The LSE tables and figures are generated from the supplemental document database, and the way that studies are entered into the supplemental database determines their representation in the LSE tables and figures.

Proper entry of data in the supplemental tables provides that each study, species, duration, major effect category, and study protocol is represented with a different key number in the LSE tables and figures across major effect categories (i.e., death, systemic, immunological, neurological, reproductive, developmental, and cancer effect categories). See Exhibit 37 for information regarding data entry into the supplemental document.

Please note that within the "systemic" major effect category are subcategories such as respiratory, cardiovascular, gastrointestinal, etc. The same study, species, duration, and study protocol across these subcategories is represented with the same LSE key number.

All NOAELs and LOAELs from the same study, species, duration, and study protocol are represented by the same LSE key numbers.

As a general rule, for a given study all NOAELs and LOAELs should be entered in the tables. One exception is when effect levels are different between males and females; in this case, the more sensitive sex is presented in the LSE figure.

Similarly, the principal author, and chemical manager may choose not to include in the LSE tables certain effects (or entire studies) that appear in the supplemental tables.

MISCELLANEOUS COMMENTS CONCERNING DATA COLLECTION FOR THE SUPPLEMENTAL DOCUMENT

Quality Assurance/Quality Control

Sufficient quality control procedures should be in place to ensure minimal discrepancies in the information extracted from papers and calculations done upon data. Because this is the basis upon which all subsequent statements shall be made, authors should use as much care as is necessary to produce a quality supplemental document. Good project management dictates that this should be accomplished with the first draft of the document.

Significant Figures

Do *not* round numbers until after *all* conversions have taken place. At that point, round value to the same number of significant figures as the datum point, e.g., 0.15 = 0.2 mg/kg/day and 0.25 = 0.3, where the reported dose was 10 ppm in feed.

If more than one experimentally determined datum point enters into the conversion, use the number of significant figures that the datum with the least number of significant figures has. In some cases, authors will want to use more significant figures than are technically called for. A common instance where this might be done is when experimenters report an administered dose as, for example, "5 mg/kg." It is safe to assume that the experimenters actually measured the substance with more precision than the single significant figure stated (i.e., 5.0 mg/kg); it would be a disservice to report the results, after rounding, with one significant figure. In such cases, adding an additional significant figure is advised. Disregard the number of significant figures that are in the conversion factors themselves unless your scientific judgment dictates that the precision of a certain conversion factor is pertinent. Standard scientific practice is to resort to scientific notation in order to present large numbers with unambiguous precision. Nevertheless, scientific notation would be confusing to some lay readers and burdensome for table preparation. Therefore, do not use scientific notation only to retain precision. For example, if 4 were converted to 2,557 round it and present it as 2,600, *not* as 2.6×10^3. Of course, this is *not* to say that scientific notation is never to be used in a profile, nor that authors are banned from using it after a particular conversion if they consider it vital. MRLs are always rounded to 1 significant figure.

"Pulse" or Other Complicated Dosing Regimens

If complicated dosing regimens are used, explain the regimen as fully and succinctly as possible under the "Exposure Duration/Frequency" (ED/F) column. You may need to resort to an inexact, simplified portrayal of the regimen that more fully conveys the effective dose, as opposed to simply listing as many details as space permits and having the rest deleted. Then, explain the regimen fully in the ADescription of Study@ section. Keep in mind that most readers will only see the abbreviated version appearing in the ED/F column of the LSE table, without the benefit of the supplemental document. Therefore, strive to make the ED/F entry as self-sufficient as possible.

ATTACHMENT B: ABBREVIATIONS AND ACRONYMS

ACGIH	=	American Conference of Government Industrial Hygienists
ADME	=	absorption, distribution, metabolism, excretion
AOAC	=	Association of Analytical Chemists
APHA	=	American Public Health Association
ASTM	=	American Society for Testing and Materials
ATSDR	=	Agency for Toxic Substances and Disease Registry
AWQC	=	Ambient Water Quality Criteria
BBDR	=	biologically based dose-response
BCF	=	bioconcentration factor
CEL	=	cancer effect level
CERCLA	=	Comprehensive Environmental Response, Compensation, and Liability Act
CM	=	chemical manager
CMR	=	*Chemical Marketing Reporter*
CPN	=	chronic progressive neuropathy
CPSC	=	Consumer Product Safety Commission
DHHS	=	Department of Health and Human Services
DOC	=	Department of Commerce
ECF	=	extracellular fluid
EEGL	=	emergency exposure guidance level
EPA	=	Environmental Protection Agency
FDA	=	Food and Drug Administration
HDSB	=	Hazardous Substances Data Bank
IARC	=	International Agency for Research on Cancer
IDLH	=	immediately dangerous to life and health
IPCS	=	International Programme for Chemical Safety (part of WHO)
K_m	=	Michaelis-Menten equilibrium constant
LOAEL	=	lowest observed adverse effect level
LSE	=	level of significant exposure
MCLG	=	maximum contaminant level goal
MRL	=	minimal risk level
MTD	=	maximum tolerated dose
NAAQS	=	National Ambient Air Quality Standards
NAPL	=	nonaqueous-phase liquid
NAS	=	National Academy of Science
NFPA	=	National Fire Protection Association
NHANES III	=	Third National Health and Nutrition Evaluation Survey
NIOSH	=	National Institute for Occupational Safety and Health
NKC	=	natural killer cell
NOAA	=	National Oceanic Atmospheric Administration
NOAEL	=	No observed adverse effect level
NOES	=	National Occupational Exposure Survey
NPL	=	National Priorities List
NRC	=	National Research Council

NTP	=	National Toxicology Program
OSHA	=	Occupational Safety and Health Administration
PA	=	principal author
PBPK/PD	=	physiologically based pharmacokinetic/pharmacodynamic (modeling)
PEL	=	permissible exposure limit
PHS	=	Public Health Statement
POTW	=	publicly owned treatment works
PVC	=	polyvinyl chloride
REL	=	recommended exposure limit
RfC	=	reference concentration
RfD	=	reference dose
SAR	=	structure-activity relationship
SMCL	=	secondary maximum contaminant level
SNARL	=	suggested no-adverse-response level
SPEGL	=	short-term public emergency guidance level
STEL	=	short-term exposure limit
TLV	=	threshold limit value
TRI	=	Toxics Release Inventory
TWA	=	time-weighted average
USDA	=	U.S. Department of Agriculture
USGS	=	U.S. Geological Survey
USITC	=	U.S. International Trade Commission
V_{max}	=	maximum velocity
VOC	=	volatile organic compound
WHO	=	World Health Organization

ATTACHMENT C: EVALUATING THE QUALITY OF A TOXICOLOGICAL STUDY

I. Test material

1. Was it purchased or synthesized in-house?

2. Was the same lot used for all experiments?

3. Were any impurities present?

   If so, were the impurities removed?

4. Is the test material stable under experimental conditions?

   If not, were any adjustments made?

5. Was a vehicle used for administration?

6. Were the doses reported in the study?

II. Animal selection

1. What is the rationale for the species selection?

2. Were the animals disease-free?

3. Is the model appropriate for the end-point effects studied?

4. Optimal criteria at specific intervals:

	Acute	**Intermediate**	**Chronic**
Number of treatment groups	3-4	3	3
Number of animal groups	6-10	10-20	50/sex/treatment
Age of animals	>6 weeks	Young adult	Young adult
Control groups	Required	Required	Required

5. Are the species, strain, sex, age, treatment schedule, and vehicle the same for control as for treated animals?

III. Study design

1. Are the route(s) expected for human exposures or other (inhalation, oral [diet, drinking water gavage, other], dermal [intact, abraded, occluded])?

