Workshop on Perinatal Exposure to Dioxin-like Compounds. I. Summary

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An international workshop reviewed 20 ongoing or recently completed studies of the effects of perinatal exposures to dioxins, dibenzofurans, and PCBs on the reproductive, endocrine, neurodevelopmental, and immune systems. Many of the observed effects are consistent with these compounds acting as "environmental hormones" or endocrine disrupters. This report summarizes the conclusions and future directions described at the workshop. — Environ Health Perspect 103(Suppl 2):135–142 (1995)

Key words: PCB, PCDD, PCDF, perinatal, transplacental, lactational, reproduction, endocrinology, neurobehavior, immunology

Background

A workshop was organized by the Hazardous Materials Laboratory of the Cal EPA on June 13–15, 1993 in Berkeley, California, to consider the effects on the reproductive, endocrine, neurodevelopmental, and immune systems in infants from perinatal exposures to polychlorinated dioxins, dibenzofurans, and biphenyl mixtures. The workshop, co-sponsored by the U.S. Environmental Protection Agency, National Institute of Environmental Health Sciences, and the California Public Health Foundation, convened an international group of scientists with expertise in pediatrics, chemistry, epidemiology, toxicology, endocrinology, and the reproductive and behavioral sciences to review and discuss current, recently completed, or planned studies of the effects of perinatal exposures to these compounds on the newborn.

The phrase "dioxin-like compounds" (DLCs) used in the workshop title refers to agents that bind to the Ah receptor. These include representatives of the coplanar, halogen-substituted multiring structures such as the polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and some of the coplanar congeners in the polychlorinated biphenyl (PCB) mixtures. The most toxic and well studied of these is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

The objectives of the workshop were: to review the current status of research in the field through presentations by researchers of ongoing, completed or planned studies; to provide a multidisciplinary forum to share insights on the different effects of exposures to DLCs, and to review the use of biomarkers in perinatal studies; and to strengthen future research by establishing contacts and encouraging collaborations between research groups and by setting priorities for future studies.

Organization

The effects of perinatal exposures on the reproductive, endocrine, neurodevelopmental, and immune systems of the offspring were discussed in consecutive sessions, and are summarized in this report. Appendix 1 presents a summary, in chronological order, of all of the studies presented in the workshop sessions, identifying for each the investigator, study design, measures of effect, measures of exposure (compounds under study, source of exposure, matrix/tissue analyzed for dose level), and study conclusions. Fuller descriptions of these studies are given in the accompanying articles, authored by the co-chairs of each session.

In the opening session, speakers gave background information and outlined the task of the workshop. A. Gilman emphasized that organochlorine residues (OCs) continue to persist in the environment. Although the levels of many OCs in western nations have declined over the past decade, populations in different parts of the world show significant deviations from these trends. Increased global use of some persistent OCs, e.g., DDT, toxaphene, PCBs, which are banned or severely restricted in western nations, has led to increased levels of OCs in the Arctic ecosystem. Total global use of DDT may, in fact, be greater in this decade than in the 1970s, when it was banned in North America. U. Ahlberg stated that concern over widespread distribution of these compounds, especially the dioxins, dibenzofurans, and PCB mixtures, and the health consequences of perinatal exposures, have led to the initiation of risk assessments by the World Health Organization (WHO).

The next two speakers contrasted exposures of infants and adults. L. Goldman described several factors that place infants at higher risk than adults from exposures to OCs: physiologic factors (lower barriers to absorption through skin, GI tract, and lungs; lower levels of detoxifying enzymes at birth); nutritional factors (breast milk as major source of nutrition; higher caloric intake per body weight); and behavioral factors (closer dermal contact with the outside and household environments; hand-to-mouth exploratory behavior). G. Lindstrom indicated that nursing infants retain almost all of the 2,3,7,8-substituted dioxins and furans that they ingest from breast milk. Nursing infants, on a body-weight basis, have a dietary intake of TCDD and its equivalents (I-TEQs) that is 100-fold greater than adults; uncorrected for body weight, infant dietary intake is 10-fold higher than in adults. Exposure of the fetus is also significant, even though transfer of DLCs from the placenta to the fetus...
is incomplete (i.e., levels in the mother are higher than levels in the fetus).

