Elliott 2003, Hoff et al. 2004, Elliott et al. 2005). Similarly, Helander et al. (2002) studied the ecotoxicology of the congeneric white-tailed sea-eagle for many decades in Sweden, in the process developing critical tissue values for PCBs in eggs.

Field research on the effects of PCBs and other contaminants on productivity and other parameters of birds nesting in the Great Lakes continued through the 1990s and into the present century (e.g., Tillitt et al. 1992, Giesy et al. 1995, Fox et al. 1998, Ryckman et al. 1998, Custer et al. 1999). As with bald eagles, the role of ecological variables was increasingly factored into understanding sources and dynamics of contaminants (Hebert and Weseloh 2006), eventually incorporating tools such as stable isotopes and fatty acid profiles (Hebert et al. 2008). Drouillard and Norstrom (2000) made valuable progress in understanding the pharmokinetics of PCBs in birds, and applied those collective advances to develop a bioenergetics model for contaminant dynamics in wild birds (Norstrom et al. 2007). The ongoing concerns about contamination of birds in the Great Lakes and elsewhere, led to more comparative egg injection studies with TCDD and non-*ortho* PCBs. These studies furthered the understanding of species variation in sensitivity and provided critical egg concentrations for the double-crested cormorant (Powell et al. 1998), and common tern and American kestrel (Hoffman et al. 1998). Several investigators (Fernie et al. 2001, 2003, Fisher et al. 2001, Smits et al. 2002) carried out a feeding study of an Aroclor mixture with the American kestrel as a laboratory model of predatory and fish-eating birds, which has yielded valuable data on a wide range of reproductive and physiological endpoints.

Currently, widespread restrictions on use of PCBs and the need to regulate dioxin releases have been in place for at least 30 years. There remain, however, numerous point sources of those compounds, associated primarily with waste dumps, and soil and sediment contamination at former manufacturing and storage sites. Birds have been used to determine the exposure and evaluate impacts to wildlife in Canada (Bishop et al. 1999, Harris and Elliott 2000, Ormerod et al. 2000, Kocan et al. 2001, Kuzyk et al. 2003, Jaspers et al. 2006), and particularly in the United States, where investigations of contamination of wild birds have been conducted as part of Natural Resource Damage Assessments. Researchers and risk assessors have looked principally at fish-eating birds and raptors (Williams et al. 1995, Hart et al. 2003, Strause et al. 2007a, 2007b), and increasingly at cavity-nesting passerines (Custer et al. 1998, McCarty and Secord 1999a, 1999b, Arenal et al. 2004). Custer and colleagues (1998, 1999, 2002, 2003, 2005) in particular have made effective use of the tree swallow and provided data on various endpoints useful for determining critical tissue concentrations.

Outside of specific hotspot areas, long-term monitoring of PCBs and other contaminants in avian indicator species has continued in some regions, such as the Great Lakes (Norstrom and Hebert 2006), and other North American aquatic environments (Rattner et al. 2004, Toschik et al. 2005, Henny et al. 2009), various marine systems including the Arctic (Barrett et al. 1996, Braune and Simon 2003), the Pacific, and Atlantic coasts of Canada (Elliott et al. 1992, 2001a, Harris et al. 2003), and the Baltic (Bignert et al. 1995). The Arctic has been a focus of ongoing study as biologists from Scandinavia, Canada, and Alaska have investigated the exposure and potential effects of PCBs and other persistent organic pollutants in high trophic-level marine birds, particularly the glaucous gull (*Larus hyperboreus*), a species, which often preys on other marine birds (Henriksen et al. 1998, Sagerup et al. 2000, 2002, Bustnes et al. 2001, Verreault et al. 2006a, 2007).