2. Is the exposure regimen daily, continuous, or intermittent (e.g., 6 h/d, 5 d/wk)?

3. Is the mortality loss for a chronic study no more than 5-10%?

4. Optimal criteria at specific intervals:

	Acute	**Intermediate**	**Chronic**
Dose Selection	At least 3	Not specified	2 (MTD and LOAEL from a 90-d dose screen)
Period of exposure	Up to 14 d	15-364 d	365 or more
Period of observation	14 d	Every 12-24 hr	Every 24 hr
Body weight measured	Weekly	Weekly	Weekly up to 13; then every 2 wk

IV. End point effects

1. Were appropriate methods used to measure end-point effects?

2. Were these methods state-of-the-art?

3. Was a dose-response relationship established?

4. Did the study sufficiently demonstrate a NOAEL or LOAEL?

5. Were appropriate statistical analyses performed?

6. Were the results statistically significant (at least $p<0.05$)?

7. Optimal criteria at specific intervals:

	Acute	Intermediate	Chronic
Organ weights recorded	Not specified	Liver, kidney, brain, gonads, heart, etc.	Liver, kidney, brain, adrenal, gonads, spleen, lung, etc.
Histopathological gross examination	Gross necropsy	Necropsy and histopathology for liver, kidney, heart, gross lesions, target organs	All tissue in at least control and highest dose group

ATTACHMENT D: EVALUATING THE QUALITY OF AN EPIDEMIOLOGICAL STUDY

V. Overall criteria

1. The study has been published or peer reviewed.

2. The paper should provide:

   A. Background (i.e., supporting rationale, definition, and explanation of the problem).

   B. Study objectives and study design, including assumptions, limitations, and statement of purpose or hypothesis.

   C. Study population and control group (i.e., method of selection, rationale and criteria for inclusion/exclusion, appropriateness and limitations of control group).

   D. Data collection method, including direction and possible magnitude of any bias introduced into the study (i.e., may be single-, double-, or triple-blind to prevent bias). QA, QC, or calibration data are presented for the data collection instrument (method).

   E. Type and length of follow-up.

   F. Account for (via matching, stratification, multivariate analysis, etc.) and clearly define major confounding factors.

   G. Procedures and statistical methods used for data analysis. Significance levels need to display a strong association ($p<0.05$) to rule out the probability of the results occurring by chance variation.

   H. Results that are related to the objectives of the study. Do the numbers in the tables add up?

   I. Discussion of limitations and biases that may have affected the results. The examination of causality (conclusion) should be supported by the results.

   J. A logical, temporal sequence of exposure-response that is toxicologically plausible.

   K. A demonstrated dose-response relationship using valid estimates of exposure and dose.

VI. Types of epidemiological studies

1. Observational studies

A. General points

a. These studies are rarely designed to provide quantitative risk information.

b. Groups are already divided on the basis of some experience or exposure (not created experimentally).

c. Sample size (N) should consider the size of the difference being detected (i.e., rare or common).

d. Small N does not mean study should not be done, rather it might indicate that nothing could be found in the population. The study may need to state that numbers were too few to detect an excess risk.

B. Main types

a. Retrospective (case-control)

(1) These studies are helpful for monitoring substance/drug exposure.

(2) A positive association is demonstrated between the exposure and the disease/effect if the diseased group is more likely to be exposed than the group not diagnosed with the disease/effect. Researcher looks historically to determine exposure after the disease/effect has been determined.

(3) Cases:

(a) The study group must be delineated precisely, not generalized (e.g., premenopausal women and lobular breast cancer).

(b) Optimally, the study should use newly diagnosed cases with specified characteristics during a specified period in a defined population. Deceased cases as well as those alive when study is undertaken should be included.

(4) Controls:

(a) Controls should be representative of the general population in terms of probability and opportunity for exposure, and should represent the population from which cases arose.

(b) Individual matching is optimal.

(5) Advantages:

(a) The number of subjects can be small because the study is initiated by the identification of cases.

(b) More than one risk factor in the same set of data can be identified.

(c) Studies can take into consideration changes in exposure.

(6) Disadvantages:

(a) Information on past events may be inaccurately recorded or not available.

(b) Information supplied by an informant may be consciously or unconsciously biased.

(c) The study yields only an odds ratio that is an estimate of relative risk (i.e., a comparison of incidence for exposed versus unexposed populations). It is advisable to select more than one control group.

b. Prospective (cohort or longitudinal)

(1) Cohort is free of disease/effect but varies in exposure to the supposed factor. The exposed group is then followed to see if the disease/effect develops. The assumption is that exposed individuals are representative of all exposed persons regarding the risk of disease/effect development.

(2) A positive association is demonstrated between the exposure and the disease/effect if the exposed group develops the disease/effect at a greater rate than those not exposed.

(3) Cohort needs to be as similar as possible to the group it is intended to represent.

(4) Advantages:

(a) Permits calculation of incidence rates among exposed and not exposed. Incidence = number of new cases/total population at risk.

(b) Permits observation of many outcomes.

(5) Disadvantages:

(a) Long-term follow-up may be difficult.

(b) Large cohort (study group) is expensive.

c. Historical prospective

(1) Combines advantages of retrospective and prospective

(2) Follows historically identified healthy exposed and unexposed cohorts for the development of disease/effect.

(3) Can calculate actual incidence and relative risk.

d. Cross sectional (prevalence): Both risk factors and disease are determined at the same time (e.g., prevalence of CHD and serum cholesterol level).

2.Experimental studies: General points

A. The impact of varying some controlled factor is studied.

B. These studies are not common, for obvious reasons.

C. Subjects should be divided into treatment groups by random allocation.

3.Occupational studies

A. Ecological

a. Generate hypotheses.

b. A group rather than individual is the unit of comparison.

B. Cross sectional (prevalence)

a. Observations of a group are made at one point in time, yielding prevalence rates. Prevalence = number of old and new cases/total population at risk.

b. These studies represent one of the most frequently used ways of identifying a disease/effect in a community (survey, screening).

c. Cases of short duration are less likely to be found than cases of long duration.

d. These studies are especially suited for subtle, subclinical health effects for which records are unlikely to exist.

e. The relationship between effects and time cannot readily be explored.

C. Case control

a. These studies are used when the disease/effect of interest is relatively rare and would require a large cohort for follow-up.

b. Environmental concentrations and biological levels are often measured.

c. Several occupations or substances may be associated with the disease/effect of interest.

d. The influence of various modifiers can be studied (synergism).

e. Previous jobs are often of greater relevance than current, therefore entire work history needs examination.

D. Cohort

a. Occupational cohort studies are usually mortality studies.

b. Cohort should be defined as broadly as possible, prevalence or incidence.

c. Eliminating workers from the cohort who are not active can lead to serious biases in assessing mortality because this can distort the age distribution of the cohort and omit workers who left because of ill health.

d. Dose-response relationships or high-risk jobs are searched for by dividing cohort into exposure level groups.

ATTACHMENT E: PHS TERMS

The following words and phrases have been used in the PHS of several toxicological profiles. Because these words may be too complex for the intended audience of the PHS, alternative wordings are provided below in an attempt to standardize the language that ATSDR chemical managers use. These terms or other "complex" terms that must be used in the PHS to clarify meaning should be defined in context.