W. Rogan and J. Jacobson described their published work which identified develop-
mental (growth retardation and ectoder-
mal abnormalities) and neurobehavioral
(cognitive and motor functions) deficits in
children whose mothers consumed PCB-
contaminated cooking oil or large amounts
of OC-contaminated fish during pregnancy
(14,15,17-19,23,24). The possibility that
these exposures cause delayed or long-term
effects, as suggested by animal studies, has
prompted followup, second-generation
reproduction studies of exposed cohorts in
Seveso, Italy and in Taiwan by P. Mocarelli
and W. Rogan, respectively.

Conclusions and Future Directions

Overall conclusions from the workshop, as
well as recommendations for future
research, are listed below. Following these,
conclusions and research needs are given
for each study area covered by a workshop
session (reproductive, endocrine, neurode-
velopmental, and immune toxicity).

General

Conclusions

The current dominant paradigm is that the
biological activities of TCDD and the DLCs
arise from their binding to the Ah receptor,
and the biological effects that occur are
believed to be Ah receptor-mediated.

Some components of PCB mixtures
(DLCs) bind tightly to the Ah receptor and
are believed to operate via Ah receptor-
dependent mechanism(s). Other compo-
nents do not, and must act through mecha-
nisms that are independent of the Ah recep-
tor (including phenobarbital-type induction
of drug-metabolizing enzymes, binding to
other (e.g., estrogen or thyroid hormones)
receptors, or altering biogenic amine concen-
trations). Other PCB components may act
via both Ah receptor-dependent and recep-
tor-independent mechanisms.

There is a similarity in response in ani-
mals and humans to TCDD and DLCs.
For every end point examined, human
response is replicated in some species of
laboratory animal: growth retardation
(monkeys, rats), ectodermal effects (mon-
keys), spatial learning/memory deficits
(monkeys, rats), and changes in lympho-
cyte subpopulations (monkeys). For well-
studied human end points such as chlorac-
ne and enzyme induction, homology exists
with several animal species.

A working hypothesis for the mechanism
of action of TCDD and DLCs is that they
act as endocrine disruptors or "environment-
al hormones" in perinatal systems. In this
way, they provide inter- or intra-cellular
signals that alter growth, differentiation and
function of cells in a tissue-, stage-, or cell-
specific manner.

Consistent with this hypothesis, TCDD and DLCs have been demonstrat-
ed to act as multisystem effectors, affecting
the developing immune, neurobehavioral,
endocrine, and reproductive systems.

As hormones or endocrine disruptors,
they may cause neoplasia by altering
patterns of differentiation/proliferation
of specific tissues in the developing or adult
organism.

Research Needs

More interaction is needed among laborato-
ry researchers, epidemiologists, and biosta-
ticians. Collaboration between laboratory
researchers and epidemiologists enables ani-
mal data to generate hypotheses for human
studies, and vice versa. Human and animal
studies need biostatistical support so that
data are useful for hazard identification, risk
assessment, and public health intervention.

Summaries are needed of human and
animal studies (male and female) of each
organ system. These summaries would
describe exposure or dose levels, nature of
effects, strength of evidence, and confi-
dence in the studies.

Better data are required for exposure
assessment.

The prenatal period is a sensitive period
(see animal and human studies) and needs
further study.

Research is needed in human popula-
tions to investigate the potential for
delayed effects in the reproductive, neu-
robehavioral, and neuroendocrine systems,
especially among postpubescent cohorts
exposed perinatally.

