

III. CASE STUDIES

A. Persistent Organic Pollutants (POPs) in humans and wildlife

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Abstract:

Since the mid-1900s, the global environment has become increasingly contaminated by Persistent Organic Pollutants (POPs), including many with dioxin-like properties. These compounds generally have low water solubility, do not degrade readily in the environment, bioaccumulate in food chains, and have been linked to adverse health effects in both humans and wildlife. The presence of such compounds in terrestrial and aquatic food chains is relevant to those concerned with both human health and environmental protection because of the many common exposure pathways and biological effects among different species. In the past, some chemicals with health risks for humans have been identified following reports of adverse effects in wildlife. Integrating human and ecological risk assessments may improve society's ability to manage the design, manufacture, use and disposal of chemicals in a safe and efficient manner. This can be achieved by encouraging a rigorous and multidisciplinary approach to evaluating the sources, transport and fate of chemicals, and their associated health risks in all environmental compartments.

1. Background

Both humans and other organisms in the environment are exposed to Persistent Organic Pollutants (POPs), including contaminants which may have either “dioxin-like” properties (i.e. those POPs that bind to the Aryl hydrocarbon receptor (*AhR*) and initiate toxic responses; 29 of the 419 PCB, PCDD and PCDF congeners are currently considered “dioxin-like”) or “non-dioxin-like” properties (including many PCBs and organochlorine pesticides), through the dietary intake of food items. The primary sources of these contaminants to humans and top predators in the environment are foods or prey items from the freshwater and marine environment, and the terrestrial food chain. Concern about the risks that the “dioxin-like” contaminants present to humans and other high trophic level organisms has increased because of the “weight of evidence” generated through multiple scientific approaches in numerous laboratory animal, wildlife and human studies.

With a large body of multidisciplinary literature, this case study provides an opportunity to demonstrate the utility of an integrated human and ecological risk assessment process. Humans and wildlife are exposed to both the “dioxin-like” and “non-dioxin-like” POPs. We draw on evidence from studies of the transport, fate and exposure aspects of all POPs (i.e. both “dioxin-like and “non dioxin-like”), but focus on the risks associated with the “dioxin-like” compounds because of their particularly potent toxicity and our reasonable mechanistic grasp of this group of chemicals. This integration of human and ecological risk assessments may be less effective in the case of certain occupational exposures for humans, different classes of chemicals that are not generally released into the environment, or where chemicals do not bioaccumulate in the food chain. However, such is the nature of risk assessments; to quantify the relative risks presented by different chemical classes, whether these are small or large. Integrated human and ecological risk assessment represents a new direction for characterizing the risks which anthropogenic contaminants present to the environment, within which humans are an integral part.

During the last half of the 20th century, the global environment has become contaminated with a number of persistent, fat-soluble chemical contaminants, commonly referred to as the POPs. Contamination of the global environment with a complex mixture of POPs has resulted from deliberate discharges and applications, as well as from the inadvertent formation of by-products of incomplete combustion or industrial processes. Classes of these POPs include the organochlorine pesticides (e.g. DDT, chlordane, toxaphene), the polyhalogenated -biphenyls (PHBs; includes PCBs and PBBs), -dibenzo-*p*-dioxins (PHDDs; includes PCDDs), -dibenzofurans (PHDFs; includes PCDFs), and the polychlorinated naphthalenes (PCNs). Other problematic persistent chemical contaminants not included in the POP group include the organo-metallic compounds (organotins and methyl mercury). The vast number of compounds which can be detected in tissue samples from organisms inhabiting even remote parts of the world (Muir et al., 1992; Ross et al., 2000a) presents a considerable challenge to policy makers tasked with regulating industry and protecting the environment. Despite this challenge, considerable progress has been made in identifying the nature of global contamination by such compounds

and understanding some of the mechanistic aspects of toxicity associated with different compounds (see Figure 1).

Adverse health effects associated with exposure to POPs have been observed in both high trophic level wildlife and humans. The concept of a “wildlife-human connection” draws on this evidence of adverse effects in highly-exposed wildlife to predict the risk of adverse health effects in humans. While it is difficult to unequivocally establish whether these compounds are adversely affecting humans or wildlife in the environment, the accumulating “weight of evidence” strongly implicates POPs, as well as the “dioxin-like” POPs, in incidents of endocrine and immune dysfunction, reproductive impairment, developmental abnormalities, and neurological function in a host of vertebrate species.