Absorbed: passed into the body through skin, lungs, or stomach

ambient: surrounding

analgesic: (noun) substance designed to reduce pain; (adjective) reduces pain

analysis: examination

analytic: related to examining or investigating; usually describes method

aquatic: found in the water; lives in the water

chemical intermediate: substance used to form other compounds

commodity: substance or product having commercial value

conclude: determine; decide; find out

consumable commodity: substance or product that can be eaten or drunk

consuming: eating; drinking

contagious: spread easily (as a disease) from person to person, animal to animal, or animal to person

correlation: connection between; association between

decomposed: changed to a simpler form, usually in soil

degradation: breakdown

eliminated: removed from the body

emission: release to the environment, including soil, water, or air

ether-like odor: sharp odor

equivocal: uncertain value or worth

excreted: left the body as waste

extractant: substance that separates other substances that are present in a mixture

experimental: tried; done in a scientific laboratory

formulated: created

formulating: manufacturing

inadvertently: not on purpose; accidentally

in conjunction with: along with; at the same time as

incremental: in small amounts (as increase or decrease)

indicate: suggest; show

inflammable: same as flammable

ingestion: swallowing

inhalation: breathing in

is a function of: is affected by; is controlled by (e.g., the long-term toxicity of "X" is a function of dose)

isomer: different form of the same chemical

malignant: causes harm to the body; often cancerous

median concentration: when all concentrations measured are listed in increasing or decreasing order, the concentration that falls in the middle of the list

metabolite: substance created when something is changed in the body, soil, or water

metabolized: changed the form or chemical structure of

nonflammable: will not burn

offspring: newborn animals or humans

permissible: allowable

prostration: inability to stand

qualitative: what kind of; usually describes a test to determine what substance(s) are present

quantity: amount

refrigerant: substance used to lower temperature; coolant

regeneration: comes back in same or different form

resembling odor of chloroform: sweet odor

residue: small amount of a substance that is present or left in the body, soil, water, or air

retardant: something that slows down or prevents

slimicide: substance that kills or prevents pests that make slime and mucus

soil fumigant: substance in smoke or vapor form that kills soil pests

solvent: substance used to dissolve other substances; often a liquid

susceptible: especially vulnerable to

technique: method

therapeutic: designed to improve health

tolerating: withstanding exposure to a substance without experiencing the expected harmful result

toxic: harmful to humans (or animals)

volatile: evaporates easily

Attachment F: Some Hotlines and Other Information Sources from which fact sheets and other risk communication information can be requested to provide ideas [not as primary source material!] for 1.7 How Can Families Reduce the Risk of Exposure to [Chemical X]?

ATSDR
http://www.atsdr.cdc.gov/
See Alerts and Health Advisories, etc.

CDC
http://www.cdc.gov/

National Center for Environmental Health
http://www.cdc.gov/nceh/ncehhome.htm

CDC Prevention Guidelines Database
http://aepo-xdv-www.epo.cdc.gov/wonder/PrevGuid/PrevGuid.htm

Consumer Product Safety Commission
Hotline, 1-800-638-2772
www.cpsc.gov

Duke Occupational and Environmental Medicine
http://gilligan.mc.duke.edu/oem/default.htm
(in particular, the archives of OEM sometimes have interesting information)

EPA
http://www.epa.gov/

Fish and Wildlife Advisories:
http://www.epa.gov/OST/fishadvice/

Air Risk Information Center Hotline (Air RISC): 1-919-541-0888;
http://www.epa.gov/earth100/records/a00119.html

Asbestos Abatement/Management Ombudsman: 1-800-368-5888;
http://www.epa.gov/earth100/records/a00193.html

Emergency Planning and Community Right-To-Know Act (EPCRA) hotline: (description)
1-800-424-9346;
http://epa.gov/epa/epaoswer/hotline/lotintro.htm#epcra

Environmental Justice Hotline: 1-800-962-6215;
http://es.epa.gov/oeca/oej.html

Hazardous Waste Ombudsman: 1-800-262-7937;
http://www.epa.gov/epaoswer/hotline/contacts.htm#ombuds

Indoor Air Quality Information Clearinghouse (IAQINFO): 1-800-438-4318
http://www.epa.gov/iaq

National Lead Information Center Hotline:1-800-532-3394;
http://www.epa.gov/opptintr/lead/nlic.htm;
email: leadctr@epamail.epa.gov

National Pesticide Telecommunications Network: 1-800-858-7378;
http://ace.ace.orst.edu/info/nptn/

National Radon Information Hotline: 1-800-767-7236;
http://www.epa.gov/iaq/radon/rnxlines.html

National Response Center Hotline: 1-800-424-8802 (Spills and Emergencies)
http://www.nrc.uscg.mil

Oil Spill Program Information Line: 1-202-260-2342: email: oilinfo@epamail.epa.gov
http://www.epa.gov/oerrpage/superfnd/web/oerr/er/oilspill/contacts.htm

Resource Conservation and Recovery Act/Underground Storage Tank (RCRA/UST),
Superfund and RCRA Hotline: 1-800-424-9346;
http://www.epa.gov/epaoswer/hotline/index.htm

Safe Drinking Water Hotline: 1-800-426-4791; email: hotline-sdwa@epamail.epa.gov;
http://www.epa.gov/OGWDW/index.html

Toxics Release Inventory - User Support Service:202-260-1531;
http://www.epa.gov/opptintr or http://www.epa.gov/earth100/records/a00249.html

Toxic Substances Control Act (TSCA) Assistance Information Service (TAIS): 1-202-554-1404
email: tsca-hotline@epamail.epa.gov
http://www.epa.gov/earth100/records/a00266.html

FDA
Main FDA Address and Phone Number (for general inquiries):
U.S. Food and Drug Administration (HFE-88) Rockville, MD 20857
Phone: 1-800-532-4440 (in the Washington, D.C., area, please call 301-827-4420)
Fax: 301-443-9767
E-mail: execsec@oc.fda.gov

http://www.fda.gov/opacom/catalog/getinfo.html

FDA Food Information & Seafood Hotline: 1-800-332-4010 (or 202-205-4314 in the DC Area)
http://vm.cfsan.fda.gov/~lrd/hotline.html

NIEHS
800-643-4794 or 919- 541-1919
http://niehs.nih.gov
(source of a number of fact sheets)

NIOSH
800-356-4674
http://www.cdc.gov/niosh/homepage.html

OSHA
Office of Information and Consumer Affairs, (202) 219-8151; http://www.osha.gov/

U.S. Government (general)
http://www.healthfinder.gov/

ATTACHMENT G: INTERPRETING RENAL PATHOLOGY IN THE MALE RAT

Risk assessment approaches generally assume that chemicals producing toxicity and neoplasia in laboratory animals pose similar hazards to humans. For most chemicals, this extrapolation remains appropriate. However, a growing body of evidence indicates that certain chemicals cause nephropathy and renal neoplasia through a mechanism that occurs in male rats but not in humans (or female rats, mice, or other species).

ALPHA$_{2u}$-GLOBULIN INDUCED RENAL PATHOLOGY IN MALE RATS

Numerous investigations have demonstrated a consistent association between the accumulation of hyaline droplets containing alpha$_2$-microglobulin (α_{2u}-g) and certain lesions in the male rat kidney (Borghoff et al. 1991; EPA 1991; Hard et al. 1993; Swenberg et al. 1989). These renal lesions have not been identified in female rats, in mice, or in other laboratory species tested. A number of chemicals (e.g., unleaded gasoline) are capable of inducing accumulation of α_{2u}-g, a low molecular weight protein, in the male rat kidney. The accumulation of this protein (which is synthesized in the liver) initiates a sequence of events that results in protein droplet nephropathy and eventually renal tumors. Exposure of male rats to chemicals inducing alpha$_{2\mu}$-globulin accumulation (CIGA) results in the following histopathological sequence of renal lesions (EPA 1991).

- An excessive accumulation of hyaline droplets containing α_{2u}-g in renal proximal tubules.
- Subsequent cytotoxicity and single-cell necrosis of the tubule epithelium.
- Sustained regenerative tubule cell proliferation, if exposure continues.
- Development of intraluminal granular casts from sloughed cell debris, along with tubule dilation and papillary mineralization.
- Foci of tubule hyperplasia in the convoluted proximal tubules.
- Renal tubule tumors.

Biochemical studies show that CIGA or their metabolites bind specifically, but reversibly, to male rat α_{2u}-g. The resulting α_{2u}-g-CIGA complex appears to be more resistant to hydrolytic degradation by lysosomal enzymes than native, unbound α_{2u}-g. Inhibition of the catabolism of α_{2u}-g, a protein only slowly hydrolyzed by renal lysosomal enzymes under normal physiological conditions, provides a possible basis for the initial stage of protein overload in the nephropathy sequence (EPA 1991; Hard et al. 1993). It has been hypothesized that the sustained protein overload results in single-cell necrosis in the tubule epithelium and increased cell regeneration (a reparative process). The increased proliferative response caused by chemically induced cytotoxicity may be a plausible reason for the development of renal tumors in male rats.