Reproductive Effects

Conclusions

PCB mixtures cause different reproductive
effects than DLCs. Lactational exposures
to PCB mixtures (Aroclor 1254) cause
infertility in male rat offspring without
affecting their sperm count (37). TCDD
decreases sperm count but does not affect
fertility (4, 5). Components of PCB mix-
tures may act like phenobarbital-type
inducers, estrogens, or effectors of thyroid
status or dopamine levels, while DLCs pre-
sumably operate through the Ah recep-
tor-mediated events.

TCDD reduced fertility in female mon-
keys (1) and may exacerbate endometriosis
(38). In utero and lactational exposures to
TCDD caused changes in sexual differenti-
ation in rat pups: feminization of males
(reduced anogenital distance, sperm count,
and accessory sex glands; abnormal mount-
ing behavior) and urogenital abnormalities
in females (absent vaginal openings, cleft
clitoris) (2,4,5).

PCB congeners produced growth retar-
dation in offspring of dosed female rats
(3); chronic PCB exposures in female
monkeys produced growth retardation in
offspring (1); and infants born to mothers
exposed to PCB/PCDF-contaminated rice
oil or contaminated fish had low birth
weights (14-23).

Birth size among male infants (Inuits)
was inversely related to PCB concentration
in breast milk of the mother (7,29).

Research Needs

The effects of perinatal exposures to
TCDD and DLCs on the reproductive sys-
tem of adult males are reasonably well-
described; information is needed on mech-
anism(s) (e.g., effects on spermatogenesis
and sexual differentiation).

Research is needed on the effects of
these compounds on nonpregnant females
(e.g., age at menarche, cyclicity, time to
conception, and endometriosis).

Animal studies indicate delayed effects
of perinatal exposures on reproductive sys-
tems. Perinatally exposed cohorts need to
be followed beyond puberty and examined
for delayed effects such as age at onset of
puberty, age at menarche, reduced fertility,
abnormal cyclicity, decreased sperm count,
and premature menopause.

Endocrine Effects

Conclusions

Exposures of pregnant female rats to small
amounts of TCDD caused changes in
indices of androgenic status in male off-
spring: spermatogenesis was inhibited; sex-
ual behavior and the pattern of LH secre-
tion was less masculine and more feminine
(2,4,5).

Prenatal exposures to specific PCBs
(#118, #153) reduced brain levels of T4 in
offspring of exposed female rats (3).

Other specific PCB congeners (#77,
#47) caused age-dependent changes in bio-
genic amine neurotransmitter levels in rats:
in adults dopamine levels were reduced by
ortho, but not coplanar, PCBs; dopamine
levels were raised by perinatal exposures to
either (9,12).

TCDD reduced responsiveness of
ventral prostate to testosterone in male

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offspring of dosed female rats without affecting responsiveness of seminal vesicles (4).

TCDD also inhibited sexual differentiation in the CNS without altering sexual dimorphisms in estrogen-receptor concentrations or volumes of brain nuclei (5).

Research Needs
The mechanistic relationships between DLCs, T4 and the neurodevelopmental system need further study.

Studies should focus on measurements of T4, TSH, and TRH, especially at different levels in the neuroendocrine axis.

Levels of both free and bound T3 should be examined.

More studies on binding of PCBs, metabolites, and DLC congeners to TBG and TTR are needed. Binding to TTR in rodents is important; the significance of the small amount of DLC-binding to TTR in humans should be explored.

Estrogen, testosterone, and corticosteroid levels should be measured in younger cohorts.

Neurobehavioral Effects
Conclusions
Neurobehavioral effects (spatial learning/memory and motor deficits) may arise from complex interactions between neuroendocrine and neurophysiological systems (e.g., specific PCB congeners decrease levels of dopamine in prefrontal cortex of adults, as well as decrease brain levels of T4 in offspring of dosed female rats, possibly affecting neuronal branching) (3,8–13).

Perinatal exposures of monkeys to PCB mixtures, and of rats to specific PCB congeners produced spatial learning/memory deficits (10–13). Cognitive functioning was impaired among children exposed in utero to mixtures of OCs, including PCBs (14,15). PCBs produced motor deficits that persisted to age 2 among children exposed in utero (17–21,23).