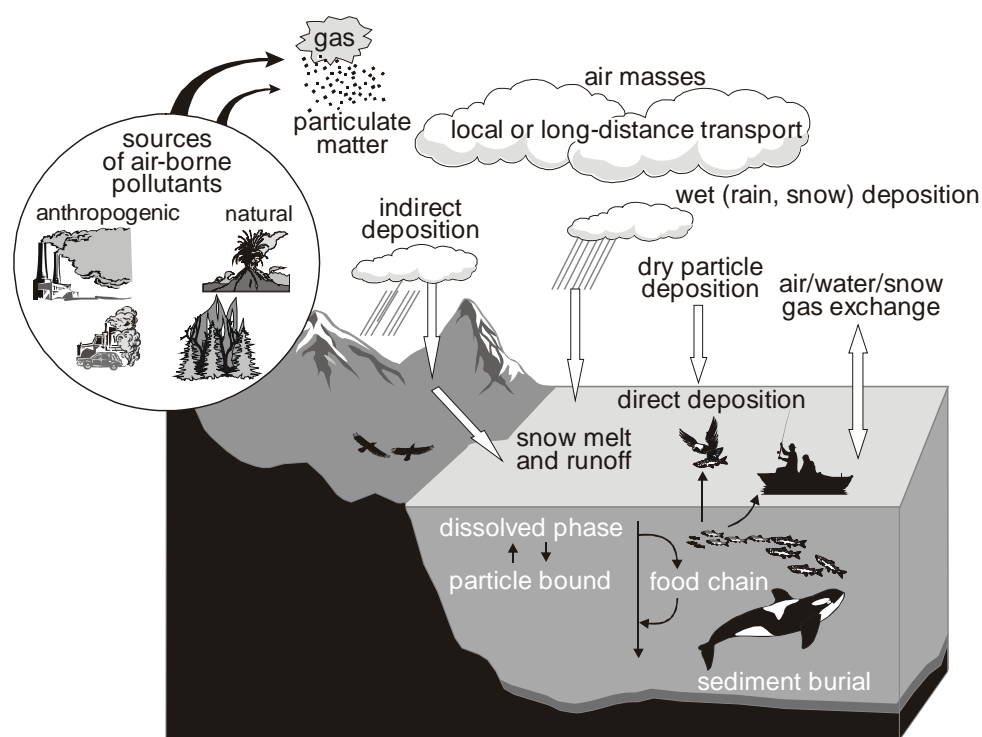


Figure 1: In addition to direct effluent discharges, Persistent Organic Pollutants (POPs) and their “dioxin-like” components are distributed globally through atmospheric processes, ensuring that even remote human and wildlife populations are exposed. While populations inhabiting industrialized regions are often considered more vulnerable to higher level exposures, subsistence-oriented aboriginal peoples in the Arctic are at risk because of their heavy reliance on aquatic food resources.

Effects observed in high-trophic level wildlife include the eggshell-thinning effects of DDT on fish-eating birds and their subsequent extirpation from large parts of the industrialized world (Hickey and Anderson, 1968; Wiemeyer and Porter, 1970); the relationship between PCBs

and developmental abnormalities in Great Lakes birds (Gilbertson et al., 1991; Tillitt et al., 1992); reproductive impairment among European seal populations (Helle et al., 1976; Reijnders, 1980); and captive feeding or free-ranging studies of birds, mink and seals in which reproductive effects, immunotoxicity and endocrine disruption have been observed (Bleavins et al., 1980; Reijnders, 1986; Brouwer et al., 1989a; Hakansson et al., 1992; De Swart et al., 1994; Ross et al., 1996a; Simms et al., 2000).

High trophic level organisms and certain human consumer groups occupy a similar niche, and are often exposed to similar types of environmental contaminants through dietary intake (see Figure 2). Certain human consumer groups, including sportsfishing families, immigrant communities, and aboriginal populations can be at increased risk because of exposure to environmental contaminants through their consumption of fish and other aquatic foods (Dewailly et al., 1989; Dewailly et al., 1994; Jacobson and Jacobson, 1996; Dewailly et al., 2000).

Evaluating the patterns, levels, trends, and effects of POPs in high trophic level consumers may therefore contribute to our understanding of both the contamination of aquatic ecosystems (freshwater and marine), and the risks posed to human health. Lessons learned from some of these more highly exposed groups of wildlife and humans are likely to be relevant to the health of the general public, where evidence is mounting that even relatively low exposures to POPs can affect human health. The use of wildlife as “sentinels” or “early warning indicators” has become an increasingly important issue in the area of human health (De Guise et al., 1995; Colborn and Smolen, 1996; Ross, 2000), although a more formally integrated human and ecological risk assessment is still lacking. Humans and wildlife share exposure to and effects of the POPs and the “dioxin-like” components of POPs, highlighting the utility of an integrated risk assessment.

2. Problem Formulation

Impetus for the assessment

Early reports of environmental contamination by POPs, high POP concentrations reported in top predators, adverse effects reported in certain wildlife (e.g. eggshell thinning following DDT exposure in fish-eating birds), adverse effects observed in laboratory animals, incidents of occupational or incidental exposures for humans (e.g. Yusho, Seveso incidents), and more recent evidence suggesting that humans are being adversely affected at low (“background”) concentrations (Koopman-Esseboom et al., 1996; Weisglas-Kuperus et al., 2000) all point to a distinct need for an integrated approach to risk assessment. Concerns about the health of high trophic level wildlife or humans represent tangible and defensible reasons for carrying out a risk assessment of these chemicals for all of these groups. Common routes of exposure and similar patterns of effects in humans and wildlife underline the benefits to combining human and ecological risk assessments for many of the POPs.