EPA has established three criteria for determining that renal lesions in male rats are caused by α_{2u}-g accumulation; a positive response in each criterion is required. These criteria are:

1) The number and size of hyalin droplets in renal proximal tubule cells of treated male rats have increased.

   The abnormal accumulation of hyaline droplets in the P2 segment of the renal tubule is necessary to attribute the renal tumors to the α_{2u}-g sequence of events. This finding helps differentiate α_{2u}-g inducers from chemicals that produce renal tubule tumors through other mechanisms.

2) The accumulated protein in the hyaline droplets must be α_{2u}-g.

   Hyaline droplet accumulation is a nonspecific response to protein overload in the renal tubule and may not be due to α_{2u}-g. Therefore, it is necessary to demonstrate, normally by immunohistochemistry, that α_{2u}-g accounts for the hyaline droplet accumulation found in the male rat.

3) Additional aspects of the pathological sequence of lesions associated with α_{2u}-g nephropathy must be demonstrated.

   Typical lesions include single-cell necrosis, sloughing of epithelial cells into the proximal tubular lumen, formation of granular casts, linear mineralization of the papilla, and tubule hyperplasia and regeneration. If the response is mild, all of these lesions may not be observed; however, some elements consistent with the pathological sequence must be present.

It should not be expected that a compound that induces α_{2u}-g accumulation will always be found to induce renal tubule tumor formation in the male rat. The ability to detect renal tumors

depends on many features that may not be present in any individual experiment (e.g., sufficient dose to induce effect without early deaths of the animals, insufficient length of exposure or follow-up and incomplete histopathology).

Nephropathy and renal tumors associated with CIGA appear to be unique responses of the male rat. Therefore:

- Nephropathy in the male rat that is associated with α_{2u}-g accumulation should not be used as an endpoint for quantitative noncarcinogenic risk assessment (MRL derivation).
- Renal tubule tumors in the male rat that are associated with α_{2u}-g accumulation should not be used to support qualitative weight of evidence that a chemical poses a cancer risk in humans; these endpoints also should not be used for dose-response extrapolations that estimate human cancer risk.

Kidney effects data related to α_{2u}-g accumulation in the male rat should be discussed in the profile and included in the LSE tables, even though it may not be used for MRL derivation. However, in these cases the association of renal lesions to α_{2u}-g accumulation and the relevance of these endpoints to risk assessment (human extrapolation) should be clearly discussed.

CHRONIC PROGRESSIVE NEPHROPATHY (CPN)

Another factor to consider in using rat kidney effects for risk assessment is the species-related condition CPN. CPN is an age-related spontaneous disorder of rats that is more severe in males than in females, and that affects certain strains more than others. CPN is more common in Sprague-Dawley and F344 rats than in the Wistar strain (Gray 1986), and it is also common in the Osborne-Mendel rat (Goodman et al. 1980). The etiology of CPN is not known, but the severity of this condition may be influenced by a number of factors, particularly dietary manipulation affecting protein content or caloric intake (Masoro and Yu 1989). If their lifespan is long enough, most rats will have this renal lesion to some degree at the time of death.

Chronic administration of CIGA to male rats may result in exacerbation of CPN, characterized by increased severity and earlier onset of the disease. However, chemicals that do not induce α_{2u}-g accumulation may cause damage by direct nephrotoxicity or may cause damage indirectly by accelerating the onset and increasing the severity of CPN. Histopathologic characteristics of CPN (EPA 1991; UAREP 1983) include some lesions that are also found in α_{2u}-g nephropathy, as well as lesions that are distinctive. Single-cell necrosis, regenerating tubules, and focal hyperplasia of proximal tubule epithelium are common to CPN and to α_{2u}-g nephropathy. CPN lesions that are *not* components of α_{2u}-g nephropathy include prominent thickening of tubules and glomerular basement membranes, hyaline casts consisting of homogenous, proteinaceous material (distinct from granular casts containing cellular debris), interstitial mononuclear cell infiltration, fibrosis, tubule atrophy, and sclerotic glomeruli. In advanced cases of CPN, sporadic tubules may contain excessive numbers of hyaline droplets similar in appearance to those induced by CIGA. However, these droplets do not show immunochemical evidence of α_{2u}-g (Hard et al. 1993).

CPN in the aging male rat can complicate the interpretation of other renal lesions. However, nephropathy in the male rat that is not attributable to either CPN or α_{2u}-g accumulation may provide endpoints that are suitable for consideration in the risk assessment process, particularly if similar effects are seen in female rats, in mice, or in other species. Generally, lesions of CPN in exposed rats should be excluded as endpoints used in quantitative risk assessment (MRL derivation). However, there may be an exception to this guideline in a few cases. Lesions of CPN in exposed rats may be considered potential endpoints for estimating noncarcinogenic risk if exposed male and female, or only female[*], rats have lesions of CPN that exhibit a clearly defined dose response. More specifically, with increasing exposure doses there should be a progressive significance of CPN lesions as characterized by (a) an earlier age of onset, (b) increasing severity, (c) an increased frequency of animals affected (one or any combination of these three items may be present). Observation of renal effects in other similarly exposed species contributes to the weight of evidence in these cases.

[*]In untreated rats, CPN is typically much more severe in males. If exposed females exhibit a dose-response, such a pattern may be obscured in the exposed male rat due to the severity of the lesion.

In cases where the above criteria are met, NOAEL values for lesions of CPN can be considered for quantitative risk assessment. A NOAEL in this situation is defined as a test dose that produces no statistically significant enhancement of CPN lesions compared with the controls. The effect description for NOAEL values should read "no enhancement of CPN in females" (and males, if appropriate). At those doses where enhancement of CPN lesions is observed, effects should be classified as less serious LOAELs or serious LOAELs, depending upon their magnitude. Less serious LOAEL values can be considered for MRL derivation if NOAELs have not been identified. The effect description for LOAEL endpoints should read "dose-related enhancement of CPN in females" (and males, if appropriate).

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ATTACHMENT H: ASSESSING CHOLINESTERASE ACTIVITY INHIBITION

Organophosphorus (OP) and carbamate compounds share a common pathophysiologyCthey combine with and thereby inhibit cholinesterase enzymes, of which acetylcholinesterase in nerve tissue is the most important. Inactivation of acetylcholinesterase results in accumulation of acetylcholine at synapses and neuromuscular junctions. Exposure to OP (e.g., disulfoton, malathion) or carbamate (e.g., baygon, carbaryl) compounds produces a broad spectrum of clinical effects indicative of massive overstimulation of the cholinergic system, including muscarinic effects (parasympathetic), nicotinic effects (sympathetic and motor), and central nervous system effects (ATSDR 1993; Gallo and Lawryk 1991; Kaloyanova and El Batawi 1991). These effects present clinically as symptoms of headaches, weakness, dizziness, blurred vision, psychosis, respiratory difficulty, paralysis, convulsions, and coma. Other typical findings include increased salivation, lacrimation, urination, and defecation. In the following discussion, OP compounds will be used as the prototype-cholinesterase inhibiting toxin.

In principle, cholinesterase activity correlates with the amount of OP compound absorbed in the organism. Therefore, cholinesterase activity is a specific test for exposure to OP compounds (Morgan 1989). There are two principal human cholinesterases, acetylcholinesterase and pseudocholinesterase. Acetylcholinesterase, also referred to as true cholinesterase or erythrocyte acetyl cholinesterase, is found mainly in nervous tissue and erythrocytes, as well as in lymphocytes (Goldfrank et al. 1990). Pseudocholinesterase is often referred to as plasma cholinesterase or serum cholinesterase. Pseudocholinesterase and lymphocyte acetylcholinesterase activities are depressed before erythrocyte cholinesterase activity, suggesting that these cholinesterases are more sensitive indicators of exposure to OP compounds (Fitzgerald and Costa 1993; Iyaniwura 1991; Sundlof et al. 1984). However, erythrocyte cholinesterase recovers more slowly (90B120 days) than pseudocholinesterase or lymphocyte acetylcholinesterase (days to weeks), and is therefore a better indicator after exposure ceases. Depression of pseudocholinesterase activity only indicates possible exposure to OP compounds, whereas depression of erythrocyte and lymphocyte acetylcholinesterases not only indicates exposure but also a neurologic effect, as they reflect inhibition of brain acetylcholinesterase activity. The toxicologic effects of OP compounds are almost entirely due to the inhibition of

acetylcholinesterase in the nervous system. Thus, the toxicity of OP compounds is most appropriately assessed in the laboratory by measurement of the erythrocyte (true) cholinesterase rather than the plasma (pseudo-) cholinesterase. Inhibition of plasma cholinesterase has not been associated with toxicity.