Research Needs
Studies employing specific PCB congeners are needed to investigate the associations between perinatal DLC exposures, spatial learning/memory deficits, and levels of dopamine and T4 in specific regions of the brain.

Test batteries for neurobehavioral effects should include standardized, narrow-band, and challenge or stress tests.

Studies of neurobehavioral effects of chemicals are difficult because known environmental factors can overwhelm any effect of the chemical. In rats, sexual differentiation of the CNS is affected by perinatal exposures to TCDD (2,4,5). In humans, our ability to examine this association between DLCs and sexual differentiation awaits the development of measures that are less affected by confounding social/"environmental" factors.

Reliable measures of disease end points are required (e.g., health care providers in clinic networks should be trained to rate neurobehavioral deficits by consistent criteria).

Immunologic Effects
Conclusions
A working hypothesis is that perinatal exposures to DLCs and PCBs alter the pattern of differentiation of cells of the immune system and, as a consequence, change the responses of immune cells. The extent and magnitude of these changes depend upon when in the development of these cells the exposures occur: exposures early in development will affect the primordial stem cells, while later exposures affect cells in a more developed system.

The thymic atrophy caused by TCDD may arise in part from the depletion by TCDD of prolymphocytes in the bone marrow. TCDD-induced thymic atrophy is accompanied by decreases in lymphocyte stem cell markers which are present only in bone marrow prothymocytes (terminal deoxynucleotidyl transferase (TdT) and recombinase activating gene (RAG) (27,28). In irradiated mice, TCDD-treated prothymocytes are unable to repopulate the thymus.

DLCs may affect the primary antibody response in humans (Inuits—PCBs and dioxins) (29) and rodents (mice—TCDD) (27,28,34,35) prenatal exposure decreases the ratio of T helper to T suppressor cells in the thymus.

TCDD may have immune-suppressive or immuno-enhancing effects in rodent species (26). Perinatal exposures to animals affect mainly T cell responses (27,28).

Perinatal exposures to PCBs affect primary antibody response, as suggested by a 20-fold higher incidence of infectious diseases (e.g. meningitis, measles) and ear infections (otitis media among 1-year-old Inuits with high PCB exposures) than among lesser exposed controls (7,29); by a low immunization rate among Inuits compared to controls (7,29); and by changes in ratios of lymphocyte subpopulations in animals and humans (7,26–30,34,35).

Research Needs
Biomarkers of immunotoxicity continue to be developed; the effect of TCDD and PCBs on lymphocyte subset ratios (e.g., CD4/CD8) is still unclear in animals and humans.

Studies are needed on the primary antibody response in children with high PCB exposures, possibly employing vaccine challenge tests.
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### Appendix 1. Studies on perinatal exposure to dioxin-like compounds presented at workshop.

