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The Impact of Endocrine Disrupting Chemicals on Wildlife

A Review of the Literature 1985-1998

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PREFACE

This project analyzes the literature on endocrine disrupting chemicals and the published evidence that endocrine disruptors may impact wildlife in the field. Information contained in this report will not only be useful to the policy making and scientific communities, it may also be used to develop a more informed perspective by the Office of Science and Technology Policy, with respect to the following activities:

a) defining parameters for including wildlife studies when updating and expanding the existing inventory of federally funded research on endocrine disruptors;
b) further developing a national strategy for research on endocrine disrupting chemicals and wildlife populations; and
c) providing input to the international scientific community regarding what is known about the impact of endocrine disrupting chemicals on wildlife.

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SUMMARY

Endocrine disrupting chemicals have been implicated as the cause of many adverse outcomes in wildlife populations, including changes in the growth, development, reproduction or survival of a variety of species. However, few wildlife studies have actually demonstrated such adverse effects under field conditions. Over one hundred chemicals have been identified as endocrine disruptors to date, but consensus on the exact list of potential disruptors does not exist. Consistent guidelines for assessing the potential impacts these chemicals may have on wildlife are also lacking.

To address the question of whether these chemicals are adversely affecting wildlife populations, a focused review of the wildlife literature for the period between 1985 to 1998 was undertaken. A total of 83 review articles and primary studies were evaluated and information about selected study parameters was entered into an on-line database developed for this project.

Study factors evaluated included: the taxa and species affected, the adverse health outcomes noted, the geographic regions in which they were found, and the specific endocrine disruptors of concern. Chemical concentrations in the ambient environment, as well as body burden levels, were noted where available, in order to document levels associated with effects on wildlife.

Next, a set of policy questions of interest to OSTP was evaluated. The results of this research are highlighted below.

First, it was found that much of the literature reviewed on the environmental effects of endocrine disruptors focused on studies pertaining to birds and study sites that were primarily aquatic in nature (primarily the Great Lakes region). The chemicals most commonly noted as exerting an endocrine disrupting effect on wildlife include metals and organochlorines. However, based on the *a priori* literature selection criteria developed for this project, it is not possible to draw conclusions about whether these are the taxa most seriously affected, and the chemicals of greatest toxicity, or whether they are just the most easily studied under field conditions. Further research

and comparison with laboratory studies will help bring focus to these outstanding questions.

It is also too premature to draw conclusions about concentration and dose-response relationships from the studies reviewed for this project. In particular, many questions remain regarding the timing of exposure and links to any adverse health outcomes noted.

A Scientific Evaluation Scoring System was developed for the project in order to introduce a level of consistency within the literature review process and ensure that the scientific evidence presented in the papers were evaluated objectively. The system highlights the fact that most wildlife studies cannot achieve the level of scientific certainty and acceptance as that attained by laboratory studies. In part, this is due to the lack of exposure data, as well as the fact that limited efforts are undertaken to control for other confounding factors in field studies.

The criteria to ascertain causality are seldom met in the wildlife literature on endocrine disrupting chemicals. In addition, it is currently not possible to assess whether chemical mixtures are more problematic to wildlife species in the environment than single chemicals. Yet there is some suggestive evidence that the developing young are more susceptible to exposure to endocrine disruptors than mature organisms, because the critical periods of development may be affected by the absence of necessary hormones or the presence of disrupting hormones.

Finally, approximately half (56%) of the endocrine disruptor studies on wildlife populations reviewed for this report were supported by federal sources (either entirely or combined with other sources). Interestingly, even though the other half of the studies were not federally funded, conclusions generated by this research are similar to those of the Committee on Environment and Natural Resources of the President’s National Science and Technology Council. This committee evaluated all ongoing federal research on endocrine disruptors during the fiscal year 1996. While there is some overlap between the research reviewed by CENR and that which was reviewed for this project, the source of funding does not appear to make a difference in the focus of,

or conclusions associated with, wildlife research on endocrine disruptors.

Thus, the results show that while much is known about the harmful effects of some of these chemicals in controlled, or laboratory environments, the results of studying their effects in the field are not as clear cut. Though there is a biological basis upon which to assume that chemical effects would be similar in the field, other mediating factors may impact their presence, route of exposure, or uptake by wildlife species. In many cases, these factors are either not identified or not controlled for in field studies. Until many of these issues are resolved, the question remains open as to whether endocrine disrupting chemicals are present in the environment at levels that may cause adverse effects in wildlife.

Recent efforts will help to address a number of the unresolved issues. One change is the trend towards the publication of more wildlife field studies over the last five years. In addition, there appears to be a greater trend toward coordination between agencies and other organizations involved in endocrine disruption research (Reiter et. al., 1998). Also, a number of studies appear to be combining field and laboratory approaches in order to corroborate in the lab what appears to be occurring in the field. Last, methods are being developed (such as 'toxicity equivalency factors', which allow for the comparability of chemical concentrations within the environment) to facilitate comparison of these diverse field studies, which should reveal adverse trends more readily.

Future efforts should continue to focus on the following issues: first and foremost, there needs to be a consistent definition of endocrine disrupting chemicals and their health impacts. Second, studies should begin to measure or discuss the other potential confounding variables that may contribute to the adverse effects noted. Third, a better assessment of chemical concentrations in the environment is needed. Finally, there are currently very limited numbers of studies available on interspecies comparisons. Greater efforts should be made to target some of the research for specific species and chemical exposure combinations so that comparisons within species may be made with greater reliability. The directions for future research described

above would improve scientific understanding of impact of endocrine disrupting chemicals.

ABBREVIATIONS

Symbol	Definition
BHC	benzene hexachloride
CDC	Centers for Disease Control
CENR	Committee on Environment and Natural Resources
chlorine-EQ	chlorine equivalent
DDD	Dichlorodiphenyl dichloroethane
2,4-D	2,4 dichlorophenoxy acetic acid
DDE	Dichlorodiphenyl dichloroethylene
DDT	Dichlorodiphenyl trichloroethane
ED's	Endocrine Disruptors
EPA	Environmental Protection Agency
FY	fiscal year
HCB	Hexachlorobenzene
HCE	Heptachlor epoxide
HCH	ß-hexachlorohexane
LC_{50}	Lethal concentration, 50% kill
mg/kg	Milligrams per kilogram
mg/l	Milligrams per liter
µg/l	Micrograms per liter
NAS	National Academy of Science
OSTP	Office of Science and Technology Policy
PAH	Polyaromatic hydrocarbons
PCB	Polychlorinated biphenyls
PCN	Polychlorinated naphthalenes
ppb	parts per billion
ppm	parts per million
SE	Scientific Evaluation
S&TPI	Science and Technology Policy Institute
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCDD EQ	2,3,7,8-tetrachlorodibenzo-p-dioxin equivalent
TEQ	Toxicity equivalency factors

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1. INTRODUCTION

BACKGROUND

Endocrine disrupting chemicals represent a broad range of synthetic chemicals that are suspected of interfering with hormones and disrupting the endocrine system in humans and animals. The endocrine system is responsible for bodily regulation, in conjunction with other systems, such as the immune and nervous systems. (Hormones traveling through the bloodstream regulate reproduction, growth, physical and mental development and health.) Over one hundred chemicals have been identified as endocrine disruptors to date, but consensus on the exact list of potential disruptors does not exist.

These chemicals are not only thought to be associated with certain adverse effects in humans, such as the increase of cancer, infertility, behavioral abnormalities and neurological disorders, they have also been implicated as the cause of many adverse effects in wildlife populations. However, few studies have demonstrated the effects of endocrine disruptors on wildlife under field conditions.

The impacts of these chemicals are of particular concern because they may affect future generations. Unfortunately the use of these chemicals is increasing. While there is growing circumstantial evidence regarding the impacts of these chemicals that is fueling the public debate (Wingspread, 1991, Colburn, 1996), there is still the need for more rigorous, objective scientific evidence to support policy and action.

Determining whether endocrine disruptors are adversely affecting wildlife populations is a challenge, not only because of the many unknowns associated with endocrine disruptors, but also because it may be difficult to distinguish many of the endocrine disrupting effects on growth, reproduction, and development from other toxic effects or from other non-chemical influences. In addition, the hormonal system is sensitive to small perturbations, which may further complicate field studies and require a more sensitive analysis of the timing of exposure or impacts of other synergistic effects.

PURPOSE

The purpose of this Science and Technology Policy Institute (S&TPI) project was to conduct a focused analysis of the available literature on endocrine disruptors to determine how likely endocrine disruptors are to affect wildlife in the field. Understanding the issues surrounding endocrine disruptor effects on wildlife may then provide important information for determining whether animal or human populations need to be safeguarded from environmental exposures. The nature and extent of effects of human exposure to endocrine disruptors is not well established, though humans appear to have been affected by these compounds (Wingspread, 1991). While other agencies are currently interested in the impacts of endocrine disruptors on humans (Centers for Disease Control, National Academy of Science) the Office of Science and Technology Policy (OSTP) determined that the scope of this particular study the scope of this project would focus specifically on the wildlife literature.

The results of this effort may be used to inform OSTP regarding: 1) defining parameters for including wildlife studies when updating and expanding the existing inventory of federally funded research on endocrine disruptors; 2) further developing a national research strategy for endocrine disrupting chemicals and wildlife populations; and 3) providing input to the international scientific community regarding what is known about the impact of endocrine disrupting chemicals on wildlife.

METHODS

In order to review the current wildlife literature on endocrine disruptors, three specific tasks were undertaken: 1) development of a master endocrine disruptors list; 2) a literature review; and 3) creation of a database for data management and as an analytic tool. These three tasks are described below.

Developing a Master Endocrine Disruptors List

A master list was compiled in order to identify the current chemicals thought to have endocrine disrupting effects on wildlife. This list then served as a guide for the literature review and analysis of wildlife field studies. To create this working list of endocrine disruptors, many sources were consulted and reviewed, including material

from the federal and state governments, industry, environmental organizations, as well as published literature from individual scientists and conference proceedings. (EPA Federal Register List of Endocrine Disrupting Chemicals, 1997, Illinois Department of Environmental Protection Endocrine Disruptors Strategy, 1997, World Wildlife Canada internet site, NAS Proposal #95-CLS-056-01, Colborn 1995, Wingspread Conference Consensus Statement 1992, Wingspread Conference III, 1996, Special Report on Environmental Endocrine Disruption 1997, Environmental Endocrine Disruptors: A Handbook of Property Data, 1997, Radian Intl., LLC internet site, Schmidt, 1994, Lester and Lovera, 1996). Lists from these twelve sources were combined. A total of 102 chemicals were identified as endocrine disruptors from these sources.