For the purpose of health effect assessment associated with OP compound exposure, the laboratory parameter to be used in profiles is measurement of acetylcholinesterase activity (in erythrocytes and/or the brain). If the rate of acetylcholinesterase inhibition is rapid, the correlation between enzyme inhibition and the severity of clinical symptoms tends to be good. When the rate of acetylcholinesterase inhibition is slow, the correlation may be low or nonexistent. This may happen during long-term occupational OP compound exposure, because the body adapts to the high levels of acetylcholine accumulated in the synapses and neuromuscular junctions (Kaloyanova and El Batawi 1991). Chronic moderate OP compound exposure results in cumulative inhibition of acetylcholinesterase activity. The appearance of symptoms depends more on the rate of fall in acetylcholinesterase activity than on the absolute level of activity reached. Some workers may exhibit 70-80% inhibition of acetylcholinesterase activity after several weeks of moderate exposure without manifesting cholinergic symptoms. Other individuals may develop symptoms at first exposure, even though the inhibition of acetylcholinesterase activity is less than 30%.

In classifying the neurological health effect endpoint of "inhibition of acetylcholinesterase activity" (in erythrocytes and/or the brain), the following guidelines should be followed. A 20-59% inhibition of enzyme activity is classified as a less serious LOAEL; enzyme activity inhibition of 60% or greater is classified as a serious LOAEL. However, in addition to the aforementioned guidelines, consideration should be given to associated clinical symptoms (see Table 3-15b in the guidance for chapter 3). If clinical effects observed at a particular exposure level are most consistent with those symptoms described in the table under moderate or severe poisoning, this exposure level should be classified as a serious LOAEL, even if the degree of inhibition of acetylcholinesterase activity is less than 60%. In those cases where inhibition of enzyme activity of less than 60% is classified as a "serious" LOAEL, the specific clinical effects that lead to this classification (as well as the percentage of enzyme inhibition) should be clearly

stated in the text of Chapter 3 and in the LSE tables. Inhibition of acetylcholinesterase activity of 60% or greater should always be classified as a serious effect. Clinical signs, if present, should be discussed in Chapter 3 and listed in the LSE table entry. In cases where erythrocyte or brain acetylcholinesterase is inhibited by less than 20% (NOAEL) and statistically significant decreases in plasma cholinesterase are observed, this fact should be stated in Chapter 3. This information is useful in quantitative risk assessment since it proves that significant absorption occurred.

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Attachment I: Age at weaning and sexual maturity for common laboratory species and humans.

Species	Age at weaning	Age at sexual maturity (puberty)
Mouse	21 days	50 days
Rat	21 days	56 days
Dog (Beagle)	42 days	240 days
Cat	49 days	240 days
Guinea pig	14 days	70 days
Hamster	21 days	60 days
Rabbit (New Zealand)	56 days	195 days
Gerbil	21 days	70 days
Monkey (Rhesus)	130 days	1825 days
Pig	14-35 days[+]	150 days
Mink	56 days	300 days
Human[a]	6 months - 2 years	13 years (female) 15 years (male)

*Source: EPA. 1988. *Recommendations for and Documentation of Biological Values for Use in Risk Assessment.* Environmental Criteria and Assessment Office, Office of Research and Development, Cincinnati, OH. EPA/600/6-87-008.
+Source: Dr. G. Gomez. North Carolina State University, Veterinary School. Personal communication, April 8, 1998. Commercial operations often begin the weaning process at 2 weeks. At 5 weeks, the sow begins a drastic reduction in milk production.
[a]Age of weaning is age at which breast feeding or formula is stopped by mother or child. Some toddlers are breastBfed longer than 2 years, and some infants are given a steady diet of solid foods before 6 months, though the latter is not recommended.

Attachment J: Historical background rates for various developmental outcomes used in interpreting National Toxicology Program (NTP) developmental studies on rabbits, rats, and mice. Appendices from Research Triangle Institute (RTI) contracted studies, used with permission of NTP. [Tables]

Attachment K: Example of Chapter 3.4 - HEALTH EFFECTS IN WILDLIFE POTENTIALLY RELEVANT TO HUMAN HEALTH (Toxicological Profile for DDT, DDD, and DDE - 2002)

3.4 HEALTH EFFECTS IN WILDLIFE POTENTIALLY RELEVANT TO HUMAN HEALTH

The 1972 EPA decision to ban DDT for most uses in the United States was significantly influenced by a large body of scientific information documenting adverse effects to wildlife (EPA 1975). These observed effects were severe, including the lethality of DDT to birds and fish and the DDE-induced reproductive effects in birds, particularly eggshell thinning (EPA 1975). Although it is difficult to draw firm conclusions about adverse effects to human health based on those observed in wildlife, it is impossible to ignore that the documented effects to wildlife have motivated the investigation of human health effects. It is reasonable to assume that the adverse effects observed in wildlife may also be a concern to humans and that wildlife are possible "sentinels" for human health (NRC 1991). In order to completely address potential concerns for human health, it is necessary to review and evaluate the observed effects of DDT/DDE/DDD to terrestrial wildlife. Exposures for wildlife to DDT and its metabolites in the natural environment are primarily associated with the accumulation and persistence of these contaminants in both aquatic and terrestrial food chains. Ingestion of contaminated food results in the deposition of DDT/DDE/DDD in tissues with subsequent reproductive, developmental, and neurological effects. The most important reproductive effect observed in wildlife concerns eggshell thinning in birds. These and other effects on terrestrial wildlife are discussed in greater detail in Appendix D with the purpose of providing a qualitative synopsis of effects in terrestrial wildlife to address potential concerns that these effects from DDT/DDE/DDD exposure may also occur in humans.

Eggshell Thinning in Birds. Eggshell thinning in birds reached widespread public awareness in the 1960s and 1970s largely because of field observations in wild raptor populations including the bald eagle, peregrine falcon, and osprey, and the association of these effects with abrupt population declines. Experimental studies established a scientific link between DDT/DDE/DDD exposure, particularly DDE, and avian eggshell thinning, which weighed significantly in the decision to ban most domestic crop uses of DDT in the 1970s (EPA 1975). In general, raptors, waterfowl, passerines, and nonpasserine ground birds were more susceptible to eggshell thinning than domestic fowl and other gallinaceous birds, and DDE appears to have been a more potent inducer of eggshell thinning than DDT (Cooke 1973b; EPA 1975; Lundholm 1997; WHO 1989). Further, reproductive disturbances associated with DDT/DDE/DDD exposure continue to be reported in North American populations of predatory birds and/or birds that migrate to regions such as South America where DDT is still used (Lundholm 1997).