| Study, presenter | Study design | Effect measures | Compound(s) | Exposure | Matrix/dose | Conclusions | References |
|------------------|--------------|-----------------|-------------|----------|-------------|-------------|------------|
| Reproduction Ayotte P | Measures of effect following *in utero* exposure of Inuits to PCBs and related contaminants | P450 induction, Ah receptor, stress protein, T-cell subsets, natural killer cell assay, primary antibody response, SCE, birth weight | PCBs (congener specific), organochlorine compounds, PCDD/PCDFs | Transplacental: maternal ingestion of fish and sea mammals | Placenta, cord blood | Chronic exposure to PCBs at 100 µg/kg produced lower fertility and abnormal finger and toenails; 25 µg/kg resulted in decreased bw and growth of offspring. | (1) |
| Reproduction Buck G | Prospective cohort of 11,717 anglers and 6,579 wives/partners. Exposure vs reproductive/developmental end points and selected chronic diseases | Standardized fertility rates; fetal growth and birth size; subclinical health effects | 68 PCBs, PCDD, PCDF, DDT, DDE, Hg, Pb, mirex, and hexa chlorobenzene | Transplacental: ingestion of sports fish (paternal, maternal consumption) | Lifetime and pregnancy-specific consumption, serum profiles, breast milk levels. | Study in progress | |
| Reproduction Cimianec J | Reproductive study of rhesus monkeys exposed to Aroclor 1254 | Body weight, hematology, serum, urinalysis, semen, fertility, clinical changes | Aroclor 1254 | Transplacental | 0, 5, 25, 100 µg/kg, 14 months | Chronic exposure of female rhesus monkeys to PCBs at 100 µg/kg resulted in decreased bw and growth of offspring. | |
| Reproduction Gray LE | Perinatal TCDD exposure of female and male LE hooded rats | Sex differentiation, urogenital malformations, sperm count, mating behavior | TCDD | Transplacental: lactational | 1µg/Kg on GD 8 and GD 15 | Perinatal exposure to TCDD affected sexual differentiation in male and female offspring of dosed female rats: males had reduced sperm count and changes in sex accessory glands; females had urogenital abnormalities. | (2) |
| Endocrine Schantz SL | Thyroid hormones and brain development in Sprague-Dawley rats exposed to PCBs | Weights of liver, brain and thyroid; total serum T3, T4; histological evaluation of thyroid; reproductive and developmental parameters | PCBs # 28, 118, 153 | *In utero* and lactational exposure | Dosing of dams with PCBs: | Perinatal exposure to two PCB congeners (118 and 153) produced lower T4 concentrations and growth retardation in offspring of dosed female rats. | (3) |
| Endocrine Moore R | *In utero* and lactational TCDD exposure in rats. Effects on: responsiveness to androgens in adulthood; sexual differentiation of CNS; spermatogenesis | Sex organ weight; DNA, protein, testosterone, 5a-dihydrotestosterone; sexually dimorphic nuclei; volumes and estrogen receptor distributions; Sertoli cell division; testis DNA ploidy | TCDD | *In utero* and lactational exposure in rats | Single oral maternal dose: 0.7µg/kg on GD 15 | Perinatal exposure to TCDD reduced responsiveness of ventral prostate to testosterone in male offspring of dosed female rats, with no effect on the responsiveness of seminal vesicles. TCDD did not affect sexual dimorphism in brain morphology. | (4,5) |
| Study, presenter               | Study design                                           | Effect measures                                                                 | Compound(s)                                                                 | Exposure | Matrix/dose               | Conclusions                                                                                     | References |
|-------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------|---------------------------|-----------------------------------------------------------------------------------------------|------------|
| Endocrine Koopman- Essebon C  | Prenatal, postnatal effects of PCBs and dioxins on human infants | Growth, neurologica l, psychomotor development; thyroid hormone metabolism (TT4, TT3, TT4, TSH) | PCBs, PCs (118, 138, 153, 180) PCDDs, PCDFs, coplanar PCBs | In utero | Maternal plasma, umbilical cord plasma | Breast milk                                                                                   | (6)        |
| Endocrine Dewailly E          | Effects of prenatal exposure to PCBs, PCDDs and PCDFs on TSH in the Inuit population | TSH and clinical parameters: weight, height, cranial and thoracic circumference | PCBs (# 28, 52, 10, 118, 138, 153, 170, 180, 183, 187) and eight chlorin. pesticides | In utero | In utero exposure assessed by breast milk levels | For male infants, birth size inversely related to PCB concentrations in breast milk of the mother. | (7)        |