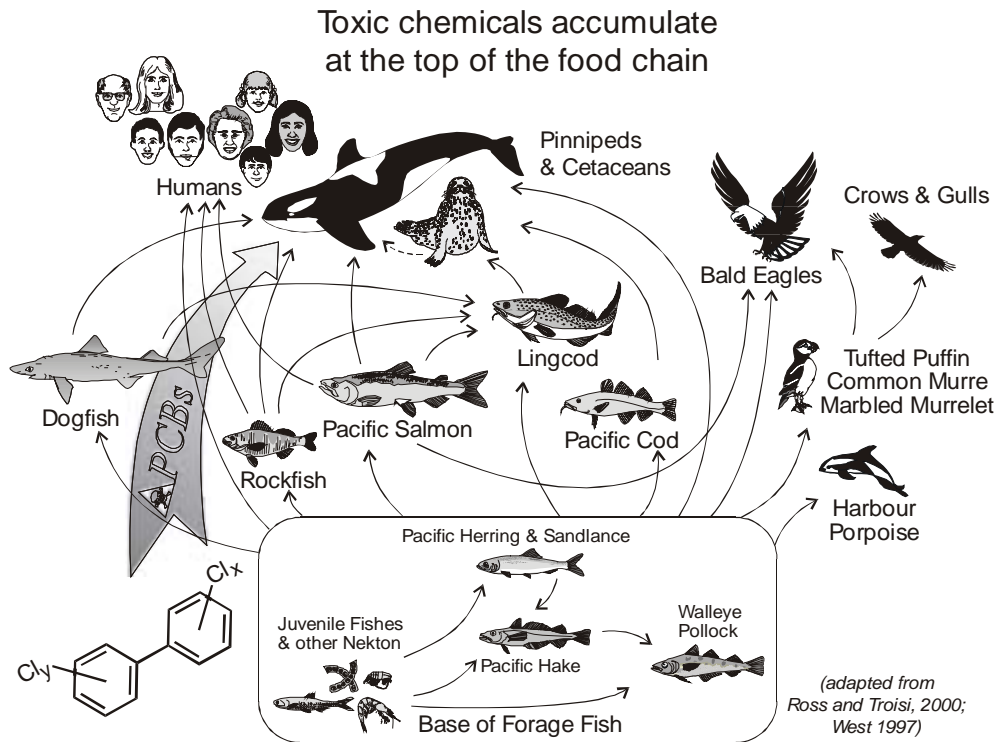


Figure 2: Aquatic food chains are vulnerable to contamination by POPs and their “dioxin-like” components as a result of the lipophilic characteristics of these chemicals and their resistance to breakdown. Organisms occupying high trophic levels are often exposed to high concentrations of such chemicals as a result of biomagnification.

Assessment questions

This case study will examine the shared exposure to complex mixtures of POPs and the common “dioxin-like” effects of POP components in both humans and wildlife by addressing:

- the nature of global environmental contamination by POPs and the “dioxin-like” components therein;
- the bioaccumulation of POPs and the “dioxin-like” compounds in aquatic food chain;
- the exposure of high trophic level wildlife and certain human consumer groups to elevated concentrations of POPs, and “dioxin-like” compounds in particular;
- the dioxin-related effects, or the risk of effects, in highly exposed human and wildlife populations or cohorts (the “human-wildlife connection”);
- the risk of adverse health effects in the general human public as a result of exposure to “background levels” of “dioxin-like” compounds;
- means of reducing environmental contamination by POPs and the risk of adverse health effects in humans and high trophic level wildlife;
- the availability of robust scientific information which is useful to managers and regulators.

Assessment endpoints

“Target” organisms can be selected on the basis of trophic level, utility or value as an ecological indicator, ease of study, and/or relevance to both human and wildlife health. Some of the better studied wildlife include the fish-eating birds and pinnipeds (seals), for which much data is available. “Endpoints” for assessment include measures of exposure (chemical contaminant patterns in predator vs prey; in different high trophic level species), as well as measures of effect (e.g. immunotoxicity, reproductive impairment), which are based on known or putative mechanisms of action (e.g. Aryl hydrocarbon receptor, *AhR*, in the case of dioxin-like compounds; see Figure 3). Identification of possible “non-dioxin” like effects (e.g. estrogen-disrupting effects via estrogen receptor or *ER*) or effects which may be due to both *AhR* mediated and “non-dioxin” like mechanisms (e.g. disruption of vitamin A and thyroid hormone physiology) should be examined in order to evaluate the relative importance of “dioxin-like” and “non-dioxin” like effects in exposed organisms.

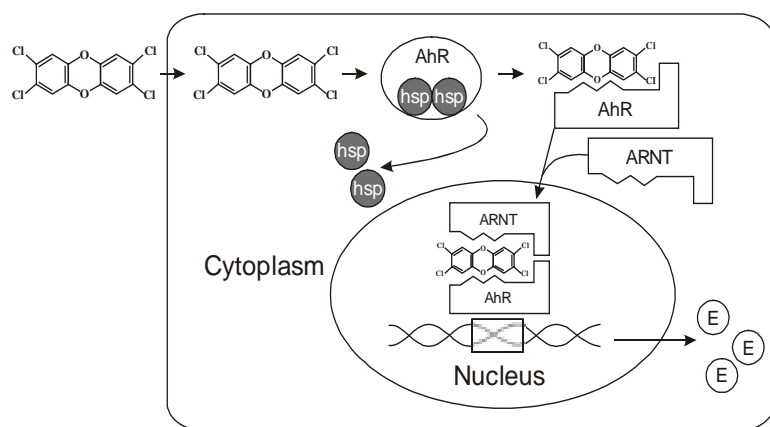


Figure 3: The Aryl hydrocarbon receptor (*AhR*) found in all vertebrates studied to date binds 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) with high affinity relative to other “dioxin-like” compounds. The binding of “dioxin-like” chemicals to the *AhR* is considered the initial step in the toxic effects observed in mammals. The potency of “dioxin-like” compounds relative to 2,3,7,8-TCDD, and the conserved nature of the *AhR* among species, provide a basis for the Toxic Equivalency Factor (TEF) approach and integrating human and ecological risk assessment. *AhR*: Aryl hydrocarbon receptor; *hsp*: heat shock protein; *ARNT*: *AhR* nuclear translocator; *E*: enzyme production.

Among the vertebrates, many physiological systems remain highly conserved, enabling extrapolation from e.g. laboratory rat to human; cormorant or seal to human; laboratory rat to seal. The conserved nature of these systems increases our level of confidence in extrapolating from one species to another, and in this case study strongly supports an integration of human and ecological risk assessment.

Conceptual models

- 1- *Global environment*: Evidence indicating the importance of atmospheric distribution and deposition of POPs into bodies of water, even at remote sites such as the Arctic, the Antarctic, and the mid Pacific Ocean, necessitates a basic understanding of POPs and “dioxin-like” compounds in the context of the global environment.