The chemicals were then grouped into three distinct categories: Group A, Group B and Group C endocrine disruptors. If the chemical had a documented endocrine disrupting effect, if there was evidence of the chemical's likely presence in the environment, and if there was evidence to suggest that the chemical has had an impact on wildlife, then it was categorized as a "Group A" endocrine disruptor. If the chemical was either not thought to be present in the environment, and/or identified on only one or two of the lists described above, then it was categorized as either a "Group B" or "Group C" endocrine disruptor, depending on the level of evidence available. Group A contains a total of 79 chemicals, Group B has 11 chemicals and Group C lists 12 chemicals. Within these groups, Group A contains primarily pesticides (N=57), organic chemicals (N=19) and a few metals (N=3), whereas Groups B and C contain primarily organic chemicals. (Group B only listed two pesticides and nine organic chemicals and Group C are all organic chemicals.) These chemicals are listed in Appendices 1-3.

Literature Review

The literature review was conducted in two phases. Phase I focused on the secondary literature, or review articles, pertaining to the effects of endocrine disruptors on wildlife. This effort was conducted in order for the team to acquire a broad sense of the available published literature and review it within a limited time frame. In

order to complete this task within the time frame allotted, it was necessary to make Phase I an extremely focused effort with defined boundaries. Thus, the literature selection criteria, while based on sound scientific reasoning, were also developed to help the project accomplish its goals within the defined time constraints.

The goal of Phase II was to review current primary wildlife field studies. The focus of this phase of the project was to gather information about specific health outcomes and chemical concentration levels associated with endocrine disrupting chemicals. Additionally, an effort was undertaken to evaluate the level of scientific evidence presented in the papers. A Scientific Evaluation Scoring System was developed in order that the papers under review could be objectively assessed for consistency across specified scientific criteria.

The two phases of the literature review are further described below.

Phase I (Oct-Dec, 1997):

Phase I involved developing a method for conducting a review of the secondary literature pertaining to the effects of endocrine disruptors on wildlife in an extremely limited time frame. Several published reviews were selected as the most complete sources for the purposes of this project (Special Report on Environmental Endocrine Disruption 1997, Kavlock et. al. 1996, Ankley et. al. 1996, Wingspread Conference I 1992, Wingspread Conference II 1995, Wingspread Conference III 1996, Wingspread Conference IV 1997). References cited in these reviews were assessed for inclusion into the evaluation based on the criteria developed to make Phase I a focused effort. Six hundred and twenty five citations were identified from these seven sources. Approximately 100 articles initially appeared to meet the criteria listed below, based on their titles or abstracts. After further evaluation, 42 articles were reviewed that did meet the selection criteria. These citations and their relevant information were then entered into an online database developed for this project.

Phase I: Literature Selection Criteria

a) The classes of wildlife reviewed included only Reptiles, Mammals, Birds and Fish. Amphibians and Invertebrates were excluded from this phase due to time constraints.

b) The geographic area of interest was confined to North America where possible, unless there were particular events or other geographic regions that provided meaningful additional data on the effects of endocrine disruption on wildlife.

c) The Phase I literature review focused on chemicals listed on the 'Group A' Endocrine Disruptors list where possible, since these chemicals were the most likely to exert an affect on wildlife.

d) Literature selected included field or other 'non-laboratory' studies where possible. (In some cases this was not possible because studies were conducted as combination laboratory and field studies. In other cases, a review article might include specific information about laboratory studies that was useful for the database.)

e) The literature search was limited to the years 1985-1995, English language only. Again, this time frame was selected to keep the review current, while still maintaining the necessary focus during the defined time constraints.

Phase II (Jan-June, 1998)

Based on OSTP's request, the next phase of the project focused on identifying primary scientific studies on the effects of endocrine disruptors on wildlife. Numerous scientific databases were reviewed to identify the appropriate articles[1]. Again, articles were identified using a set of criteria agreed upon by OSTP and RAND to expand the review tailored to OSTP's interests, while still maintaining the focus. In addition, it was agreed that we would develop criteria to determine the level of scientific certainty to increase the level of objectivity in the review process. The additional criteria set forth included the following:

Phase II: Additional Literature Selection Criteria

a) Reptiles, Mammals, Birds, Fish and Amphibians for the years 1996-1998;

b) Amphibians for the years, 1985-1995;

c) Literature containing data on concentration levels of chemicals in the environment;

d) Literature in which the documented health outcome has been noted as an endocrine disrupting effect;

Forty-one additional articles were selected for review and inclusion in the database during Phase II. Table 1 summarizes the paper identification and selection process used for Phase II. (We do not include a similar table for the Phase I selection process because Phase I contained primarily review articles and therefore cannot be grouped individually by taxa.)

[1] The databases reviewed include: Toxline, Zoological Record Online, Biosis Previews, Environmental Bibliographies, Pollution Abstracts, National Technical Information Service

Table 1

Results of Phase II Literature Search (1996-Present)

Taxa	Titles Found In Literature Search for Phase II	Abstracts Requested For Phase II	Papers Obtained That Met Phase II Criteria
Fish	139	30	8
Amphibians	126	43	13
Reptiles	35	8	2
Mammals	26	23	2
Birds	90	77	16

Database Creation

An Excel database was created as a data management and analytic tool for both phases of the review. All articles that were read and met the defined criteria were entered into the database. Duplication, or double counting between review articles and primary articles, was not an issue because the dates of the papers reviewed for Phase I and Phase II were distinct.

Information entered in the database included effects of endocrine disruptors on determinants of growth, development, reproduction and survival in wildlife. Data on body burden or ambient concentrations of the chemicals were also sought. Once the relevant information was entered, the database was sorted using numerous variables in order to conduct the analysis. For example, the layout of the database enabled us to identify which endocrine disrupting chemicals had been repeatedly cited as a concern and at which concentration levels, which species were studied most often, and which adverse health outcomes were most commonly noted. Equally important, the database was also used to identify where the major gaps in the literature appeared to be. A total of 83 papers were entered into the database for this project. This database is now available to OSTP and may serve as a model for further analysis or expansion. Please refer to Appendix D for a full listing of the variables included in the Excel database file.

2. LITERATURE REVIEW FINDINGS

The analytic strategy focused on addressing seven policy questions of interest to OSTP. These questions are presented below and then addressed sequentially in this chapter.

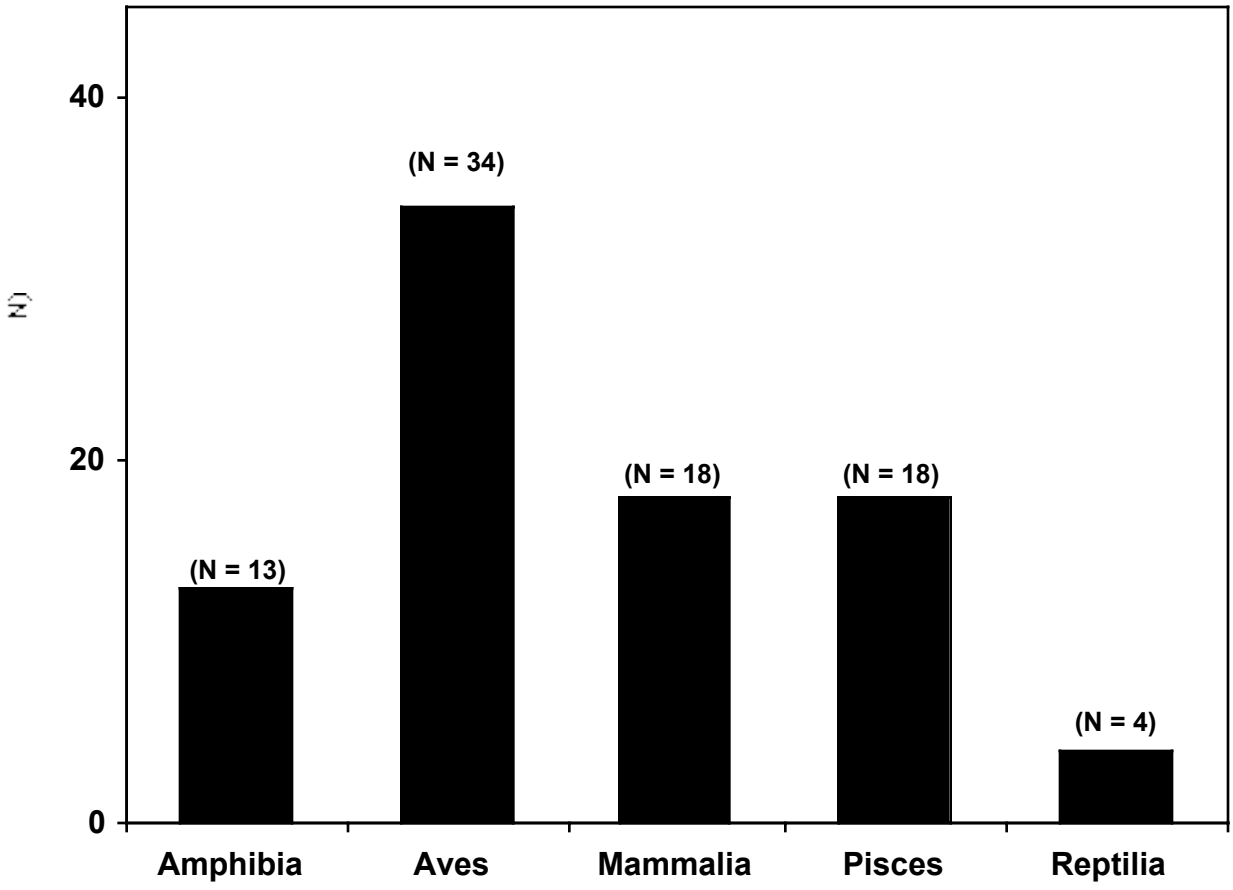
1. Within the wildlife literature, where is the scientific evidence strongest for the effects of endocrine disruptors in the environment: by organism, chemical, site or outcome?
2. Are concentrations of endocrine disrupting chemicals in the environment significant? Is there any information in the wildlife literature that links environmental concentrations to the effects, e.g. dose response relationships?
3. What is the state of scientific evidence in the literature reviewed?
4. What can be said regarding the 'association' versus 'causation' of exposure to endocrine disrupting chemicals and adverse health outcomes noted in wildlife?
5. Is there evidence to suggest that chemical mixtures are more problematic than single chemicals in the environment?
6. Is there field evidence to suggest that developing young are more susceptible to exposure to endocrine disruptors than mature organisms?
7. Are there differences in emphasis between federally funded research and other research pertaining to endocrine disrupting chemicals in wildlife? How do the results from this review compare with reviews of federally funded research?

1. Within the wildlife literature, where is the scientific evidence strongest for the effects of endocrine disruptors in the environment: by organism, chemical, site or outcome?