Monitoring of PCBs and dioxins in wildlife has been complemented by the use of biomarkers, often measured nondestructively in blood or by bioassay methods, to assess relationships between exposure and various endpoints such as hepatic cytochrome P450-associated monooxygenase

activities (Fossi et al. 1986, Rattner et al. 1993, 1994, 1997, 2000, Sanderson et al. 1994a, 1994b, Davis et al. 1997, Custer et al. 1998, Feyk et al. 2000, Kennedy et al. 2003, Fox et al. 2007a), gene mutations (Stapleton et al. 2001), porphyrin metabolism (Fox et al. 1988, Kennedy et al. 1998), immune system responses (Grasman and Fox 2001, Grasman et al. 1996, Bustnes et al. 2004, Fox et al. 2007b), thyroid hormone levels (Smits et al. 2002, McNabb and Fox 2003, Saita et al. 2004), retinoids (Spear et al. 1990, Elliott et al. 1996b, 2001b, Kuzyk et al. 2003, Murvoll et al. 2006), sex steroids (Verreault et al. 2006b), stress hormones (Martinovic et al. 2003), disease (Hario et al. 2000), and behavior (McCarty and Secord 1999b). Further developments of analytical methodology have led to surveys of PCB and other organochlorine (OC) metabolites in wild birds and some examination of relations with biomarkers (Fangstrom et al. 2005, McKinney et al. 2006).

Most recently, advances in molecular biology have furthered understanding of the mechanisms of dioxin-like toxicity to birds and of the basis for variation in species sensitivity. The cytochrome P450 response of birds exposed to Ah receptor ligands has been shown to be unique, with birds having two distinct CYP1A isoforms (Gilday et al. 1996, Mahajan and Rifkind 1999). Kennedy et al. (1996) developed avian *in vitro* assays and showed that the magnitude of *in vitro* response to CYP1A induction may be predictive of species differences in embryotoxicity *in ovo*. Application of molecular techniques examined the interspecific variation of response to TCDD-like exposure, and showed that sensitivity is closely associated with differences in the molecular structure of the Ah receptor and to differences in preferential induction of CYP1A isoforms (Head 2006, Karchner et al. 2006, Head and Kennedy 2007, Yasui et al. 2007). Sensitivity to dioxin-like compounds among avian species varies according to amino acid differences in the Ah receptor ligand binding domain (Head et al. 2008). Consistent with previous toxicological data, chickens exhibit high sensitivity, while of particular interest some upland game birds, passerines, and an albatross exhibit moderate sensitivity. All other species tested to date, including raptors, waterbirds, and waterfowl, appear relatively insensitive to dioxin-like toxicity (Head et al. 2008).

In summary, beginning with the identification of the chick edema factor, the collaboration among biologist, chemists, and toxicologists over the past 50 years has successfully investigated many aspects of the exposure and toxicology of PCBs, PCDDs, and PCDFs in birds. Field studies have made correlative links between dioxin-like chemicals and alterations in the metabolic, endocrine, and immune functions of populations of avian top predators and aquatic insectivores. In some instances, reproductive success has been significantly affected, although it has often proved difficult to separate causal factors, including other contaminants and cumulative anthropogenic and natural stressors. The particular sensitivity of the chicken to these chemicals has now been linked to the structure of its Ah receptor. One or two changes in the amino acids of the receptor's binding domain causes greatly reduced sensitivity to dioxins. That likely explains in large part the findings that, despite widespread exposure to PCBs, dioxins, and furans at concentrations that would severely compromise reproduction of chickens, there is limited evidence of a significant impact on populations of wild birds. That contrasts to the population declines associated with DDT and dieldrin, and more recently the veterinarian pharmaceutical, diclofenac. Nevertheless, given the ongoing problems posed by numerous contaminated sites, and the global nature particularly of PCB contamination, we can expect these chemicals to remain an issue for sometime into the current century.

CONCLUSION

As pointed out in a recent review, the field of wildlife toxicology has been shaped by chemical use and misuse, ecological mishaps, and research in the allied field of human toxicology (Rattner 2009). The development and use of new chemicals, and unexpected and unpredicted contamination problems continue to drive this discipline. In some instances, environmental release of toxicants could have resulted in species extinction (e.g., bald eagle, sparrowhawk, *Accipiter nisus*, and California condor) had not regulatory and remedial actions been undertaken. Dramatic advances in analytical technology over the past 50 years now permit routine detection and measurement of minute

quantities of chemicals in a myriad of matrices. However, our greatest challenge remains the extrapolation of exposure data from laboratory and field studies to effects in diverse species and free-ranging populations, which are often subject to multiple environmental and toxicological stressors.

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