Numerous experimental studies have shown that dietary exposures to DDT/DDE/DDD are associated with eggshell thinning and breakage in wild birds including the barn owl (*Tyto alba*) (Mendenhall et al. 1983), the American kestrel (Porter and Wiemeyer 1969), the mallard duck (*Anas platyrhynchus*) (Heath et al. 1969; Risebrough and Anderson 1975; Vangilder and Peterle

1980), the black duck (*Anas rubripes*) (Longcore et al. 1971), the Japanese quail (*Coturnix coturnix japonica*) (Kenney et al. 1972), the bobwhite quail (*Colinus virginianus*) (Wilson et al. 1973) and the the Ringed turtle doves (*Streptopelia risoria*) (Haegele and Hudson 1973; Peakall 1970; Peakall et al. 1975). These experimental results have verified that the field observations of eggshell thinning and reductions in wild raptor populations are associated with releases of DDT. Possible mechanisms of eggshell thinning in birds have been extensively studied and reviewed (Cooke 1973b; EPA 1975; Lundholm 1997; Peakall et al. 1975; WHO 1989). The leading hypothesis for DDE-induced thinning involves an inhibition by *p,p*=-DDE (but not by *o,p*=-DDE or DDT or DDD isomers) of prostaglandin synthesis in the shell gland mucosa (Lundholm 1997). Overall, there is still some question as to the primary mechanism and reviewers have suggested that these may differ between bird species or differ with environmental conditions or physiological state for a given species. There is some question, however, as to the relevance of avian eggshell thinning to human health. There is no anatomical or physiological counterpart of the shell gland, a specialized segment of the oviduct, in humans. The shell gland lays down calcite ($CaCO_3$, calcium carbonate) onto the developing avian egg to form the eggshell (EPA 1975). Mechanisms of action that involve a direct action of DDT/DDE/DDD on the shell gland itself probably have no human relevance, but mechanisms of action that involve intermediate effects, such as reduced blood calcium, may have relevance to human health.

Reproductive Effects. Exposure to DDT/DDD/DDE is associated with reproductive toxicity in avian wildlife including embryolethality (Heath et al. 1969; Longcore et al. 1971; Porter and Wiemeyer 1969), decreased egg size and weight (Jefferies 1969; Peakall 1970; Wilson et al. 1973), delayed oviposition after mating (Cecil et al. 1971; Jefferies 1967, 1969; Peakall 1970; Richie and Peterle 1979; Vangilder and Peterle 1980), ovarian effects (Bitman et al. 1968; Gish and Chura 1970; Keith and Mitchell 1993) and testicular effects (Burlington and Lindeman 1950; George and Sunararaj 1995; Gish and Chura 1970; Locke et al. 1966). Several authors have speculated that these effects are associated with DDT-induced hormonal imbalances (Jefferies 1967) such as DDT induced estrogen-like inhibition of FSH and LH secretion by the pituitary inhibiting ovary development.

In most studies, egg production is not affected by DDT/DDD/DDE exposure (Azevedo et al. 1965; Chen et al. 1994; Davison et al. 1976; Davison and Sell 1972; Heath et al. 1969; Jefferies 1969; Longcore et al. 1971; Mendenhall et al. 1983; Porter and Wiemeyer 1969; Risebrough and Anderson 1975; Scott et al. 1975; Shellenberger 1978; Vangilder and Peterle 1980; Wilson et al. 1973). There are, however, a few reported cases of decreased egg production especially in birds with restricted diets (Cecil et al. 1971; Gish and Chura 1970; Haegele and Hudson 1973; Kenney et al. 1972). Egg fertility and hatchability are not consistently affected by DDT/DDD/DDE exposure. Some studies report significantly decreased fertility and hatchability (Porter and Wiemeyer 1969; Vangilder and Peterle 1980; Wilson et al. 1973), while others do not document significant effects (Azevedo et al. 1965; Haegele and Hudson 1973; Jones and Summers 1968; Scott et al. 1975; Shellenberger 1978). When considered collectively, egg production, fertility, and hatchibility were largely unaffected in numerous studies in a variety of bird species. This may be inconsequential to the overall reproductive success of birds since DDT/DDD/DDE exposure is clearly associated with decreased embryonic survival or fledgling success (Keith and Mitchell 1993).

DDT exposure has been shown to be associated with reduced post-hatch survival in avian wildlife. This effect has been observed in laboratory testing with mallards, pheasant, black duck, chicks; Japanese quail and ringed turtle doves (Azevedo et al.1965; Genelly and Rudd 1956; Haegele and Hudson 1973; Heath et al. 1969; Jones and Summers 1968; Keith and Mitchell 1993; Longcore et al. 1971; Porter and Wiemeyer 1969; Shellenberger 1978). The mechanism of DDT-induced reduced survival after oral exposures to DDT or DDE in maternal birds is hypothesized to be associated with increased body burdens of DDT/DDD/DDE in chicks as either a result of direct toxicity to the chick, or a reduction in parental care-giving among treated birds resulting in chick malnutrition and poor survival.

The implications of these observed effects in wildlife to human health is uncertain as the mechanisms of toxicity are not thoroughly understood. The consistency of the observed reproductive effects to avian wildlife and the field observations of effects to birds and reptiles have stimulated the investigation of reproductive effects in mammalian models that are more directly relevant to humans. *In vitro* mechanism of action studies have resulted in the identification of some DDT isomers and metabolites as androgen antagonists and estrogen agonists. There have been a number of intriguing mechanistic studies of DDT isomers and metabolites in fish that relate to reproductive and developmental effects (Das and Thomas 1999; Faulk et al. 1999; Khan and Thomas 1998; Loomis and Thomas 1999; Sperry and Thomas 1999; Thomas 1999). There are some interesting parallels between mammalian wildlife and human health studies. Similar to the associations made between DDT and preterm deliveries in humans (Saxena et al. 1980, 1981; Wassermann et al. 1982), premature births in California sea lions (*Zalophus californianus californianus*) are associated with elevated DDT concentrations (DeLong et al. 1973). However, the effect could not be solely, causally isolated to DDT due to the presence of PCBs.

Developmental Effects. The developmental effects of DDT/DDD/DDE on reptiles and avian wildlife have received considerable attention. Studies of alligator populations at Lake Apopka in Florida, where a pesticide spill occurred in 1980, have reported various reproductive effects including reduced clutch viability (Woodward et al. 1993), altered steroidogenesis (Crain et al. 1997; Guillette et al. 1995), abnormal ovarian morphology and plasma 17β-estradiol levels (Guillette et al. 1994), and reductions of phallus size and serum testosterone (Guillette et al. 1994, 1995, 1996, 1997, 1999). The authors hypothesized that the estrogenicity of DDT and other contaminants induced hormonal imbalance in the alligators, causing the observed effects (Guillette and Crain 1996). The contribution of DDT/DDE/DDD (only one component of the mixture of pesticides present) to the observed effects is uncertain. However, other experimental findings support the hypothesis that certain DDT-related compounds induce estrogenic effects in reptiles which could potentially adversely affect reproduction in a population (*in ovo* DDE exposures in alligators by Matter et al. 1998). In general, reptiles may be particularly susceptible to the endocrine-altering effects of DDT/DDE/DDD, as sex in many species are determined by environmental factors (temperature, etc.,) compared to the genetic sex determining mechanisms in birds and mammals (Crain and Guillette 1998). Organochlorine contaminants in general and *p,p*=-DDE, specifically, are thought to influence sexual dimorphism in the common snapping turtle (*Chelydra serpentina*)(de Solla et al. 1998). Snapping turtles in Ontario, Canada, lacked the normal sexual dimorphism in the distance between cloaca and plastron which was attributed to the antiandrogenic effects of *p,p*=-DDE.

DDT exposure is also associated with developmental abnormalities in amphibians and avian wildlife. DDT exposures are associated with delayed tadpole metamorphosis in the frog (*Rana temporaria*) (Cooke 1972, 1973a) and altered facial features (Cooke 1970a). Developmental effects in avian wildlife associated with exposure to DDT/DDD/DDE include a reduced growth (Seidensticker 1968), decreased ability to thermoregulate (Vangilder and Peterle 1980), behavioral alterations (Heinz 1976), reduced testicular development (Burlington and Lindeman 1952), and development of ovarian tissue and oviducts in genetic males (Fry and Toone 1981). Wildlife species may be appropriate sentinels of developmental effects in humans because certain effects, particularly reduced early survival in young, occurred consistently across several species under various exposure conditions.