Taxa

The majority of papers reviewed focused on Birds (N=34). The number of papers on Fish and Mammals were similar in number (N=16 each), whereas fewer papers focused on Amphibians (N=13) and Reptiles (N=4) (Figure 1). It must be stressed that the *number* of papers reviewed for each taxon does not necessarily reflect the level of scientific evidence for that taxon. Rather, the distribution of papers is likely to have been affected by our *a priori* selection criteria, (such as the focus on field studies, or North America). For example, bird egg collection might be more easily conducted in the wild than observation of larger mammals, such as polar bears. This hypothesis might help explain why field studies of birds might be more prevalent for this project.

Figure 1
Total Number of Papers Reviewed by Taxa



Chemicals

Forty-nine different chemicals were identified in the papers reviewed, with 27 being studied more than once and 22 being studied only once (Table 2). The most often studied chemicals included PCBs, which were examined in 32 different studies, DDT and its metabolites which were examined in 25 studies, and metals (including aluminum, cadmium, copper, iron, lead, mercury, selenium and zinc) which were examined in 22 studies. Since these chemicals do not usually occur in isolation in the environment, most field studies examined these chemicals as part of complex mixtures. Therefore, it was difficult to discern the marginal effects of individual chemicals since they were part of mixtures. The

effects of individual chemicals were usually studied under controlled conditions such as in laboratory studies. It is likely that the endocrine disruptors most frequently cited in this report were noted more for their persistence in the environment rather than because they are considered the most serious or most widely used. In fact, some of these chemicals are no longer manufactured and others are being phased out for certain industrial uses in the United States.

Table 2

Chemicals Studied In Endocrine Disruptors Publications

Chemical	Number of Studies in Which Chemical Appears*
PCBs	32
DDT and its metabolites	25
Metals (aluminum, cadmium, copper, iron, lead, mercury, selenium, zinc)	22
Dioxins	17
Dieldrin	11
Furans	10
Chlorine-eq	9
PAH, Lindane, nonarachlor	5
Hexachlorobenzenes, Organochlorines, Oxychlordane, Mirex	4
Heptachlor epoxide, Kepone, Dicofol, b-Hexachlorohexanes, Methoxychlor, Chlordane	3
2,4-D, Atrazine, Cyanazine, Estradiol, Hydrocarbons (Petroleum), Organohalogens, Toxaphane	2
Aldecarb, Alkylphenol ethoxylates, Arsenic, BHC, b-sitosterol, Carbofuran, Cesium-137, Chlorobenzene isomers, Cobalt-60, Diazinon, Endosulfan, Endrin, Malathion, Perylene (jet fuel), PHAH, Phthalates, Polychlorinated Naphthalenes, sewage, Stigmastanol, Tamoxiphen, Trifluralin, Vinclozolin	1

*Of the 83 studies evaluated, some covered multiple chemicals. Therefore, the number of total studies identified in Table 2 is greater than the number of studies reviewed (N=83).

Study Sites

In addition to North American sites, some non-North American locations were examined in some papers. Out of 125 study sites reviewed, 69 different site locations were reported. The most commonly studied sites included the Great Lakes, which were examined in 16 studies; the Baltic Sea, which was examined in 8 studies; Green Bay, Wisconsin and the St. Lawrence River, which were each examined in 4 studies; and Alaska, the Arctic, California, Lakes Apopka and Woodruff, Florida, and Prince Edward Sound, Alaska, which were each examined in 3 studies. Eighty-two (66%) of the study sites were aquatic in nature, such as bays, rivers, lakes, seas, harbors, and straits. Nineteen study sites were from a single review article (AK, CA, CO, CT, FL, MA, MD, NV, OR, RI, SC, TX, WA, WY, Australia, Finland, Great Britain, Ontario, Quebec) (Blus, 1996). Thirteen studies were performed solely in the laboratory, while 24 studies were performed in both the field and in the laboratory (Field/Laboratory). PCBs, the most commonly studied chemicals (32 studies), were studied at 24 different sites (Figure 2). DDT and its metabolites, the second most commonly studied group of chemicals (25 studies), were studied at 42 different sites (Figure 3).

Figure 2

Location of Field Studies Published on the Effects of PCB's on Wildlife, 1985-1998

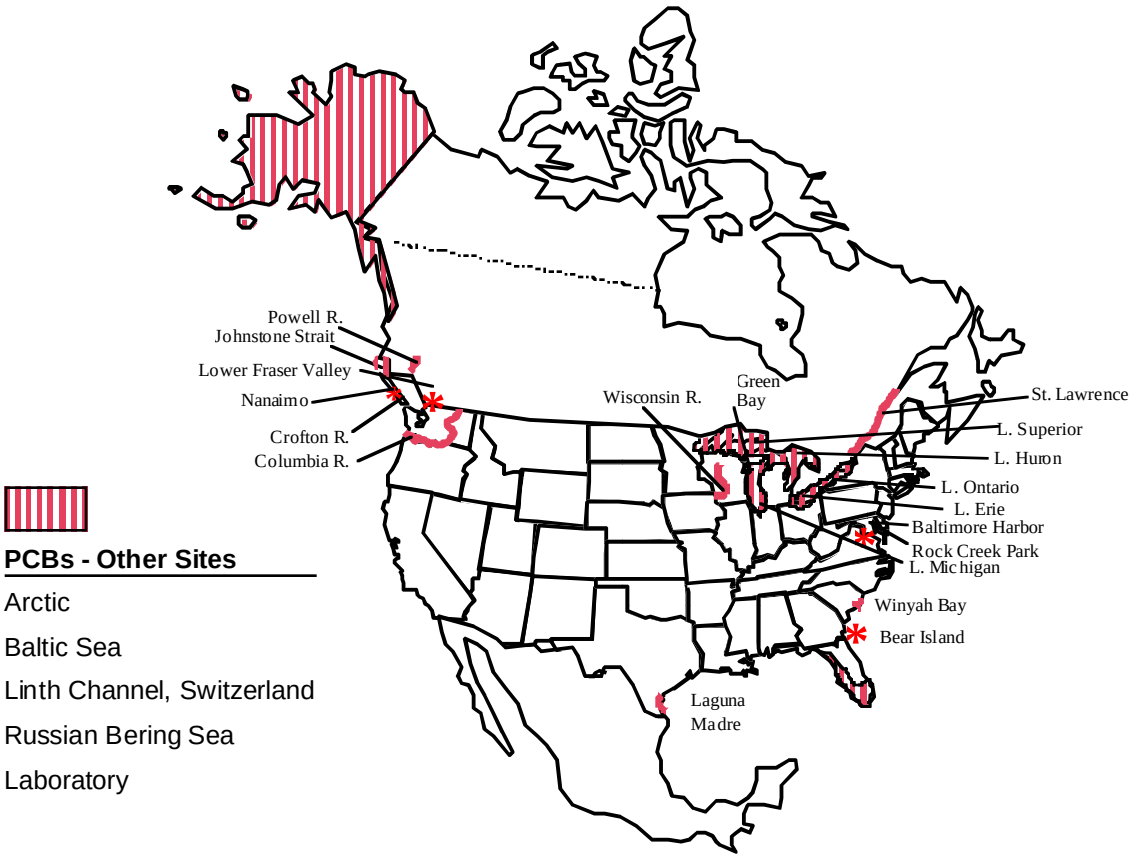
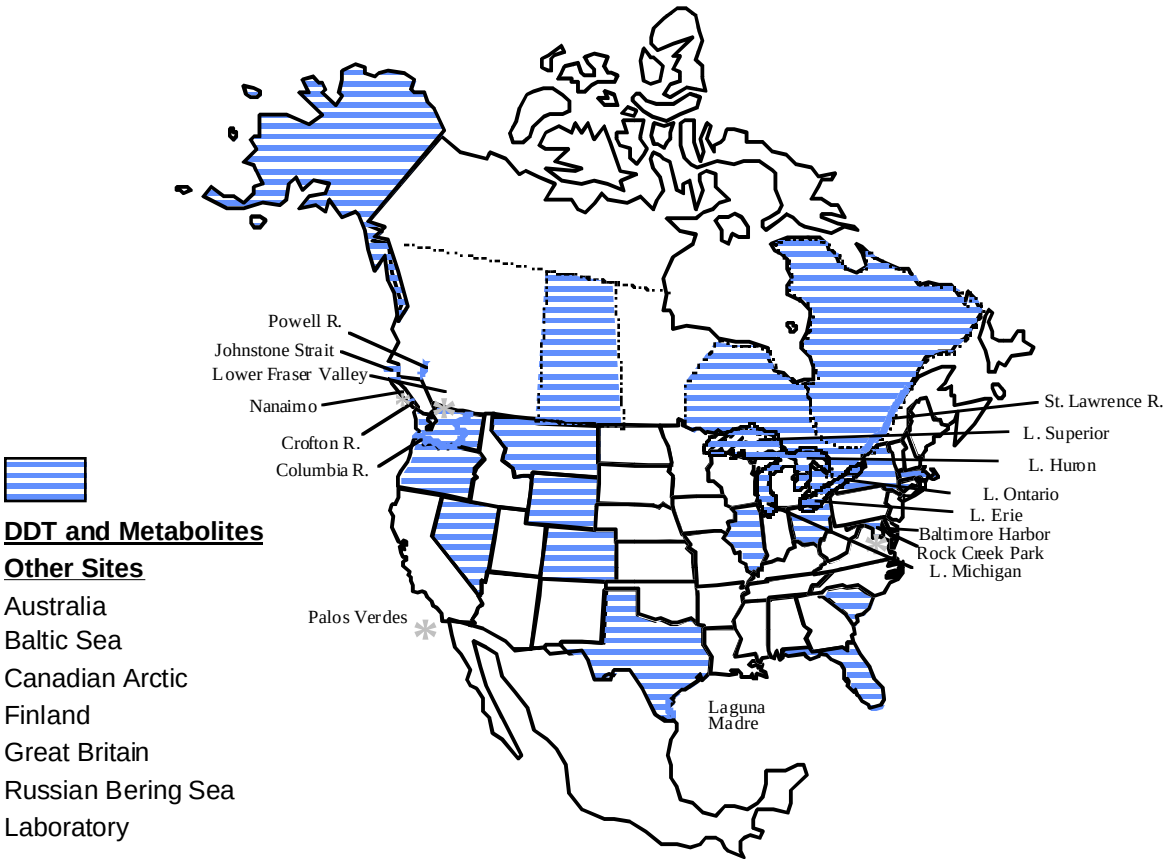


Figure 3

Location of Field Studies Published on the Effects of DDT and its Metabolites on Wildlife, 1985 - 1998



Health Outcomes

The literature reviewed for this study focused on a few general categories of health outcomes. The primary outcomes noted in the literature include mortality and lesser adverse effects, such as reproductive failure, congenital malformations and other size and skeletal changes (Table 3). In part this can be explained by the selection criteria we used for the literature review. Studies reporting health outcomes believed not to result directly from exposure to endocrine disruptors--such as cancers not associated with the reproductive/endocrine system--were excluded from this review. The chemicals most frequently associated with these effects include metals and the organochlorines (Table 4).