- 2- *Ecosystem approach*: An ecosystem-based approach should form the basis for the integrated risk assessment, characterizing movement, transport and fate processes, as well as compartmentalization in the environment.
- 3- *Food chain basis*: An emphasis on food chains (freshwater, marine, terrestrial) is integral to the process, since most POPs bioaccumulate in the food chain.
- 4- *Target organisms and sentinel species*: The use of wildlife as sentinels of environmental contamination and indicators of human health risks associated with low level exposure to “dioxin-like” POPs is particularly relevant. Laboratory animal studies will help document mechanisms of action under more controlled circumstances.

Analysis plan

- 1- *Transport and fate literature*: Review of transport and fate models for POPs, with an emphasis on sources, atmospheric transport, food chain biomagnification, watershed studies in freshwater systems, soil-air and sediment-water exchange (ongoing source) and air-plant and water-sediment exchange (sink).
- 2- *Toxicokinetic literature*: Review of toxicokinetic models in wildlife and humans to assess route of intake and elimination, half-life of POPs in organisms, and temporal models to characterize past and future trends in biota.
- 3- *Toxicological literature*: Literature review of toxicological information from laboratory animal studies, wildlife toxicology studies, human health studies.

2.6 Summary

Common routes of dioxin-like POP exposure and effects observed in wildlife in the environment, humans and domestic animals accidentally exposed, and the general public strongly support an integrated risk assessment approach. The conserved basis of vertebrate physiology (e.g. AhR, endocrine regulation), and common dioxin-related reproductive, immunological, and neurological effects observed, enable interspecies extrapolation and form a basis for an integrated risk assessment.

3. Characterization of Exposure

POPs and their “dioxin-like” components represent ubiquitous and often unintentional global environmental pollutants. Their introduction into the environment through various processes (leakage, discharge, combustion, incineration, agricultural application) and their physicochemical properties have led to a contamination of aquatic food chains in particular. Their presence as complex mixtures in the food of wildlife and humans (i.e. prey, cattle, fish, crops and forest ecosystems) ensures a broad exposure on a global basis.

3.1 Sources and emissions

Production: Manufacture, distribution and application (closed vs open) of industrial compounds; formation of unintentional by-products through low temperature combustion and

herbicide production; use of elemental chlorine in bleaching process used by pulp and paper mills; natural sources (e.g. forest fires, volcanoes); and continued cycling of persistent chemicals in the environment.

Formulation: Different products and product formulations (e.g. for PCBs: *Aroclor*[®] 1242, 1254, 1260 in North America; *Clophen*[®] in Europe; *Sovol*[®] in Russia where production capacity only recently ceased). Pattern changes in the environment as a function of intra-compound (i.e. congener-specific) differences in chemical characteristics, abiotic or biotic degradation, and metabolic elimination by different organisms in the food chain.

Use: Estimates of quantities produced intentionally or unintentionally, and released into the environment should be itemized. Point sources vs diffuse sources should be evaluated in the context of a mass-balance approach to environmental distribution.

3.2 Distribution pathways

Documenting the initial production and formulation, distribution, use and disposal of deliberately manufactured POPs is an important prerequisite to understanding sources, pathways and fate in the environment. The subsequent importance of soils and sediments as ongoing sources (former agricultural application areas; contaminated landfill, industrial and harbour sites) reflect the persistence of many contaminants (Hermanson and Hites, 1989; Jantunen et al., 2000). Exchange among different environmental compartments on regional and global scales represents a critical component of characterizing the cycling of POPs once released into the environment (Hornbuckle et al., 1994; Swackhamer et al., 1998; Macdonald et al., 2000). Additionally, understanding the processes, both natural and anthropogenic, which produce some of the other POPs (e.g. dioxins and furans), produces a foundation for understanding how these chemicals may enter the natural environment. Such information, when coupled with the chemical characteristics of the POPs in question, and the nature of environmental processes affecting their movement, provide the baseline needed for risk assessment purposes. Given the “ubiquitous” distribution of many POPs, this work on distribution pathways is clearly relevant to both humans and wildlife.

3.3 Transport and fate models

- 1- *Global distribution*: Atmospheric distribution is known to be an important part of the distribution of POPs in the global environment. Global models have been developed to describe the influence of the physicochemical characteristics of POPs in their atmospheric distribution to remote, colder polar regions of the world (Wania and Mackay, 1995; Wania and Mackay, 2001). Transport and fate models used may include formalized approaches such as the Quantitative Water Air Sediment Interaction (QWASI) fugacity model developed for Lake Ontario (Mackay, 1989) and mass-balance studies of certain basins and watersheds (e.g. Great Lakes) (Eisenreich et al., 1981; Hornbuckle et al., 1994; Hoff et al., 1996). System-wide reviews of data have provided detailed overviews of contamination of the

Arctic. These include both abiotic as well as food chain-based assessments (Muir et al., 1992; Muir et al., 1999), and transect-based studies of contaminants in marine waters and air samples (Iwata et al., 1993), and comprehensive international assessments (CACAR, 1997; AMAP, 1998).