Neurological and Behavioral Effects. Neurological effects (tremors, convulsions, hyperactivity, and behavioral changes) were observed in mammalian wildlife, amphibians, and avian wildlife experimentally exposed to DDT or DDE, particularly after administration of lethal doses or after administration of lower doses when food intake was restricted. Tremors were the most commonly reported neurological effect and have been reported in the brown bat (the short-tailed shrew (*Blarina brevicauda*) (Blus 1978), the free-tailed bat (*Tadarida brasiliensis*) (Clark and Kroll 1977) the big brown bat (*Eptesicus fuscus*) (Luckens and Davis 1964) and Pipistrelle bats (Jefferies 1972). Studies generally did not offer explanations as to the possible mechanisms that caused tremors, although it is reasonable to assume a mechanism similar to that seen in laboratory animals. Diets were experimentally restricted in several studies to simulate the health effects of DDT/DDE/DDD mobilized from fat during periods of energetic stress in the wild such as may occur, for example, during periods of nesting, migration, or thermal or other stress. Reviews (EPA 1975; WHO 1989) have postulated that during periods of energy stress, DDT mobilized from fat is redistributed to the brain (presumably because of the high lipid content in brain tissue) where it induces neurological effects and death. A study in bats (Clark and Kroll 1977) demonstrated that DDT residues in the brain increase substantially when the diet was restricted. Although a direct action on the central nervous system in wildlife has not been confirmed by observations of brain lesions, one study documented significant decreases in brain neurotransmitter levels associated with increased brain DDE residue levels after sublethal dietary exposures (Heinz et al. 1980). Alterations in neurotransmitter levels may explain changes in bird behavior that were observed in several species. Neurological effects observed in amphibians exposed to DDT/DDE/DDD in water include uncoordinated movement (Cooke 1970b) and hyperactivity (Cooke 1972, 1973a), tremors, lack of muscular coordination and weakness (Harri et al. 1979). Most available data suggest that wildlife species exhibit neurological effects similar to those observed in humans. These neurological effects, however were observed in wildlife at lethal exposure levels or in energy-stressed animals at lower exposure levels.

In avian wildlife DDT/DDD/DDE exposures are associated with decreased brain dopamine levels with a significant negative correlation observed between neurotransmitter levels and DDE residues in the brain (Heinz et al. 1980). Tremors have also been observed in bald eagles (*Haliaetus leucocephalus*) (Chura and Stewart 1967; Locke et al. 1966), kestrels (*Falco sparverius*) (Porter and Wiemeyer 1972), double-crested cormorants (*Phalacrocorax auritus*) (Greichus and Hannon 1973), pheasants (Azevedo et al. 1965), bobwhite quail (*Colinus virginianus*) (Hill et al. 1971), Japanese quail (Davison et al. 1976; Gish and Chura 1970), house

sparrows *(Passer domesticus)* (Boykins 1967), cardinals (*Richmondena cardinalis*), and blue jays (*Cyanocitta cristata*) (Hill et al. 1971), homing pigeons (*Columba livia)* (Jefferies and French 1971) (Jefferies and French 1972), and domestic chickens (Glick 1974). Balance disturbances have also been observed (in some cases prior to death) in pheasants that (Azevedo et al. 1965), Bobwhite quail (*Colinus virginianus*) (Hill et al. 1971), cardinals (*Richmondena cardinalis*), and blue jays (*Cyanocitta cristata*) (Hill et al. 1971). Neurological effects in avian wildlife are also manifested as behavioral effects. These include the delayed onset of nocturnal restlessness indicative of normal migratory behavior (Mahoney 1975), significantly decreased courting behavior (Haegele and Hudson 1977), and decreased nest attendance by parental birds (Keith and Mitchell 1993).

Other adverse effects observed in wildlife species are described in detail in Appendix D. This section only provides a summary of reproductive, developmental and neurological effects that are the primary adverse effects to terrestrial wildlife associated with DDT/DDD/DDE exposure.

Attachment L: Metabolic enzymes whose expression or activity varies developmentally: Table 2 from Leeder, JS and Kearns, GL. 1997. Pharmacogenetics in Pediatrics: Implications for Practice. Pediatric Clinics of North America 44:55-77.

Table 2. Developmental Patterns for the Ontogeny of Important Drug-Metabolizing Enzymes

Enzyme(s)	Known Developmental Pattern
Phase I Enzymes	
CYP2D6	Low to absent in fetal liver but uniformly present at 1 week of postnatal age. Poor activity (approximately 20% of adult) at 1 month of postnatal age. Adult competence attained by approximately 3B5 years of age.
CYP2C19, CYP2C9	Not apparent in fetal liver. Inferential data using phenytoin disposition as a nonspecific pharmacologic probe suggest low activity in first week of life, with adult activity reached by 6 months of age. Peak activity (as reflected by average values for V_{max}, which are 1.5B1.8-fold adult values) may be reached at 3B4 years of age, which declines to adult values at the conclusion of puberty.
CYP1A2	Not present to an appreciable extent in human fetal liver. Adult levels reached by 4 months and may be exceeded in children 1B2 years of age. Activity slowly declines to adult levels which are attained at the conclusion of puberty. Gender differences in activity are possible during puberty.
CYP3A7	Functional activity in fetus is approximately 30%B75% of adult levels of CYP3A4.
CYP3A4	Low activity in the first month of life, with approach toward adult levels by 6B12 months of postnatal age. Pharmacokinetic data for CYP3A4 substrates suggest that adult activity may be exceeded between 1B4 years of age. Activity then progressively declines, reaching adult levels at the conclusion of puberty.

Attachment M: Alternate Names for Enzymes

Phase II Enzymes

NAT2 Some fetal activity present by 16 weeks. Virtually 100% of infants between birth and 2 months of age exhibit the slow metabolizer phenotype. Adult phenotype distribution reached by 4B6 months of postnatal age, with adult activity present by approximately 1B3 years of age.

TPMT Levels in fetal liver are approximately 30% of those in adult liver. In newborn infants, activity is approximately 50% higher than in adults, with a phenotype distribution that parallels that in adults. In Korean children, adult activity appears at approximately 7B9 years of age.

UGT Ontogeny is isoform specific as reflected by pharmacokinetic data for certain substrates (e.g., acetaminophen or chloramphenicol). In general, adult activity as reflected from pharmacokinetic data seems to be achieved by 6B18 months of age.

ST Ontogeny (based on pharmacokinetic studies) seems to be more rapid than that for UGT; however, it is substrate specific. Activity for some isoforms (e.g., that responsible for acetaminophen metabolism) may exceed adult levels during infancy and early childhood.

CYP, cytochrome P450; NAT2, *N*-acetyltransferase-2; TPMT, thiopurine methyltransferase; UGT, glucuronosyltransferase; ST, sulfotransferase.
Data summarized from information and references presented in the text.

Phase I Enzymes

Standard Name	Alternate Names
CYP1A2	7-ethoxy resorufin o-deethylase EC1 P450d (human, rat) P-448 (rat) LM_4 (rabbit) MC_4 (hamster) Mkah2 (monkey) P-450-D3, P-450-D2, Dah2 (dog) DP-4501A-61 (chicken) P_3, P_2 (mouse)
CYP2C9	(methyl) hydroxylase for several compounds, e.g., tolbutamide, phenytoin, tieneilic acid EC1.14.99

MP-1, MP-2 IIC1. Human-2, mp-4, HM2, pHLS.5, hPA6 (human)

CYP2C19 S-mephenytoin hydroxylase
EC 1.14.13
11a (human)

CYP2D6 Nifedipine oxidase
EC 1.14.99
db1 (human)

CYP3A4 nf-25, hPCN1, nf-10 (human)

CYP3A7 HFLa, HFL33, Hlp2 (human)

Phase II Enzymes

n-acetyltransferase 2 (NAT2)

Acetyltransferase, arylamine
beta.-Naphthylamine N-acetyltransferase
4-Aminobiphenyl N-acetyltransferase
5-HT N-acetyltransferase
Acetyl CoA-arylamine N-acetyltransferase
Acetyltransferase, 2-naphthylamine N-
Acetyltransferase, 4-aminobiphenyl
Acetyltransferase, p-aminosalicylate N-
Acetyltransferase, procainamide N-
Arom. amine N-acetyltransferase
Arylamine acetylase
Arylamine acetyltransferase
Arylamine N-acetyltransferase
Dapsone N-acetylase
Dapsone N-acetyltransferase
E.C. 2.3.1.5
Indoleamine N-acetyltransferase
p-Aminosalicylate N-acetyltransferase

thiopurine s-methyltransferase (PMT)