Table 3
Endocrine Disruptors and Associated Health Outcomes Described in Wildlife

General Category Groupings (Health outcome subgroups described)	Positive Studies (N)*	Negative Studies (N)	Total (N)*
Congenital malformations (includes congenital malformations “all”, “reproductive”, and “other”, embryonic alterations, and genetic changes)	20	22	42
Immune function effects	6	2	8
Mortality (includes embryonic mortality and adult mortality)	31	15	46
Adverse reproductive outcomes (includes demasculinized males, decreased hatching success, hormonal changes, masculinized females, decreased reproductive performance and delayed sexual maturation)	32	20	52
Size/skeletal changes (includes growth retardation, size changes and skeletal abnormalities)	22	16	38

*Some studies reviewed assessed more than one health outcome, therefore the numbers of positive studies and total studies identified in Table 3 are greater than the number of studies reviewed (N=83).

Table 4

Endocrine Disruptors and the Most Common Health Outcome Subgroups Described in Wildlife

Health Outcome	Studies Positive (N)	Studies Negative (N)	Total*	Chemicals	Specific Outcomes	Species
Mortality (embryonic)	19	10	29	Metals, DDT, chlorine - eq, dieldrin, dioxins, furans, lindane, aluminum, PCB's, toxaphene	Decreased/early hatchability, difficulty producing viable offspring, decreased litter size, increased interrupted pregnancies, early stage mortality	Amphibians, birds, mammals, fish
Mortality (adult)	12	5	17	DDT, cadmium, copper, iron, mercury, zinc, PAH, toxaphene, dieldrin, dioxins, furans, mercury, selenium, PCB's	Decreased survival and maturation, early mortality	Birds, mammals, fish
Size Changes	19	7	26	BHC, chlorine-eq, DDD, DDE, DDT, DDT, dieldrin, dicolfol, TCDD, furans, HCB, HCE, lindane, malathion, mirex, metals, organocholorines, oxychlordane, PCB's, PHAH	Eggshell thinning, organ/body weight changes, weight reduction, embryo length reduction, mass at metamorphasis, egg mass abundance and density	Amphibians, fish, mammals, fish, reptiles

Table 4

Endocrine Disruptors and the Most Common Health Outcome Subgroups Described in the Wildlife (cont.)

Health Outcome	Studies Positive (N)	Studies Negative (N)	Total*	Chemicals	Specific Outcomes	Species
Reproductive Performance	14	11	25	Aldecarb, carbofuran, chlorine-eq, DDE, dieldrin, TCDD, endrin, furans, heptachlorepoxide, lindane, malathion, aluminum, mercury, selenium, organochlorines, PCB's, PHAH, PCN's	Complete reproductive failure, decreased number of hatchlings, fledglings or eggs, decreased fertility, egg laying delayed, fewer territories/nests established	Amphibians, birds, mammals, fish
Hormonal Changes	12	4	16	17b-Estradiol, atrazine, b-sitosterol, cyanazine, DDE, DDT, dicofol, endosulfan, kepone, mercury, methoxychlor, PAH, PCB's, 'sewage', tamoxiphen	Decrease in sex steroids, induction of vitellogenin, impaired estrogen receptor function, male-to-female reversal	Mammals, fish, reptiles

*Some studies reviewed assessed more than one health outcome. Therefore, the number of total studies identified in Table 4 is greater than the number of studies reviewed (N=83).

In summary, birds were the most frequently cited taxa, metals and organochlorines the most frequently cited chemicals, aquatic sites the most frequently studied locations, and embryonic mortality, size changes, and adverse reproductive performance the most frequently cited health outcomes in this literature review of endocrine disruptors in wildlife. However, based on the *a priori* literature selection criteria developed for this project, it is not possible to draw conclusions about whether these are the taxa most seriously affected, the chemicals of greatest toxicity, the sites of greatest occurrence, the health outcomes of greatest concern, or whether they are just the most easily studied under field conditions. Further research and comparison with laboratory studies will help answer these remaining questions.

2. Are concentrations of endocrine disrupting chemicals in the environment significant? Is there any information in the wildlife literature that links environmental concentrations to the effects, e.g. dose-response relationships?

This literature review looked at two types of measures of endocrine disrupting chemicals and wildlife exposures: “Body burden,” or the amount of chemical that was documented in the species during the study; and “ambient concentration,” or the amount of the chemical documented in the environment in which the species lived, ate or nested during the research period.

The advantage of evaluating the body burden of a chemical is that there is little question that the species was exposed to a particular chemical. Analytical techniques can determine the amount of a chemical that is present or stored in the body or shells of a particular species during a specific point in time. However, many of the chemicals that fall into our endocrine disrupting classification have very different toxicokinetic properties. While many of the chemicals, such as the organochlorines tend to be stored in the fatty tissue and can be detected for long periods of time, other chemicals, or their metabolites, are not.

Studies designed to evaluate the health consequences of chemicals at different concentrations tend to be laboratory studies, where the doses of chemicals can be carefully controlled. Those studies that did

note a dose-response relationship in the field are referenced in Table 5.

The ranges described for tissue levels associated with effects vary from below the detection level (ND) to .008 ppb for organochlorines and 4,000-27,000 ppm for mercury. However, negative effects were noted at even higher concentrations in some studies, such as those results published by Hart, et al., (1991) and Zimmerman, et al. (1997; Table 5).

Table 5

Chemical Concentrations and Dose-Response Relationships

Author	Chemical	Species	Concentration (Converted To ppb)	Dose-Response Outcome	Negative Studies Concentration (Same Chem/Species, Converted To ppb)
Henschel, 1995	TCDD	great blue heron	ND-.00881 ppb eggs	dose-response relationship noted over 5 year study. As levels increased, increased cerebral asymmetry noted	Hart, 1991, 10 ppb eggs
White, 1995	TCDD	wood duck	.014-.127 ppb eggs	dose-response relationship noted with nesting success, hatching success and duck production	
Grasman, 1995	chlorine eq, DDE	Caspian tern	3,460-3,780 ppb eggs	inverse exposure-response relationship associated with multiple organochlorine exposure and T-cell function	Mora, 1996, (Caspian Tern/DDE), 110 ppb eggs
Tillet, 1992	TCDD, PCB	double crested cormorant	100-1,480 ppb eggs	strong dose-response relationship between bioassay derived TCDD-EQ in eggs and egg mortality	Zimmerman, 1997 2,000-113,000 ppb extractable lipids
Weiner, 1996	mercury	rainbow trout	4,000,000-27,000,000 ppb	large single dose methylmercury more toxic than chronic accumulated dose, decreased activity and appetite, increased mortality	
Mahaney, 1994	hydrocarbons (petroleum)	green tree frog	10,000 ppb, 55,000 ppb, 100,000 ppb	Tadpole growth significantly lower at 2 lower concentrations. Weight gain over time showed decreasing trend with increasing oil concentrations.	

Documented health effects based on ambient concentration data were also limited, though data to determine effect and no effect levels were available for four endocrine disruptors of concern: Aldicarb, Lindane, lead and PCBs. Aldicarb, at concentrations between 1.5-3.0 ppm in drinking water was correlated with decreased fertility in the common quail (*Coturnix coturnix*), but had no effect on egg production or eggshell thinning (Jansen, 1996). Similarly, concentrations of Lindane between 1.0 –9.0 ppm in drinking water were associated with decreased incubation times, reduced egg mass and decreased hatchability in the Common Quail, but had no effect on egg production or eggshell thinning (Jansen, 1996). Concentrations of lead, documented at 1.0-12.0 µg/l in spawning ponds, were thought to be associated with embryonic mortality in the Spotted Salamander (*Ambystoma maculatum*), whereas concentrations of 0.05 µg/l appeared to have no effect on embryonic mortality (Blem, 1991). PCBs in the diet of salmon at a concentration of 500 mg/kg for 90 days reduced growth by 40%, while 50 mg/kg had no effect on growth (Niimi, 1996). Likewise, 2.9 mg/l PCBs in the diet of trout for 90 days appeared to reduce growth by 10%, while 0.2-1.5 mg/l had no effect on growth (Niimi, 1996). In addition, 8.0-15.0 mg/l PCBs in the diet and water of Fathead Minnows (*Pimephales promelas*) was the 96 hour LC_{50}, while 0.3-2.8 mg/l caused no mortality (Niimi, 1996).

One of the major difficulties in making dose-response, general body burden, or even ambient comparisons in wildlife studies is that collectively, these studies do not focus on any particular species or chemical of concern. Therefore, it is extremely difficult to compare across doses and outcomes, because it is rare to encounter more than one or two articles that have evaluated the same species and chemical exposure. For example, in this review alone, there were 154 positive effects described and 104 negative effects cited for different endocrine disruptor exposure and species combinations. And in only extremely few cases were the same adverse health outcomes detected in the studies that evaluated similar species and chemical exposure combinations.

Another point is that many of the body burden studies appear to focus on the lipophilic chemicals, such as the organochlorines (PCB’s and DDT). However, there are some chemicals (such as permethrin) that are defined as endocrine disruptors but do not share these persistent

properties. Unfortunately there are only limited studies documenting the effects from these less persistent chemicals with evidence of chemical concentration data in the field.

In sum, it is premature to draw conclusions about dose-response relationships for the studies reviewed for this project. What is not always clear from a field study is how long the species has been exposed and whether it is the exposure under study that accounts for the presence of the chemical in the body. Though certain of the studies did evaluate body burden in wildlife, many questions remain regarding the timing of exposure and links to any adverse health outcomes noted. Few studies specifically described 'dose-response' relationships, but rather focused only on positive or negative results. Ambient concentration data were also limited. And collectively, there does not appear to be a focus on any particular species or chemicals of concern, making it difficult to combine data from various studies.

3. What is the state of scientific evidence in the literature reviewed?

In order to introduce a degree of consistency within the review process, a scoring system was developed to objectively evaluate the level of scientific evidence present in the papers under review. Therefore, all studies evaluated under Phase II of this project (primary research papers) were given a Scientific Evaluation (SE) score. Though this scoring system still requires further evaluation and refinement, the criteria did allow the reviewers to ensure that similar criteria were being utilized when reviewing the literature. SE scores range from 0-5, where scores of 4 or 5 are evidence of greater scientific certainty in conclusions while lower scores represent lesser scientific certainty or evidence. The Scientific Evaluation criteria and scoring system are shown in Table 6.