| Neurobehavior Seegal R        | Comparison of effects of Aroclor 1016 and 1260 on nonhuman primates | Alteration in brain biogenic amine concentrations (decreases exp. in DA concentrations); alterations in brain biogenic amines; increases of biogenic amine concentrations | Aroclor 1016 and 1260 Aroclor 1016, PCBs (77, 47) | Adult exposure for 20 weeks (0.8–3.2 mg/kg/day) | Brain tissue (caudate, hypothalamus, substantia nigra putamen); Brain tissue (see above) | PCBs cause age-dependent neurochemical changes: in adults, o-substituted, but not coplanar, PCBs reduce neurotransmitter (dopamine) levels; in newborns, perinatal exposure to o-substituted or coplanar PCBs elevates dopamine. | (8,9)      |
| Neurobehavior Schantz SL       | Effects of PCB congeners and mixtures on cognitive functioning in rats and monkeys | Cognitive functioning | Aroclor 1248 PCBs (28,118 and 153) | In utero and lactational | Chronic exposure (monkeys) | GD 10–16 (rats) | Perinatal exposure of monkeys (chronic; PCB mixtures) and rats (GD 10–16; PCB 28, 118 [mono-o], 53 (di-o) produced spatial learning/memory deficits, suggesting changes in prefrontal cortex. | (10–13)   |
| Neurobehavior Jacobson J       | Effects of in utero exposure to PCBs and related contaminants on physical growth; cognitive functioning in children | Cognitive functioning, physical growth | Aroclor 1260 | Transplacental; lactational | Umbilical cord serum, breast milk | Short-term memory/attention and physical growth impaired among children with in utero exposure to PCBs. | (14,15)   |
| Neurobehavior Rogan W          | Perinatal PCB exposure and child development in North Carolina (n=930) | Morbidity, developmental delay (Brazelton, Bayley, McCarthy Scales) | PCBs, DDE PCBs, PCDFs (degraded PCB oil) | Transplacental; lactational | Cord blood, breast milk, formula | In North Carolina, prenatal exposure to PCBs produced motor deficits among children: at birth, the more highly exposed were hypotonic and hyporeflexic. In Taiwan, perinatal exposures to degraded PCB oil caused growth retardation, cognitive deficits, and ectodermal abnormalities, including excess pigmentation, deformed nails, and hirsuitism. | (16–24)   |
| Study, presenter       | Study design                                                                 | Effect measures                                                                 | Compound(s)     | Exposure            | Matrix/dose                  | Conclusions                                                                 | References |
|-----------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------|---------------------|-----------------------------|-----------------------------------------------------------------------------|------------|
| Neurobehavior         | Quantitative EEG and lymphocyte phenotype assessment after exposure to dioxin | Frontal lobe abnormalities in elect. conductivity, CD4/CD29 and λ & κ light chain depression, attention/conc. deficits, incr. rates of respiratory infections | TCDD            | Transplacental       | TCDD levels of 0.02 to 2.2 ppb measured in house dust 10 years post exposure | At incompletely assessed exposure levels, frontal lobe abnormalities in EEG activity as compared to EEG measurements of historical controls. Suggestive of effects on attention/concentration and rates of respiratory infections. |            |
| Smoger G              | Times Beach                                                                   |                                                                                                                                          |                 | House dust           |                             | Study to start in September, 1993                                           |            |
| Immunotoxicity        | Neonatal PCB exposure and neurodevelopmental deficits; cohort study           | Immunologic status, thyroid status, neurodevelopment                               | PCBs (#138, 153, 180); Pb, Cd, Hg, Al | Transplacental; lactational | Cord blood, breast milk       | Study in planning phase                                                      |            |
| Weisglas-Kuperus N    | Study of 0- to 2-year-old children exposed to PCBs and heavy metals in utero   | Birth status; physical growth; health status; psychomotor, mental abilities; information processing, neurobehavior                    | PCBs (total); PCDDs /PCDFs; Hg, Pb | Transplacental         | Maternal serum: Aroclor 1260 x = 15.14 μg/L md = 11.0 SD = 12.0 range = 1.6–65.0 | Ongoing study (25)                                     |            |