- 2- *Environmental compartmentalization*: Predictive estimates for biomagnification in the food chain may be generated from the physico-chemical characteristics of different compounds, such as the octanol-water coefficient (K_{ow}) (Shaw and Connell, 1984; Oliver and Niimi, 1988; Hawker and Connell, 1988). For example, “dioxin-like” PCBs with a log K_{ow} of >4.0 are particularly bioaccumulative and largely persistent in food chains.
- 3- *Metabolic degradation*: The metabolic capacity of organisms to selectively attack certain compounds, leading to either detoxification and elimination or to the formation of toxic metabolites must be assessed. This has been carefully examined in the case of PCBs, where congeners with adjacent unsubstituted pairs of C positions on the phenyl rings are more prone to metabolic attack and removal through the production of soluble metabolites (e.g. hydroxy-PCBs) (Boon et al., 1997). The relative ability of organisms (e.g. marine mammals) to remove certain types of PCBs may allow for a degree of risk assessment by characterizing the persistent vs the less persistent compounds, as well as the inferred induction of detoxifying enzymes in the liver (Boon et al., 1994; Kannan et al., 1995). Conversely, the formation of hydroxy-PCB and other POP metabolites (“reactive intermediates”) following enzymatic processes in mammals, may play an important role in the disruption of certain endocrine processes (Brouwer et al., 1998; Sandau et al., 2000). Documenting pattern changes as a consequence of these metabolic processes at each level of the food chain represents an important element in characterizing the exposure of humans and wildlife as it relates to transport and fate.
- 4- *Degradation processes*: Both abiotic and biological processes have been identified that can lead to the slow degradation of POPs and “dioxin-like” compounds (Abramowicz, 1995), although considerable variation exists between different chemicals and under different conditions. Sedimentation represents a mechanism by which the biological availability of contaminants in food chains may be reduced (i.e. sediments as a “sink”), even though little or no degradation may take place. Despite such processes, the persistence of many of the POPs and “dioxin-like” components in the environment remains a characteristic of these chemical classes, and represents a reason for an integrated risk assessment.

3.4 External and internal exposure models

Integrated human and ecological risk assessment must be sufficiently flexible to be applicable to a wide range of circumstances and target species. Using external and internal exposure models from better understood species may be the most effective approach in many cases, but attention should be given to the ecological circumstances for the species or case in question. Position in the food chain, feeding habits, migratory routes, metabolic considerations,

phylogenetic relationships and life histories are but some of considerations which may affect exposure models (Hickie et al., 1999). In the case of POPs, high trophic level organisms are vulnerable to accumulating high concentrations of POPs, but considerable variation exists among species. For example, cetaceans appear to be able to metabolically eliminate many dioxin-like PCBs, PCDDs and PCDFs, but are prone to accumulating the non-dioxin-like (or “globular”) PCBs (Tanabe et al., 1988; Kannan et al., 1989).

3.5 Measures of exposure-related parameters

Environmental transport and fate models are relevant to both humans and wildlife, although dietary exposure will vary as a function of diet (i.e. position in the food chain, species consumed, quantities consumed). Measures of exposure are routinely documented for contaminant concentrations in study subjects (human or wildlife): 1) tissue concentrations, measured on a lipid weight basis, provides a means of evaluating both a measure of accumulated exposure that can be related to effects or risk of effects; 2) tissue concentrations, measured on a wet weight basis, provide a means of assessing intakes by predators or humans (i.e. when contaminant concentrations are measured in prey or foodstuffs consumed), but also provide a basis of estimating body burden (when contaminants are measured in any organism); and 3) daily intake (e.g. ng/kg body weight/day). The first two measures are taken routinely in studies of both humans and wildlife, while the third requires detailed knowledge of dietary intakes, something that is often lacking for wildlife. Toxicokinetic models allow the body burden and daily intake to be interconverted. Expressing contaminant data in terms of body burden or tissue concentration is advantageous because these measures incorporate toxicokinetic considerations and therefore allow interspecies comparisons.

3.6 Analytical tools

Chemical contaminant analysis will be dependent on a dedicated chemical analysis laboratory, preferably with high resolution mass spectrometry capabilities sufficient to generate congener-specific data for “dioxin-like” PCBs, PCDDs and PCDFs. Aroclor-based estimates of total PCBs and low-resolution congener-specific approaches to PCB analysis will provide only a limited capacity to evaluate pattern changes through the food chain, metabolic removal, biomagnification, and the risks associated with different types of contaminants. In addition, such methods will be unable to distinguish between “dioxin-like” and “non dioxin-like” components of these chemicals. Interlaboratory calibration exercises are carried out routinely, and certified reference materials are used.

Since “dioxin-like” chemicals have been identified, in part, by their ability to bind to a common receptor protein found in many vertebrates (i.e. the *AhR*), bioassays using this receptor offer an alternative means of quantifying “dioxin-like” contaminants in environmental samples which have toxicological relevance. Existing assays include the Chemical-activated luciferase gene expression (CALUX) assay for total TEQ (Murk et al., 1996) and the H4IIE assay (Kennedy et al., 1992). Such mechanistically-based assays provide a cost-effective and

integrated screen for determining contaminant concentrations, which can be followed by more costly and comprehensive chemical analyses. Additional, rapid screening techniques including immunoassays and chemical screens are under development.

3.7 Summary

The global distribution of “dioxin-like” POPs, coupled with their persistence in the environment and in biota, highlight the need for integration of human and ecological risk assessments. Exposure of both humans and wildlife through the consumption of contaminated foods represents a shared feature within an integrated risk assessment. Chemically- and biologically-based analytical and toxicological methods exist which can be applied equally to studies of both humans and wildlife.

4. Characterization of Effects

4.1 Reported effects and modes of action

Many of the effects of the toxic POPs were first identified in fish-eating wildlife, but precise mechanisms of action and chemicals involved were subsequently elucidated in carefully-controlled experimental designs in laboratory animals. *In vitro* and *in vivo* (Silkworth et al., 1986) receptor-based assays have strengthened the understanding of mechanism of action of POPs including the dioxin-like compounds.

The Toxic Equivalency Factor (TEF) approach allows a “ranking” of the toxic risks of the PCBs, PCDDs and PCDFs, as well as the different congeners within each group, relative to 2,3,7,8-TCDD (Safe, 1992; Birnbaum, 1999). Using internationally-derived TEFs (Van den Berg et al., 1998), coupled with information from mechanistic laboratory animal experiments (Vos et al., 1978; Ross et al., 1997), Ross et al. (Ross et al., 1995) ascribed the immunotoxicity observed in captive harbour seals fed Baltic Sea herring to the “dioxin-like” effects of PCBs. Evidence is accumulating that implicates PCBs and dioxin-like TEQs in neurotoxic and developmental effects in human infants exposed through mother’s milk (Koopman-Esseboom et al., 1994; Seegal, 1996; Schantz et al., 1996; Patandin et al., 1999). An assessment of the relative risks presented by the different classes of chemicals is not always easy, but the TEF approach allows us to deal with one important toxic subset within a complex mixture and help to simplify the ranking of chemicals of concern.