Table 6

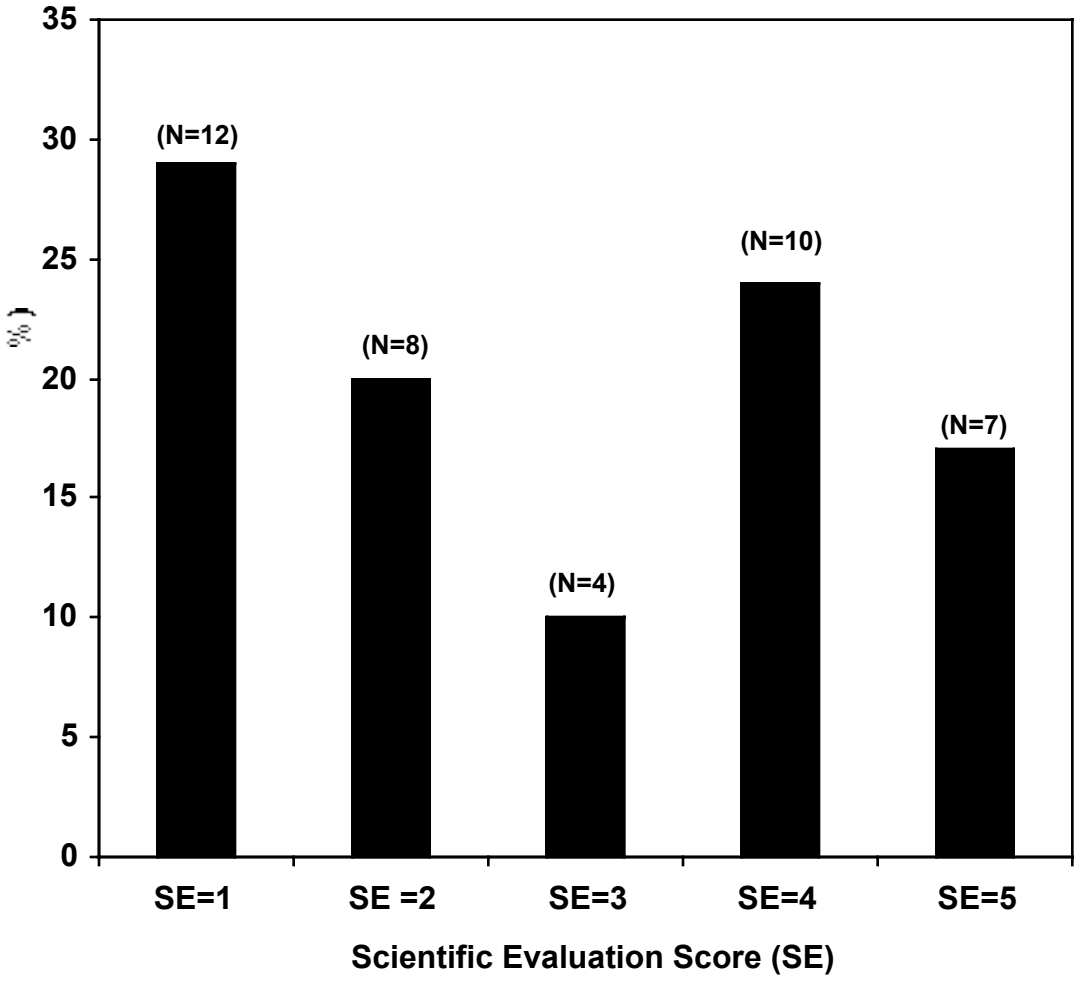
Scientific Evaluation Criteria

Scientific Criteria	Evidence	Score	Evidence	Score
Is it a single chemical or mixture?	Single	1	Mixture	0
Is timing from exposure to outcome discussed?	Yes	1	No	0
Is the outcome based on acute or chronic exposure?	Acute	1	Chronic	0
Is evidence from a laboratory or controlled study available?	Yes	1	No	0
Are concentration data available and described?	Yes	1	No	0

Figure 4 presents the distribution of Scientific Evaluation scores for the 41 papers included in the Excel Database for Phase II. The distribution of papers is not uniform across scores. Rather, the papers are weighted most heavily around SE scores of 1 and 4.

Figure 4

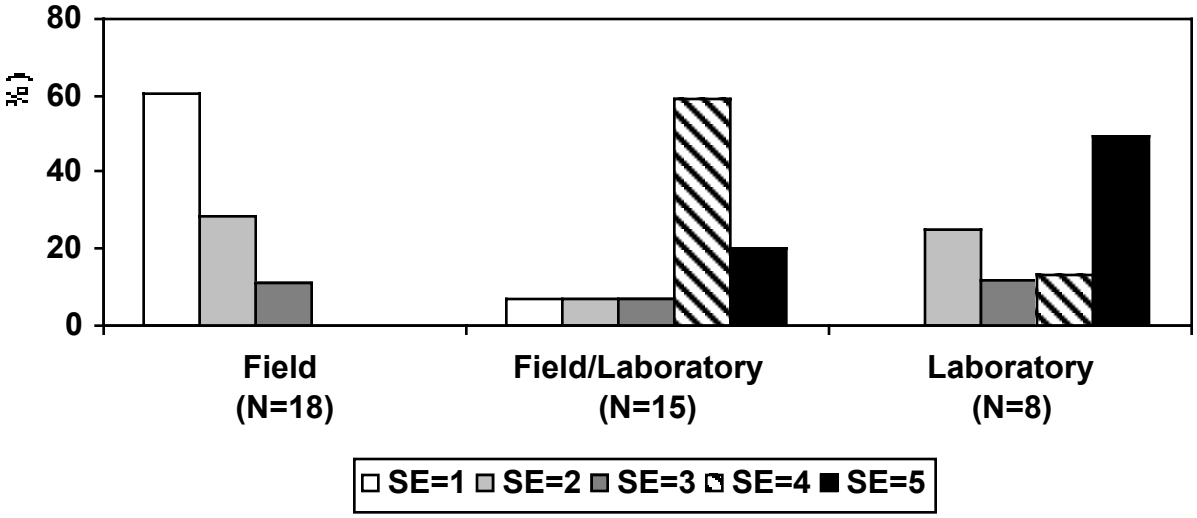
Distribution of Scientific Evaluation Scores



Next, the distribution of SE scores was compared against 'study type'. Studies were grouped into three general categories, "field" only, "laboratory" only, or a combination of "field/laboratory". The "field/laboratory" category includes studies that either had two components, 1) a field component, and; 2) a verification or follow-up laboratory component, or studies in which animals were kept captive in field-like settings. These types of studies were called "field/laboratory" so that the more controlled field studies were evaluated as a separate category from other field studies (Figure 5).

Figure 5

Scientific Evaluation Scores by Study Type



The distribution of scores varies both within and between study type. The field studies have the lowest SE scores, with 89% of the papers receiving a score of 1 or 2, and no papers receiving a score in the 4 to 5 range. An important factor contributing to these low scores is the lack of solid exposure data, including the timing, concentration and type of exposure (acute versus chronic).

In comparison, the laboratory studies have the highest SE scores (SE=5) within a study type, but this is based on a small number of papers. Thus, using the objective criteria stated above, the ability to corroborate findings in a laboratory or controlled setting appears to greatly enhance the level of scientific evidence presented in the literature. Almost by definition, wildlife field studies cannot achieve the same level of certainty. However, with greater care in identifying confounding factors and focusing the research in more controlled settings, the quality of wildlife studies will also attain a higher degree of scientific certainty and acceptance.

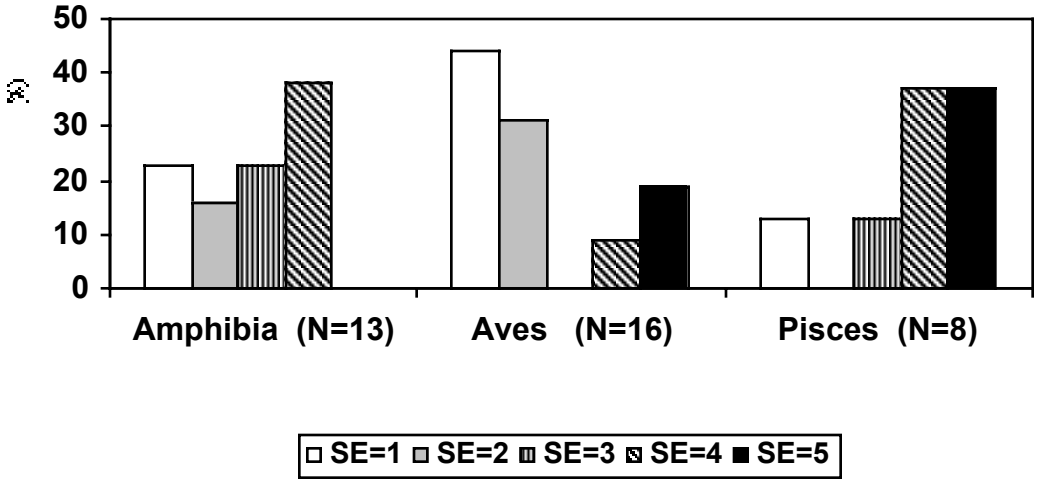
Finally, the distribution of SE scores was stratified according to taxa. Unfortunately papers on mammals and reptiles were too limited (n=2) to allow for adequate analysis. In general, it appears that the fish studies received higher SE scores whereas the amphibian scores were lower (Figure 6). This may in part be explained by the fact that fish appear to have the largest fraction of studies

that fall into the laboratory or field/laboratory categories. In addition, much of the endocrine disruptor research has targeted the contaminated waters of the Great Lakes region, which is the largest freshwater reservoir in the world. This research, which focuses on the contaminated fish in this region, has been ongoing for decades and is perhaps more refined than research focusing on some of the other taxa studied for this project. One reason may be that certain fish are good indicator species for understanding the effects that endocrine disruptors may be exerting.

To summarize, the SE scores developed allowed for a more consistent and objective analysis across the literature reviewed for Phase II of the project. Not surprisingly, the scores highlighted the fact that field studies had the lowest level of scientific certainty, primarily due to their lack of chemical exposure data, whereas the laboratory studies had the highest level of scientific certainty. Further efforts to improve information on confounding factors, chemical concentrations and other data will help wildlife studies attain a high degree of certainty and acceptance in the future.

Figure 6

Scientific Evaluation by Taxa



4. What can be said regarding the 'association' versus 'causation' of exposure to endocrine disrupting chemicals and adverse health outcomes noted in wildlife?

The method of determining whether an agent, or in this case, an endocrine disruptor, is *causing* an outcome of concern is not an exact science. Rather, a set of generally recognized criteria is used to infer causality (Kelsey, et al, 1986).

Specifically:

1. The hypothesized cause should be distributed in the population in the same manner as the disease.
2. The incidence of the disease should be significantly higher in those exposed to the hypothesized cause than in those not so exposed.
3. Exposure to the hypothesized cause should be more frequent among those with the disease than in controls without the disease when all other risk factors are held constant.
4. Temporally, the disease should follow exposure to the hypothesized causative agent.
5. The greater the dose or length of exposure, the greater the likelihood of occurrence of the disease.
6. For some diseases, a spectrum of host responses should follow exposure to the hypothesized agent along a logical biological gradient from mild to severe.
7. The association between the hypothesized cause and disease should be found in various populations when different methods of study are used.
8. Other explanations for the association should be ruled out.
9. Elimination or modification of the hypothesized cause or of the vector carrying it should decrease the incidence of the disease (e.g., control of polluted water).
10. Prevention or modification of the host’s response on exposure to the hypothesized cause should decrease or eliminate the disease (e.g., immunizations).
11. When possible, in experimental settings the disease should occur more frequently in animals or humans appropriately exposed to the hypothesized cause than in those not so exposed.
12. All of the relationships and findings should make biological and epidemiological sense.