| Nuckly G              | Study of in utero exposure and effects associated with seafood consumption in the Faeroe Islands | Neurodevelopment                                                                 | PCBs, Hg, Pb, Se | Transplacental       | Maternal hair, cord tissue, cord blood                                   | Study in planning phase                                                      |            |
| Needham L             | Study of in utero exposure and effects associated with seafood consumption in the Faeroe Islands | Neurodevelopment                                                                 | PCBs, Hg, Pb, Se | Transplacental       | Maternal hair, cord tissue, cord blood                                   | Study in planning phase                                                      |            |
| Immunotoxicity        | Effects of 2,3,7,8-TCDD on humoral immunity and lymphocyte sub-populations in mice and rats | Antibody plaque-forming cell (PFC) response to immunization with sheep erythrocytes and splenic lymphocytes; subpopulation analysis | TCDD            | Adult exposure       | Single ip injection of rats or mice at doses ranging from 0.1–30 μg/kg | Species differences were found among adult rodents in the immunotoxic effects of single injections of TCDD (0.1–30 μg/kg); mice were more sensitive, and immunosuppressed; rats were immuno-enhanced, with decreased T suppressor cells (CD4–CD8+), as occurs in a primary antibody response. | (26)       |
| Smialowicz R          | Effects of TCDD on the thymus of mice                                         | Developing T-cells and B-cells, by stem cell markers (TdT and RAG)                | TCDD            | in utero            | Single exposure to dams: 1–30 μg/kg on GD 14–18                          | In mice, fetal thymus more sensitive than adult. Thymic atrophy may result from direct effect of TCDD on bone marrow cells, i.e., TCDD decreases lymphocyte stem cell populations (prothymocytes) and the induced thymic atrophy may result from the inability of prothymocytes to repopulate the thymus. | (27,28)   |
| Gasiewicz T           | Effects of TCDD on the thymus of mice                                         | Developing T-cells and B-cells, by stem cell markers (TdT and RAG)                | TCDD            | in utero            | Single exposure to dams: 1–30 μg/kg on GD 14–18                          | In mice, fetal thymus more sensitive than adult. Thymic atrophy may result from direct effect of TCDD on bone marrow cells, i.e., TCDD decreases lymphocyte stem cell populations (prothymocytes) and the induced thymic atrophy may result from the inability of prothymocytes to repopulate the thymus. | (27,28)   |
| Immunotoxicity | Study design | Effect measures | Compound(s) | Exposure | Matrix/dose | Conclusions | References |
|---------------|--------------|-----------------|-------------|----------|-------------|-------------|------------|
| Dewailly E    | Immune effects in Inuit infants | Humoral and cellular immunity; infectious diseases | PCDD, PCDF, coplanar PCBs, chlor pesticides | In utero, lactational | Breast milk | Higher incidences of infectious diseases (e.g., meningitis, measles, and otitis) in 1-year old Inuit infants than in control population of southern Quebec. Among Inuit infants whose levels of exposure to PCBs, PCDDs, and PCDFs are elevated, some dysfunctional primary immune responses were observed. | (29) |
| Helge H       | Effect of TCDD on lymphocyte subsets and P450A dependent enzyme activity in monkeys, human infants, and children | Lymphocyte subsets by FacScan; breath test (13C-caffeine-methacetin) for P450A activity | TCDD | Monkey (s.c. injection) | Monkeys: 10 ng/kg | Dose-dependent, reversible changes in ratios of lymphocyte subpopulations (especially loss of CD4+CDw29+) and induction of P450A1/P4501A2 in marmosets at doses of 10 ng/kg and below; no difference in lymphocyte ratios from breastfed and formula-fed infants. | (30–35) |
| Biomarkers    | Biochemical responses in exposed human populations | Ah receptor levels, Cyp1A1, TNF, clinical endpoints, health surveys | TCDD | Adult occupational and accidental exposure | Chronic exposure (Boehringer) Acute exposure (Seveso) | Ongoing studies of populations (Seveso and Boehringer cohorts) with exposures to TCDD in which levels of Ah receptor, CYP1A1, TNF and IL-1B genes are measured. | (36) |