4.2 Biomarkers and indicators

Common mechanisms of action identified across taxa for “dioxin-like” toxicities have led to the development of biomarkers of exposure and effect in both humans and wildlife. Several biomarkers have been used routinely for the dioxin-like contaminants, largely based on their affinity for the AhR and consequent induction of the cytochrome P4501A enzyme system. While study animals have often been sacrificed in order to collect the liver samples necessary for such

studies, liver biopsies taken under general anesthesia, and skin and blood samples, have been used successfully as a minimally-invasive means of obtaining reliable dioxin-related enzyme induction information from certain mammalian species (Fossi, 1994; Bandiera et al., 1997). Results from biomarker studies of fish, birds and amphibians also provide information on the effects of dioxin-like POPs (Kennedy et al., 1992; Hahn and Stegeman, 1994; Stegeman and Livingstone, 1998).

The immune system is an organ system that is particularly vulnerable to “dioxin-like” toxicity, with observations of thymus atrophy and reduced T-lymphocyte function representing patterns of effects considered “typical” of dioxin exposure at low levels in both laboratory animals and wildlife (Vos et al., 1978; Grasman et al., 1996; Ross et al., 1996b). However, while the immune system represents a sensitive target for many POPs, no biomarkers exist for assessing immune function. This necessitates a more applied research strategy which incorporates the “relative” functionality of many immunological endpoints.

Another strategy has been to assess non-immunological biomarkers to shed light on toxic injury to an organism and provide a measure against which immunological insults can be compared. Biomarkers have been used in wildlife studies where the mechanistic link to particular classes of chemicals within the complex mixture are less certain. For example, the disruption of vitamin A physiology observed in seals and fish-eating birds can be due to both “dioxin-like” and “non-dioxin-like” effects as a result of exposure to PCBs, PCDDs and PCDFs (Brouwer et al., 1986; Brouwer et al., 1989b; Simms and Ross, 2001). Concurrent alterations in vitamin A and immune function endpoints have been noted in studies of wildlife exposed to POPs (De Swart et al., 1994).

4.3 Exposure-response modelling

All humans and wildlife are exposed to complex dietary mixtures of POPs and related contaminants. However, certain groups (species, populations, cohorts or age groups) may be more exposed than others, enabling an assessment of adverse health effects based on differential exposures. Such approaches have been used in assessing the effects of POPs in human cohorts (e.g. nursing infants, subsistence-oriented humans) (Dewailly et al., 2000; Weisglas-Kuperus et al., 2000). In addition, semi-field studies in which two groups of animals are fed different diets have provided useful information on the effects of complex mixtures (e.g. (De Swart et al., 1994; De Swart et al., 1996; Ross et al., 1996a)).

4.4 Extrapolations

Studies carried out to date suggest that many aspects of physiology are conserved among species, providing a basis for inter-species extrapolations. For example, the AhR has been identified in numerous organisms including fish, amphibians, reptiles, birds and mammals (Hahn, 1998). As a consequence, the risk of dioxin-associated toxicity to different species may be estimated, and AhR-mediated effects observed in one species can form a basis for assessing

risk in other species where constraints would otherwise preclude assessment (e.g. humans, endangered Monk seals, or large whales). Extrapolation from studies of highly exposed human groups (occupational or subsistence groups) to the general public will provide a link vital to this risk assessment. However, caution is required when extrapolating: although different species often exhibit similar patterns of effects (i.e. mechanisms of action) as a result of the conserved nature of many physiological systems, inter-species differences in sensitivities do exist.

4.5 Direct and indirect effects

Dioxin-like chemicals are well known to bind with high, but varying, affinities to the AhR in vertebrates, which in turn, triggers a cascade of enzyme induction responses, immunotoxicity, oxidative stress, cytokine production, hormonal and growth factor perturbations and a number of other less well documented effects (Birnbaum, 1994). Indirect toxic effects may include the formation of reactive, water-soluble intermediates from the more metabolizable compounds following metabolic attack by the mixed function oxidase system (e.g. CYP P4501A). A significant challenge to scientists and risk assessors is to delineate mechanistic, cause-and-effect relationships in humans and wildlife, something that will require data support from carefully controlled laboratory experiments using laboratory animals (*in vivo*) and/or bioassays (*in vitro*).

Additional indirect effects of contamination of organisms in the environment may arise in certain cases. For example, even though crabs exposed to pulp mill-associated dioxins and furans may not suffer from toxic effects, a resulting fishery closure could have negative socio-economic effects for dependent human fishers and communities.

Acute human exposures are infrequent and often poorly documented, but several incidences of poisoning have occurred after accidental mixing of PCB/PCDD/PCDF and edible oil products or animal feeds. Symptoms have included weight loss, chloracne and immunotoxicity (Nakanishi et al., 1985; Takayama et al., 1991). Altered sex ratio in offspring has also been documented (Mocarelli et al., 1996). Chronic exposure to low or moderate levels represents a more insidious health risk to high trophic level organisms and humans, principally because of the persistence and ubiquity of POPs in the global environment.

4.6 Summary

The common mechanism of action of “dioxin-like” compounds (i.e. via the AhR) leads to a similar hazard identification process across vertebrate species. The development of the Toxic Equivalency Factor (TEF) approach has demonstrated the utility of an integrated approach to evaluating the potential effects of particular “dioxin-like” compounds in complex mixtures on both humans and wildlife.