Clearly, most, if not all, of the above criteria are seldom met in wildlife field studies on endocrine disruptors. At this point, much of the available wildlife data arise from specific events in distinct locations, from “major accidental spills” and/or “continuous dumping” of contaminants into the environment. Examples include the Exxon Valdez oil spill (Kocan 1995, Hose 1996) or releases of PCBs in the Great Lakes region of the United States (Leatherland 1992). Certainly some studies have documented health effects in different species. Some have even noted the presence of environmental concentrations of endocrine disrupting chemicals. However, even in cases where there is circumstantial evidence, many of the criteria required to attribute causality are not met. For example, there is a case identified downstream of the Kraft Mill entry point (Davis, 1992), where the downstream Fenholloway River is impoverished in fish species and the only species present contains a high percentage of masculinized females. In comparison, all other downstream entering tributaries, streams and springs are rich in fish species and show no indication of masculinization. In this case, criteria such as temporality, or specifying that the exposures preceding the outcome, as well as the elimination of other explanations for the association have not been described.

In most cases it is difficult to establish a clear cause-and-effect relationship where numerous chemical and non-chemical stressors might be responsible, either alone or in combination, for a particular health effect. Many environmental factors produce (or “are associated with”) toxicity. For example, in natural aquatic ecosystems, variations in water temperature, hardness, pH, and dissolved oxygen are just a few of the variables that may either directly contribute to an adverse health outcome in wildlife, or may modify the effect of endocrine disrupting chemicals. To complicate matters, in many cases the magnitude of these effects either alone, or as modifying factors, is unknown.

In summary, most, if not all, of the above criteria are never present in wildlife field studies on endocrine disruptors. At this point, much of the available wildlife data arises from specific events in distinct locations. However, even in cases where there is circumstantial evidence, many of the criteria required to attribute

causality are never met. The strongest evidence for causation derives from laboratory studies for species where it is possible to replicate their natural environment, as well as administer controlled exposures. However, there are currently very limited data available even for same species laboratory studies. In addition, not enough is currently known about the threshold doses, latency periods, or the range of possible health outcomes for each species. While this is not a unique problem, and is true for understanding the effects of many non-endocrine disrupting chemicals in the environment, the state of the science on endocrine disrupting effects on wildlife in field studies is currently insufficient to be able to attribute causation. Still, many of the studies reviewed do generate clues regarding the effects of these chemicals and their mechanisms of biological disruption, however they should only be identified as risk factors *associated* with the outcomes noted, until more is understood about their true effects.

5. Is there evidence to suggest that chemical mixtures are more problematic than single chemicals in the environment?

Before the effects of chemical mixtures may be evaluated, the impact of single chemical exposures must be understood. Currently, the research on endocrine disruptors has not been able to clarify the effects of single chemical exposures on different species, partially due to the confounding fact that most endocrine disruptors in the environment are usually part of complex mixtures of chemicals. More information is needed regarding the mechanisms and sites of action of single compounds, as well as on their entire range of possible outcomes. Methodological advances are also necessary to compare the toxic effects of exposures to different compounds across different species. New research is beginning to address this issue, with the development of toxicity equivalency factors (TEQ) to compare toxicity between chemical compounds (Cook, 1997).

The impact of chemical mixtures on wildlife is clearly an area that needs further attention. As described in other areas of environmental health, the effects of chemical mixtures can produce synergistic effects depending on the type of mixture and whether they have common or different modes of action. Further research is needed to integrate

information on individual chemicals, in order to obtain data to allow development of predictive models for the effects of multiple chemicals. Given the level of uncertainty described above, it is not possible to assess whether chemical mixtures are more problematic than single chemicals in the environment at this time.

6. Is there field evidence to suggest that developing young are more susceptible to exposure to endocrine disruptors than mature organisms?

The notion that the developing young are more susceptible to exposure to endocrine disrupting chemicals than mature organisms makes scientific sense. There are critical periods in the life cycle where adverse organizational and or activational effects can occur via the absence of necessary hormones, or the presence of a disrupting hormone. Organizational effects are typically permanent effects that most likely occur during a critical period of development, such as during sex differentiation, whereas activational effects may occur during maturation (Bern, 1992). Thus, inappropriate alterations of hormone levels may cause permanent or transient effects, depending on the timing of exposure.

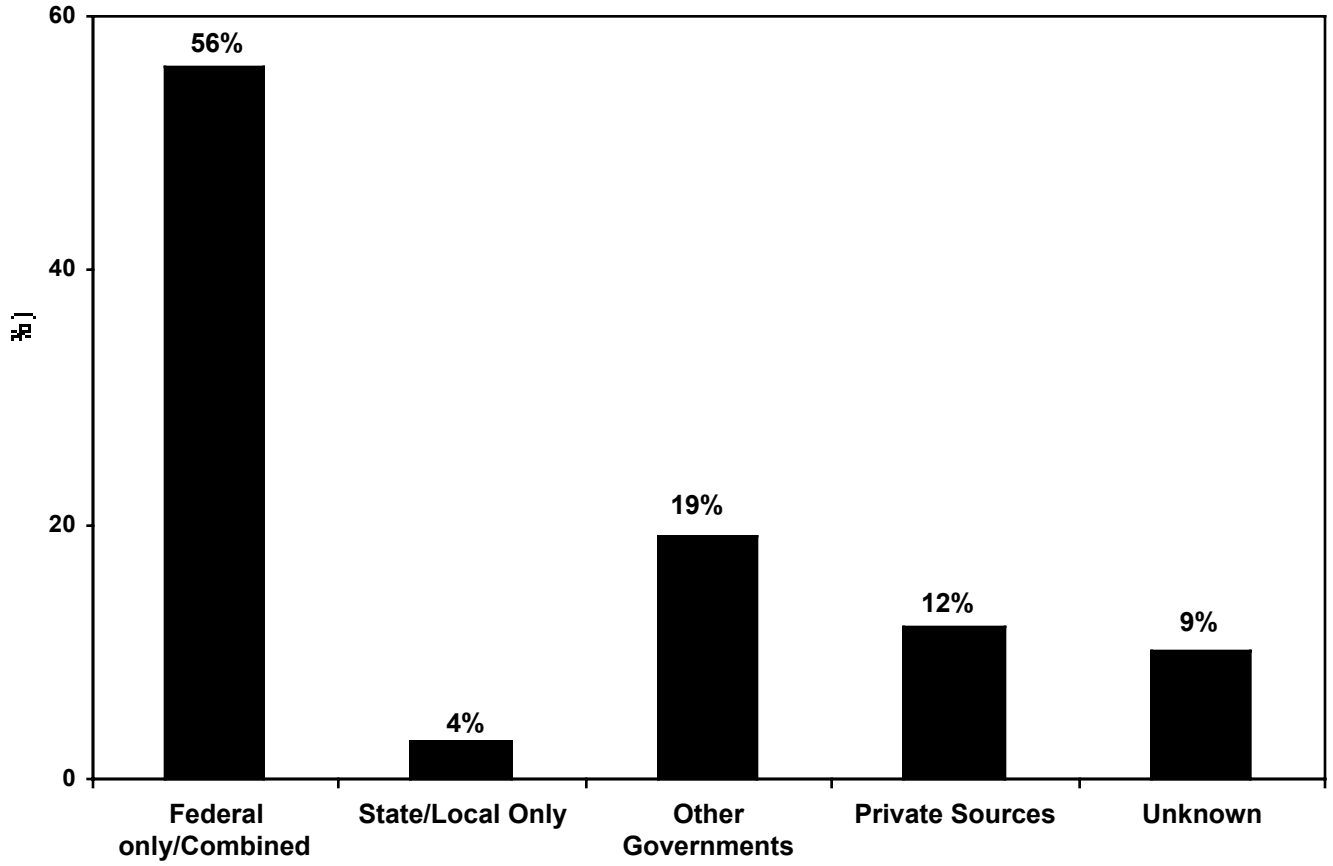
There is some limited evidence from the field suggesting that the early stages of development are the critical periods sensitive to the effects of endocrine disruptors. In one study, spawning fish seemed to be more susceptible than juveniles to some endocrine disruptors (Dahl, 1980). Similar results were obtained in a study on the effects of PCB's in lake and rainbow trout (Walker, 1992). Also, certain laboratory studies have demonstrated that exposures of the developing young and organisms in-utero may be a contributing factor to outcomes observed in wildlife populations (Bern, 1992). One consequence of exposure to environmental estrogens early in development is the feminization of the male reproductive system, which occurs at both structural and genetic levels (McLachlan, 1992). Though this evidence is suggestive, it must be stressed that no comprehensive and accurate exposure data are consistently available from field studies.

7. Are there differences in emphasis between federally funded research and other research pertaining to endocrine disrupting chemicals in wildlife? How do the results from this review compare with those from reviews of federally funded research?

A limited analysis was conducted to assess the distribution of funding sources for the studies reviewed in Phase II of this project. Funding sources were grouped into five categories: U.S. federal sources; state and local sources; private sources, which include both private foundations, as well as private corporations; other governments, such as Canada and The Netherlands; and unknown sources, (for papers that did not cite a funding source) (Figure 7).

Figure 7

Funding Sources



More than 50% of the studies were performed in research institutes and universities and were supported either entirely by federal funds or by a combination of federal and other funding sources. Other governments funded 19% of the studies evaluated, but it must be stressed that the literature selection criteria for this project focused primarily on North America and therefore, does not fully represent the scope of research conducted or funded by other governments. Only 12% of the studies reviewed for Phase II were funded entirely by private sources - one study was funded by industry; the remaining were funded by private foundations. A few studies (4%) were funded at the state or local level. The remaining studies, labeled 'unknown,' were articles that did not identify their funding sources.

This analysis was then compared with the recent evaluation of research on endocrine disruptors conducted by the Committee on Environment and Natural Resources (CENR) of the President's National Science and Technology Council. This council is charged with 'ensuring that science and technology are considered in the formulation of federal policies and that federal organizations have coordinated science and technology budgets and programs' (Reiter et al, 1998). The CENR evaluated all ongoing federal research on endocrine disruptors during the fiscal year 1996 and focused their efforts on identifying research gaps and developing a coordinated interagency plan to address research needs of high priority.

Many of the conclusions identified by the CENR are similar to those of this report. Specifically, the CENR found that the range of wildlife species studied should be expanded. Also, studies that gather information on the normal endocrine patterns in wildlife and their role in regulation of differentiation are needed. In addition, there is a need to expand the endpoints beyond effects on reproduction and development. The CENR also concluded that research focused on sentinel species and biomarkers will assist in characterizing the level of risk and the full range of biological responses associated with exposures to endocrine disruptors.

The similarity in some conclusions reached between the CENR and our evaluation may in part be explained by the fact that there is some overlap between the studies reviewed by the CENR and the studies

reviewed in Phase II for this project (which both include federally funded studies conducted during FY 1996). What is more interesting, however, is the fact that almost 50% of the studies reviewed for our effort were *not* federally funded. While it is likely that there are some researchers who may be receiving both federal and other funds, it does not appear that there is a difference in focus or conclusions associated with the source of funding for wildlife research on endocrine disruptors.

3. DISCUSSION

While there are some positive and recent changes in the focus and direction of the endocrine disruptor literature as it pertains to wildlife, there are still a number of challenges that need to be overcome before the state of the science will be at a point to make definitive statements regarding the impact of these chemicals on wildlife in the environment.

First and foremost, there needs to be a consistent definition of what endocrine disrupting chemicals are and how their health impacts are defined. There is currently little consensus on how to evaluate the adverse effects attributed to endocrine disruptors. For example, many species have different critical periods of sensitivity to effects from exposure. Therefore, an endocrine disruptor may only act as such for certain species, or during certain periods of the life cycle. In addition, effects may be primary, such as a direct affect from an exposure, versus an effect that is further removed in time and development. For example, consider the indirect effect of alterations in pH level in a pond due to acid precipitation. The changes in pH may result in the release of certain metals, thereby affecting certain species during critical stages of development. At what point is the effect attributed to the metal, as opposed to the primary insult or exposure (pH)? Until these issues are more clearly defined, the research will continue to reflect an inconsistent attribution to the effects of endocrine disruptors on wildlife populations.

Second, many of the studies do not measure or discuss the other potential confounding variables that may contribute to the adverse effects noted. Factors such as water chemistry, canopy density, weather conditions, or general population declines within species, are just a few examples of variables that may or may not be evaluated. This too, limits the possibility of drawing conclusions regarding the impact of specific chemicals on wildlife.

A third related issue is that many of the studies lack the minimum criteria considered essential for a well designed study. In addition to not controlling for some very important variables, many field studies

lack other aspects of scientific design necessary to understand the relationship between exposures and adverse health outcomes. For example, many field studies do not or cannot define whether the exposure preceded the outcome of concern. In addition, when an identified endocrine disruptor is part of a chemical mixture, some studies cannot determine whether the endocrine disruptor is responsible for the observed effect, or whether the mixture itself may be responsible for the adverse health outcome. Finally, many studies lack controls as comparison groups. All of these study design issues contribute to the fact that the state of the wildlife literature is not at a point where definitive cause-and-effect relationships between endocrine disruptor exposures and health outcomes may be drawn.

Fourth, a better assessment of chemical concentrations in the environment is needed. Only a few wildlife studies report on the ambient concentrations of chemicals in the field or quantify the body burden of these chemicals in different species. Without these data it is impossible to estimate to what degree the species have been exposed. Yet, even with such estimates available, problems are evident. Ambient concentration data may not represent the exposure truly associated with the adverse effect--it might only be the chemical that is detectable during the time of the study or that has remained persistent over time. Body burden data may be difficult to assess in field studies, and even if obtained, may also not represent the relevant exposure unless ambient concentration data are collected during the same study. Surprisingly, very few field studies report both ambient and body burden concentrations. Clearly, the data on chemical concentrations and exposure, while difficult to assess, are truly the missing link in many of the wildlife studies to date.

Finally, there are very limited numbers of studies available that allow comparisons of the same species. Instead, hundreds of studies focus on a wide variety of species and chemicals, thus limiting the scientific community’s ability to evaluate the data for consistency in outcomes and trends reported.

Even with the challenges reported above, there are still some positive changes that appear to be occurring. One such change is the trend towards the publication of more wildlife field studies over the

last five years. With the proliferation of such research, more clues will be generated regarding the impact endocrine disruptors have on wildlife. In addition, there appears to be a greater trend toward coordination between agencies and other organizations involved in endocrine disruption research (Reiter et al., 1998). It is likely that such coordination will result in a more focused research agenda and will result in overcoming a number of the challenges raised above. Also, a number of studies appear to be combining the field and laboratory approach, in order to corroborate what appears to be occurring in the field. These hybrid studies not only result in research that can be more easily reproduced in the future, but also allow for better control of confounding variables and chemical concentration assessment. Lastly, methods are being developed (such as 'toxicity equivalency factors', which allows for the comparability of chemical concentrations within the environment) so that these diverse field studies may be more easily compared in the future and adverse trends will become more apparent.

4. CONCLUSION

Is there currently enough scientific evidence to conclude that endocrine disrupting chemicals are adversely affecting wildlife populations? While controlled laboratory investigations demonstrate that certain synthetic and naturally occurring chemicals can affect the endocrine systems of birds, fish, mammals, reptiles and amphibians, the evidence is not clear for similar exposures in the environment. There are few definitive studies establishing that endocrine disruptors affect wildlife under field conditions. Thus the concern for effects on wildlife is based on a preponderance of circumstantial evidence and the reasonable possibility that endocrine disruptors *could* cause harmful effects to wildlife. Many factors, including the effects from endocrine disruptors, could be responsible, either alone or in combination, for some of the outcomes noted in the literature reviewed for this report. Therefore, while there is a biological basis upon which to assume that the chemical effects would be similar in the field, other mediating factors may impact their presence, potential for exposure or uptake in the wild. This is not unlike our understanding of many non-endocrine disrupting chemicals. Until many of these issues are resolved, the controversy over whether endocrine disruptors are present in the environment at levels that may cause adverse effects in wildlife remains an open question.

5. DIRECTIONS FOR FUTURE RESEARCH

This review of the literature on endocrine disruptors represents a focused look at the continually increasing research in this area. Even from this focused review, however, it was possible to identify several gaps in the state of the science on endocrine disrupting chemicals in wildlife and directions for future research.

As discussed, we found a lack of research that identified thresholds and dose responses for chemicals that have endocrine disrupting effects. There were data on no-effect and effect levels for only four of the 69 different chemicals studied (refer to Policy Question #2) and these data were very limited. However, without controlled dose-response experiments to definitively determine the threshold where these chemicals begin to show endocrine disruption, it is difficult to point to concentrations of these chemicals in the environment that may be harmful to wildlife. In addition, without knowing the precise concentrations of chemicals in the environment that are responsible for endocrine disrupting effects, it is difficult to distinguish between effects caused by anthropogenic sources and naturally occurring phytoestrogens. Therefore future research should focus on acquiring data on chemical concentrations of endocrine disruptors in the environment--both at baseline levels and also after an exposure has occurred. Additionally, a framework to review research on endocrine disruptors would go a long way toward addressing our inability to aggregate data from the various studies.

Another area of investigation that warrants further attention is whether effects attributed to endocrine disruptors are really occurring through a mechanism of action unique from that of other toxic chemicals. For example, one effect commonly attributed to endocrine disrupting chemicals is embryonic mortality. However, many toxic chemicals that have no endocrine disrupting properties, such as cyanide, botulinum toxin and strychnine, may also cause embryonic mortality. Another effect commonly attributed to endocrine disrupting chemicals is cancer. However, many carcinogenic chemicals, such as benzene and radon, have no endocrine disrupting properties.

Currently most work on endocrine disruptors in wildlife is focused on local problems of interest to individual investigators, resulting in a hodge-podge of studies on numerous chemicals across numerous taxa and species. This makes comparisons of the effects of endocrine disrupting chemicals very difficult. In addition, very few studies combine field observations with controlled laboratory experiments. Without these combined field/laboratory study designs, it is difficult to: 1) determine dose-response effects; 2) establish threshold levels of concern; and 3) discern the effects of individual chemicals that are usually found in complex mixtures in the environment. The directions for future research described above would be beneficial to understanding of endocrine disrupting chemicals.

APPENDIX A: ENDOCRINE DISRUPTOR LIST, GROUP A

Common Name	Sub Group Common Name	CAS Number *	IUPAC/Scientific Name **	Type
DBCP		96-12-8	1,2-dibromo-3-chloropropane	N
2,4,5-T		93-76-5	2,4,5-trichlorophenoxyacetic acid	H
2,4-D		94-75-7	2,4-dichlorophenoxyacetic acid	H
Alachlor		15972-60-8	2-chloro-N-(2,6-diethylphenyl)-N-(methlxymethyl)acetamide	H
Aldicarb		116-06-3	methyl-2-(methylthio)propionaldehyde o-(methylcarbamoyl)oxime	N
Aldrin		309-00-2	hexachloro-1,4,4a,5,8,8a-hexahydro-endo-1,4-exo-5,8-dimethanonaphthalene	I
Amitrole (Aminotriazole)		61-82-5	3-amino-1,2,4-triazole	H
Atrazine		1912-24-9	chloro-4-(ethylamino)-6-(isopropylamino)-S-triazine	H
Benomyl		17804-35-2	methyl-1-(butylcarbamoyl)-2-benzimidazolecarbamate	F
Lindane	a-BHC	319-84-6	(1-a,2-a,3-b,4-a,5-b,6-b)-1,2,3,4,5,6-hexachlorocyclohexane	I
Lindane	b-BHC	319-85-7	(1-a,2-b,3-a,4-b,5-a,6-b)-1,2,3,4,5,6-hexachlorocyclohexane	I
Lindane	HCB	118-74-1	hexachlorobenzene	I

* Chemical Abstracts Service Registry number
** International Union of Pure and Applied Chemistry

Type:
B: Biocide
I: Insecticide
H: Herbicide
N: Nematoxide
F: Fungacide
C: Industrial Organic Chemical
M: Metal

Common Name	Sub Group Common Name	CAS Number *	IUPAC/Scientific Name **	Type
Lindane	g-BHC (True Lindane)	58-89-9	g-benzene hexachloride	I
Lindane	g-HCH	58-89-9	(1-a,2-a,3-b,4-a,5-a,6-b)-1,2,3,4,5,6-hexachlorocyclohexane	I
Lindane	a-HCH	319-84-6	a-1,2,3,4,5,6-hexachlorocyclohexane	I
Lindane	b-HCH	319-85-7	b-1,2,3,4,5,6-hexachlorocyclohexane	I
Bisphenol-A		80-05-7	4,4'-dimethylmethylenediphenol	C
butyl- to nonylphenols	p-nonylphenol	104-40-5	4-nonylphenol	C
butyl- to nonylphenols	p-octylphenol	1806-26-4	4-octylphenol	C
butyl- to nonylphenols	p-sec-butylphenol	99-71-8	p-sec-butylphenol	C
butyl- to nonylphenols	p-tert-butylphenol	98-54-4	4-tert-butylphenol	C
butyl- to nonylphenols	p-tert-pentylphenol	80-46-6	p-(a,a-dimethylpropyl)phenol	C
Cadmium		7440-43-9	cadmium	M
Carbaryl		63-25-2	1-naphthyl-N-methylcarbamate	I
Chlordane		57-74-9	1,2,4,5,6,7,8,8-octa-8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindan	I
Chlorobenzene		108-90-7	Chlorobenzene	C