5. Risk Characterization

5.1 Combining exposure and effects

In humans, the World Health Organization (WHO) has set a Tolerable Daily Intake (TDI) of 1-4 pg TEQ/kg/day based on knowledge gained largely from laboratory animal studies and epidemiological investigations. Much work remains to be done on the links between exposure, burden and effects, although laboratory animal models (e.g. rodents, cows, fish, non-human primates, and birds) provide a basis for a mechanistic understanding in this area. Such work clearly requires a critical and multidisciplinary approach to evaluation, extrapolation and

understanding mechanism of action in a dose-dependent manner. Human risk assessments typically consider “adjustment factors” to allow for i) differences in sensitivity among humans (i.e. some humans are more sensitive than others); ii) variability among species (i.e. humans are “more sensitive” than laboratory animals); and iii) differences between acute and chronic exposures (effects may be more pronounced in a chronic exposure regime). In this manner, data from laboratory animal-based studies and/or human studies may be combined in order to describe “risk” even in the absence of direct evidence in humans.

In the case of wildlife, both “real world” and captive dosing studies have enabled scientists to document the adverse effects of POPs, although ethical and logistical constraints are increasingly requiring studies to be non-invasive. Exposure regimes for wildlife studies can be divided as follows: i) captive experiments relating dose-related single chemicals exposures to effects; ii) captive experiments with realistic dietary exposures (i.e. fish from areas of differing degrees of contamination fed to top predator) vs effects; and iii) studies of free-ranging wildlife that are exposed to varying degrees of contamination vs effects.

5.2 Determining causation

A mechanistic understanding of contaminant exposure and toxic effect is lacking for many species. In some cases, this is due to the challenges associated with working with a particular species. In other cases, the complexity of the mixtures of POPs and other chemical stressors to which humans and wildlife are exposed renders it virtually impossible to tease out a particular chemical responsible for an effect. Most research which has identified chemicals of concern, and the nature of their toxicity, has relied upon laboratory animals, including rodents. A reliance on the conserved nature of many organ, endocrine and immune systems, as well as certain processes (e.g. reproduction, circulation and development), provides a basis for comparison between laboratory (surrogate) study animal and the organism in question. Establishing a mechanistic basis for a particular chemical and its related toxic effects in a laboratory setting provides an initial a foundation for extrapolation and interpretation when working with humans or wildlife that are either difficult to work with or are exposed to complex POP mixtures.

5.3 Combining lines of evidence

Inherent technical, logistical, ethical and legal challenges associated with carrying out conclusive or mechanistic research in certain species (including humans, cetaceans and endangered wildlife) underscore the need to combine lines of evidence. These difficulties may include: non-availability of specialized reagents needed for clinical or toxicological research (e.g. cell surface markers for immunology) for all species; size of the species in question (e.g. many whale species); working with human subjects, where considerable constraints exist in carrying out research; and working with endangered species, where legal statutes limit any form of invasive sampling and access to populations. Both human and wildlife toxicology groups partially overcome such obstacles by relying on laboratory animal models and in vitro assays. Ultimately, a combination of lines of evidence best serves the managers responsible for implementing regulations (Ross et al., 2000b).

5.4 Uncertainty

While mechanism of action may be highly conserved among species, differences in sensitivity for various responses can exist, necessitating a critical examination of assumptions, observed or predicted effects, exposure and metabolic variables, and biological or ecological differences. “Biomarkers” of exposure and effect have been useful in identifying toxic effects in different organisms. For example, circulating thyroid hormone levels have been found to be affected by exposure to PCBs in laboratory animals, seals and nursing human infants (Koopman-Esseboom et al., 1994; Brouwer et al., 1998), providing a means for interspecies comparison of adverse effects. In such instances, the “risk” of other undocumented toxic effects may be predicted with greater confidence than had the risk assessment been based solely on “exposure” variables (e.g. concentrations of POPs in diet; intake rates).

5.5 Presentation of results

A central context for an integrated human and ecological risk assessment will be a “weight of evidence” approach which allows for data, or summaries of data, to be incorporated from studies of different species, under varying degrees of control. A number of examples can be used for “dioxin-like” compounds. For examples, a “weight of evidence” model designed for use in marine mammals (Ross, 2000) could be adapted for use in an integrated human and ecological risk assessment (see Figure 4).