* Chemical Abstracts Service Registry number
** International Union of Pure and Applied Chemistry

Type:
B: Biocide
I: Insecticide
H: Herbicide
N: Nematoxide
F: Fungacide
C: Industrial Organic Chemical
M: Metal

Common Name	Sub Group Common Name	CAS Number *	IUPAC/Scientific Name **	Type
Cyanazine		21725-46-2	Chloro-4-(1-cyano-1-methylethyl)amino)-6-(ethylamino)-s-triazine	
DDT		50-29-3	2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane	I
DDT metabolite	DDD	72-54-8	2,2-bis-(4-chlorophenyl)-1,1-dichloroethane	I
DDT metabolite	DDE (p,p'-DDE)	72-55-9	2,2-bis(4-chlorophenyl)-1,1-dichloroethylene	I
Dicofol (Kelthane)		115-32-2	1,1-bis-(chlorophenyl)-2,2,2-trichloroethanol	I
Dieldrin		60-57-1	(1a-a,2-b,2a-a,3-b,6-b,6a-a,7-b,7a-a)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene	I
dioxin (PCDD)	2,3,7,8-TCDD	1746-01-6	2,3,7,8-tetrachlorodibenzodioxin	C
Endosulfan		115-29-7	6,9-methano-2,4,3-benzodioxathiepin,6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-3-oxide	I
Endrin		72-20-8	1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo-endo-5,8-dimethano-naphthalene	I
Esfenvalerate		66230-04-4	[S-(R*,R*)]-4-chloro-a-(1-methylethyl)benzeneacetic acid cyano(3-phenoxyphenyl)methyl ester	I

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Type:
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M: Metal

Common Name	Sub Group Common Name	CAS Number *	IUPAC/Scientific Name **	Type
Fenoxycarb		72490-01-8	ethyl-(2-(4-phenoxyphenoxy)ethyl)carbamate	I
Fenvalerate		51630-58-1	cyano-(3-phenoxyphenyl)methyl-4-chloro-a-(1-methylethyl)benzene acetate	I
Furans (PCDF)	2,3,7,8-TCDF	51207-31-9	2,3,7,8-tetrachlorodibenzofuran	C
Heptachlor		76-44-8	3,4,5,6,7,8,8a-heptachlorodicyclopentadiene	I
Heptachlor epoxide		1024-57-3	2,3,4,5,6,7,7-heptachloro-1a,1b,5,5a,6,6a-hexahydro-2,5-methano-2H-indeno[1,2-b]oxirene	I
Iprodione		36734-19-7	3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide	I
Kepone (Chlordecone)		143-50-0	1,1a,3,3a,4,5,5,5a,5b,6-decachlorooctahydro-1,3,4-metheno-2H-cyclobuta[c,d]pentalen-2-one	I
Lead		7439-92-1	lead	M
Malathion		121-75-5	diethyl [(dimethoxyphosphinothioyl)thio]butanedioate	I
Mancozeb		8018-01-7	manganese (II) ethylenebis (dithiocarbamate)	F
Maneb (EBDC fungicides)		12427-38-2	manganese ethylenebisthiocarbamate	F
Mercury		7439-97-6	mercury	M

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Common Name	Sub Group Common Name	CAS Number *	IUPAC/Scientific Name **	Type
Methomyl		16752-77-5	methyl N-(methylamino)carbonyl)oxy)ethanimidothioate	I
Methoxychlor		72-43-5	2,2-bis(p-methoxyphenyl)-1,1,1-trichloroethane	I
Metiram		9006-42-2	tris(amine)(ethylenebis(dithiocarbamato)zinc(2+)(tetrahydro-1,2,4,7-dithiadiazocene-3,8-dithione), polymer	F
Metribuzin		21087-64-9	4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one	H
Mirex		2385-85-5	1,2,3,4,5,5-hexachloro-1,3-cyclopentadiene dimer	I
Nitrofen		1836-75-5	2,4-dichloro-1-(4-nitrophenoxy)benzene	H
Octachlorostyrene		29082-74-4	pentachloro(trichloroethenyl)benzene	C
Oxychlordane		27304-13-8	octachlor epoxide	I
Parathion		56-38-2	diethyl-p-nitrophenyl monothiophosphate	I
PBB (mixture)		67774-32-7	polybrominated biphenyl	C
PCBs	3,3’,4,4’,5,5’-hexachlorobiphenyl	26601-64-9	3,3’,4,4’,5,5’-hexachlorobiphenyl	C
PCBs	3,3’,4,4’,5-pentachlorobiphenyl	25429-29-2	3,3’,4,4’,5-pentachlorobiphenyl	C

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Common Name	Sub Group Common Name	CAS Number *	IUPAC/Scientific Name **	Type
PCBs	3,3′,4,4′-tetrachlorobiphenyl	32598-13-3	3,3′,4,4′-tetrachlorobiphenyl	C
PCBs	Aroclor 1254	27323-18-8	polychlorinated biphenyls	C
Pentachlorophenol (PCP)		87-86-5	2,3,4,5,6-pentachlorophenol	C
Permethrin		52645-53-1	(1RS)-cis,trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate	I
Polycarbonates				C
Pyrethroids	allethrin	584-79-2	2-methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate	I
Pyrethroids	cypermethrin	52315-07-8	3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid cyano(3-phenoxyphenyl)methyl ester	I
Selenium		7782-49-2	Selenium	M
Styrene		100-42-5	vinyl benzene	C
Toxaphene		8001-35-2	mixture of many chemicals	I
trans-Nonachlor		39765-80-5	4,7-methano-1H-indene, 1,2,3,4,5,6,7,8,8-nonachloro-2,3,3a,4,7,7a-hexahydro-, (1-a,2-b,3-a,3a-a,4-b,7-b,7a-a)-	I
organotin compounds	tributyltin (TBT)	56-35-9	bis-(tri-n-butyltin) oxide	B, F,C
organotin compounds	tributyltin methacrylate	2155-70-6	tributyl(2-methyl-1-oxo-2-propenyl)oxy)stannane	B

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Common Name	Sub Group Common Name	CAS Number *	IUPAC/Scientific Name **	Type
organotin compounds	triphenyltin acetate	900-95-8	triphenyltin acetate	B
organotin compounds	triphenyltin hydroxide	76-87-9	triphenyltin hydroxide	B
trifluralin		1582-09-8	a,a,a-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine	H
Vinclozolin		50471-44-8	3-(3,5-Dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedione	I
Zineb		12122-67-7	zinc ethylene-1,2-bisdithiocarbamate	F
Ziram		137-30-4	zinc dimethyldithiocarbamate	F

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APPENDIX B: ENDOCRINE DISRUPTOR LIST, GROUP B

Common Name	Sub Group Common Name	CAS Number*	IUPAC/Scientific Name**	Type
2,4-Dichlorophenol		120-83-2	4,6-dichlorophenol	C
Chlorpyrifos (Dursban)		2921-88-2	phosphorothioic acid o,o-diethyl o-(3,5,6-trichloro-2-pyridinyl) ester	I
Diflubenzuron		35367-38-5	N-((4-chlorophenyl)amino)carbonyl)-2,6-difluorobenzamide	I
Phthalate	butylbenzyl phthalate (BBP)	85-68-7	1,2-benzenedicarboxylic acid butyl phenylmethyl ester	C
Phthalate	di-n-butyl phthalate (DBP)	84-74-2	1,2-benzenedicarboxylic acid dibutyl ester	C
Phthalate	di-n-pentyl phthalate (DPP)	131-18-0	1,2-benzenedicarboxylic acid, dipentyl ester	C
Phthalate	dicyclohexyl phthalate (DCHP)	84-61-7	1,2-benzenedicarboxylic acid, dicyclohexyl ester	C
Phthalates	dihexyl phthalate (DHP)	84-75-3	1,2-benzenedicarboxylic acid, dihexyl ester	C
Phthalates	diethyl phthalate (DEP)	84-66-2	1,2-benzenedicarboxylic acid diethyl ester	C
Phthalates	diethylhexyl phthalate (DEHP)	117-81-7	1,2-benzenedicarboxylic acid bis(2-ethylhexyl) ester	C
Phthalates	dipropyl phthalate (DprP)	131-16-8	1,2-benzenedicarboxylic acid, dipropyl ester	C

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APPENDIX C: ENDOCRINE DISRUPTOR LIST, GROUP C

Common Name	Sub Group Common Name	CAS Number*	IUPAC/Scientific Name**	Type
Indeno(1,2,3-cd)pyrene		193-39-5	o-phenylenepyrene	C
p-nitrotoluene		99-99-0	4-nitrotoluene	C
PAH	acenaphthene	83-32-9	1,8-ethylenenaphthalene	C
PAH	anthracene	120-12-7	paranaphthalene	C
PAH	benz(a)anthracene	56-55-3	1,2-benzanthracene	C
PAH	benzo(a)pyrene	50-32-8	3,4-benz[a]pyrene	C
PAH	benzo(b)fluoranthene	205-99-2	3,4-benzofluoranthene	C
PAH	benzo(k)fluoranthene	207-08-9	8,9-benzofluoranthene	C
PAH	benzophenone	119-61-9	diphenyl ketone	C
PAH	chrysene	218-01-9	1,2,5,6-dibenzonaphthalene	C
PAH	phenanthrene	85-01-8	phenanthrene	C
pyrene		129-00-0	benzo[def]phenanthrene	C

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N: Nematoxide
F: Fungacide
C: Industrial Organic Chemical
M: Metal

APPENDIX D: DATABASE VARIABLES

- First author
- Second author
- Year of publication
- Project reviewer
- Source (Wingspread I, Wingspread II, Wingspread III, Wingspread IV, EPA Risk Assessment Forum, EPA Workgroup/Ankley, EPA Workgroup/Kavlock, other)
- Paper type (primary, review, reanalyzed, other)
- Scientific certainty score (1-5)
- Chemical name
- Study site
- Taxa (aves/birds, mammalia/mammals, pisces/fish, reptilia/reptiles, amphibia/amphibians)
- Scientific name (genus, species)
- Common name
- Gender
- Study type (field, laboratory, field/laboratory)
- Exposure route
- Developmental stage at time of exposure
- Application rate
- Ambient concentration
- Body burden
- Other
- General outcome
- Specific outcome
- Study result (positive, negative)
- Comments

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