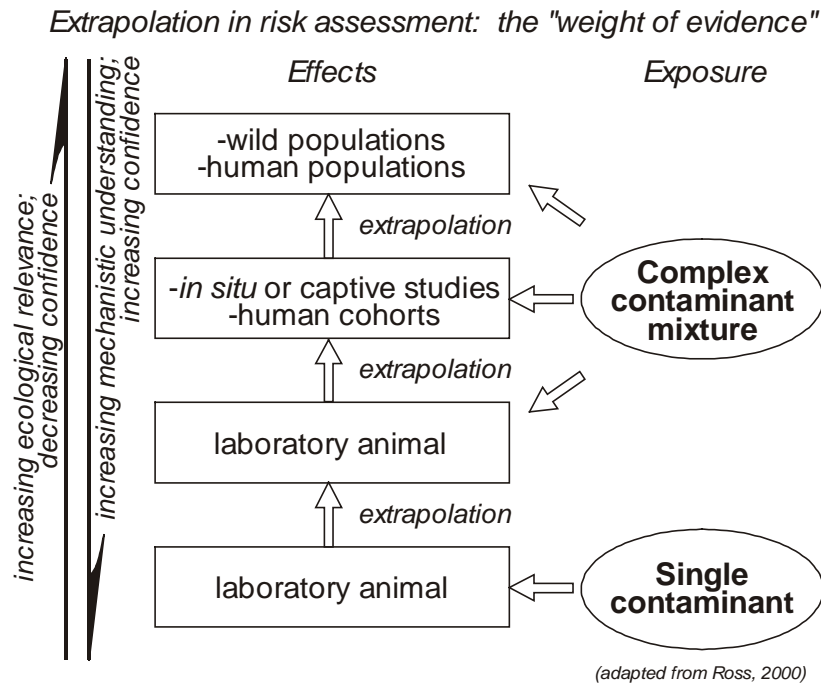


Figure 4: Given the challenges inherent in establishing cause-and-effect in humans or specific wildlife species exposed to complex mixtures of “dioxin-like” compounds, a “weight of evidence” gathered from different experimental approaches would be beneficial to an integrated risk assessment model. Contributing to this scheme are the extensive *in vitro* and molecular studies which provide further insight into the mechanism of action of POPs and additional means of assessing inter-species differences in sensitivity (Jensen and Hahn, 2001; Kim and Hahn, 2001).

5.6 Summary

A major advantage of an integrated approach to risk assessment is the ability to gain mechanistic understanding that provides a link between exposure and effect based on multiple lines of evidence. In the case of human health, it is difficult to directly demonstrate a conclusive link between exposure and effect. In this case, knowledge gained from laboratory animal and wildlife studies, and epidemiological investigations, has led to the concept of tolerable daily intake as one measure of characterizing risks associated with exposure.

6. Risk Management and Stakeholder Participation

A comprehensive evaluation of contaminant levels in different parts of the marine food chain, with an emphasis on the high trophic level consumers, provides a mechanism for education and outreach that should be easily recognizable by the public: many humans share the top of the food chain with fish-eating marine mammals, and can therefore be exposed to relatively high levels of persistent and fat-soluble toxic chemicals.

6.1 Summary

There is a need for commonality when describing human health and ecological risks in an integrated manner. The common routes of contaminant exposure and shared effects in humans and wildlife provide a background for communicating these issues to the public and to managers.

7. Risk Communication

Several aspects of risk management bear mention, including the management of chemical production, transport, application and disposal; remediation efforts related to cleaning up sites of contamination (old disposal sites, industrial areas, sediments); and human behaviour where food selection can influence the degree to which consumers are exposed to “dioxin-like” compounds and other POPs.

Given the persistence and global distribution of such chemicals, though, it is inevitable that exposure of humans and wildlife will continue for some time. In the interim, risk reduction strategies could be developed which involve education, consumption guidelines, and community outreach programmes, each of which incorporate the concepts of stakeholder groups, socio-cultural values, and conservation strategies. For example, the Inuit from the Canadian Arctic are exposed to high levels of “dioxin-like” POPs through the consumption of “country foods”, exceeding the ADI by up to ten times (Kuhnlein et al., 1995). These foods are an important part of their cultural heritage, so that encouraging a switch to non-traditional “western” foods may be counter-productive. However, the elimination of beluga whale skin and blubber alone was estimated to reduce dietary exposure by approximately 50% because of the high degree of contamination of these particular lipid-rich products (Dewailly et al., 1996). While changing the subsistence-orientation of such peoples may have undesirable socio-cultural effects, such findings emphasize the need for continued regulatory vigilance on a global scale.

Other human groups that consume fish have been targetted for risk communication. While consumption advisories for fish from the heavily industrialized Great Lakes region of North America are common, an advisory exists even at the remote Lake Laberge in the Yukon Territory in northern Canada. High POP concentrations in fish there appear to be due to an influx of atmospheric pollutants and altered trophodynamic structure (AMAP, 1998).

While subsistence-oriented humans and fish-eating wildlife are particularly prone to accumulating high levels of these contaminants, certain lifestages are more vulnerable than others (Birnbaum, 1994; Birnbaum, 1995). Nursing infants, for example, have been found to be exposed to high levels of contaminants through mother’s milk, coinciding with a sensitive time for growth and development (Dewailly et al., 1993a; Dewailly et al., 1993b; Koopman-Esseboom et al., 1994). The same has been observed in high trophic level wildlife (Addison and Brodie, 1987; Gilbertson et al., 1991; Fry, 1995; Nisbet et al., 1996; Simms et al., 2000). Particular care to reduce animal fat consumption by females from birth to post-reproductive age represents one important element of risk management in the case of humans.

Options to reduce the risk of exposure to “dioxin-like” compounds by humans and wildlife include the destruction of existing stockpiles of PCBs and related compounds (e.g. >800°C incineration); changes to the manufacturing and combustion processes that lead to the formation of such compounds (e.g. dioxins and furans as by-products of pesticide and herbicide manufacture, as by-products of the pulp bleaching process, or as by-products of low temperature combustion); and the remediation of contaminated sites. Given the extent that atmospheric processes result in the global distribution of POPs, coordinated efforts among industrialized and developing nations would be beneficial (e.g. UNEP Convention on elimination of 12 priority POPs; UN-Economic Commission for Europe work toward remediation of contaminated sites). The design and manufacture of new chemicals could also be carried out in such a manner so as to avoid the creation of new chemicals with “dioxin-like” properties (e.g. persistent; fat-soluble; endocrine modulators; *AhR* active).

7.1 Summary

The persistence, and in some cases continued production (deliberate or inadvertent), of “dioxin-like” compounds, coupled with their risk to both humans and biota, necessitate an integrated approach to managing aspects of POP production, waste, remediation and exposure. Both humans and wildlife are exposed to complex mixtures of POPs and their “dioxin-like” components, and continued international regulatory diligence is required for effective multispecies risk management. While fisheries closures and consumption advisories can be implemented by health authorities in certain cases, risk communication with stakeholders represents an important challenge.

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