Methyltransferase, mercaptopurine (9CI) (CA INDEX NAME)
Mercaptopurine methyltransferase
Thiopurine methyltransferase

glucuronosyltransferase (UGT)

Glucuronosyltransferase, uridine diphospho- (9CI) (CA INDEX NAME)

1-Naphthol-UDP-glucuronosyltransferase
4-Hydroxybiphenyl UDP-glucuronosyltransferase
4-Methylumbelliferone UDP-glucuronosyltransferase
4-Nitrophenol UDP-glucuronyltransferase
Ciramadol UDP-glucuronyltransferase
E.C. 2.4.1.17
Glucuronosyltransferase, uridine diphosphoglucuronate-4-hydroxybiphenyl Glucuronyltransferase
Glucuronyltransferase, uridine diphospho-
Nitrophenol UDP-glucuronosyltransferase
p-Hydroxybiphenyl UDP glucuronyltransferase
p-Nitrophenol UDP-glucuronyltransferase
p-Nitrophenylglucuronosyltransferase
p-Phenylphenol glucuronyltransferase
phenol-UDP-glucuronosyltransferase
UDP glucuronosyltransferase
UDP glucuronyltransferase
UDP-glucuronate-4-hydroxybiphenyl glucuronosyltransferase
UDPGA transferase
UDPGA-glucuronyltransferase
Uridine 5'-diphosphoglucuronic acid transferase
Uridine 5'-diphosphoglucuronyltransferase
Uridine diphosphate glucuronyltransferase
Uridine diphosphoglucuronosyltransferase
Uridine diphosphoglucuronyltransferase

sulfotransferase (ST)
3'-Phosphoadenosine 5'-phosphosulfate sulfotransferase
6-Hydroxymethylbenzo[a]pyrene sulfotransferase
PAPS-Sulfotransferase
PAPS-Sulphotransferase
Phosphoadenosine phosphosulfate transferase
S-Sulfotransferase

Sources:
P450 enzymes

Medline citations

Nelson, DR et al. 1993. The P450 superfamily: update on new sequences, gene mapping, accession numbers, early trivial names of enzymes, and nomenclature. DNA and Cell Biology 12:1-51.

Parkinson, A. 1996. Biotransformation of xenobiotics. In Casarett and Doull's toxicology: the basic science of poisons. Fifth edition. Klaassen, CD, editor, McGraw-Hill, New York.

Phase II enzymes:
Chemical Abstracts, as searched on February 17, 1998.

ATTACHMENT N: DEVELOPING ADEQUACY OF THE DATABASE SECTION

Adequacy of the database sections are found in Chapters 3, 6, and 7. Under each of the sections entitled "Adequacy of the Database," ATSDR has supplied boilerplate as follows.

> **Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of [substance x] is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of [substance x].**
>
> **The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.**

"NTP" should be used the second and third time the boilerplate is included in the profile. It is only necessary to define NTP when first used in the profile.

GENERAL GUIDANCE

The categories of data needs to be discussed within each chapter are indicated in the Outline for Toxicological Profiles (Exhibit 1). These subheadings should be identified without assigning section numbers. They should be indented, bold, and followed by a period, two spaces, and then text.

The text that accompanies each data need should be a synthesis of existing data. References should be cited. The word "adequate" should not be used when discussing data needs. The text should not convey Agency judgement of priority for filling data needs. Please do not prioritize data needs.

In stating what information currently exists, be specific, and pay particular attention to routes of exposure and threshold effect levels, when appropriate. Draw conclusions based on the information identified. If there does not appear to be a need for additional information at this time, state this. For example, "Analytical methods are available for measuring carbon tetrachloride in air, water, soil, and solid waste, and most of these methods have good sensitivity and specificity." If there are no data, give reasons why there may be a shortage of data in that area. For example, particular routes of exposure may not be relevant or there may not exist a known exposed population necessary for an exposure registry. If appropriate, state what additional information would be useful and why.

Justify the need for additional research by relating how the information will aid in assessing potential toxicity or human exposure, with particular focus on the exposure conditions of concern at or near hazardous waste sites. Clearly state the need for all additional research. Consider supplementing all data needs with related substance information as appropriate.

GUIDANCE FOR INDIVIDUAL SECTIONS

Chapter 3 Data Needs

General

Present human data (inhalation, oral, and dermal) before animal data (inhalation, oral, and dermal). For each of the three exposure routes (inhalation, oral, and dermal) for which insufficient data have been identified, additional studies should be proposed.

Acute-Duration Exposure

1. Is there sufficient information in humans (or several animal species) to identify target organs following exposure via all three routes? Do the animal data support the human data? Comment, as necessary, on the appropriateness of the animal species. *Remember that the emphasis is on target organs in humans.*

2. State whether the data were sufficient to derive oral and inhalation MRLs. If not, state what information is lackingCeither inadequate identification of target organs or levels of exposure (LOAELs or NOAELs) that cause the effect.

3. In the absence of route-specific toxicity data, state whether pharmacokinetic data are available that may support the identification of target organs across routes of exposure. The end result may be that qualitatively we would expect similar endpoints, but the levels (that cause the effects) may or may not be possible to predict.

4. Lethality data are generally needed only to place other toxicity information into perspective; it is unlikely that additional lethality data will ever be requested.

5. State what additional route-specific exposure information is necessary.

6. Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for brief periods; therefore, this information is important.

Intermediate-Duration Exposure

1. Same as Acute-Duration Exposure items 1-5.

2. Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for similar durations.

Chronic-Duration Exposure and Cancer

Chronic toxicity data and carcinogenicity data should be discussed in order using two separate paragraphs.

Chronic Toxicity Data

1. Same as Acute-Duration Exposure items 1-5.

2. Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for similar durations.

Carcinogenicity Data

1. Discussion should focus on the qualitative evaluation of carcinogenic potential across routes of exposure and the mechanism(s) of action.

2. Regarding mechanism(s) of action, draw needs from peculiarities noted in the data, i.e., bolus versus nonbolus effects, vehicle effects, initiation versus promotion, route-specificity, etc.

3. In the absence of route-specific data, state whether pharmacokinetic data may support the carcinogenic potential of the substance across routes of exposure.

4. Because the Agency has not formally adopted a nonthreshold policy for carcinogens or the use of modeling to derive low-level risks, it is not appropriate to request additional studies for purposes of generating data necessary for modeling.

Genotoxicity

1. Do human data indicate whether the substance may act by a genotoxic mechanism?

2. Do *in vivo* animal data (and/or *in vitro* studies) lend support to the substance's genotoxic potential?

3. In the absence of genotoxicity data, are there "structural alerts" (e.g., electrophilic centers) that suggest the substance is genotoxic?

4. What additional *in vivo* and *in vitro* studies would be important to either confirm or refute the substance's genotoxic potential? If either the *Salmonella* mutagenicity test or an *in vitro* test for chromosome aberrations is positive, consider requesting *in vivo* tests of chromosome aberrations in (known) exposed humans or animals.

5. If genotoxicity testing has only been performed at the maximum tolerated dose (MTD), consider suggesting lower dose values.

Reproductive Toxicity

1. When developing this discussion, remember that the Agency places extreme importance on the acquisition of reproductive toxicity data; in fact, it is desirable to have such data from inhalation and oral routes prior to developing MRLs.

2. State whether there is sufficient information in humans (or several animal species) to indicate whether the substance affects reproductive health following exposure via all three routes. Do the animal data support the human data? *Remember that the emphasis is on human health significance.*

3. In the absence of route-specific data, state whether pharmacokinetic data may support the substance's potential to affect reproduction across routes of exposure. The end result may be that qualitatively we would expect similar health outcomes, but the levels (that cause reproductive effects) may or may not be possible to predict.

4. If intermediate-duration (90-day) studies are needed, consider including discussion of this data need, i.e., reproductive organ pathology should be examined in the 90-day study.

5. Multigeneration studies could be recommended after data are available to indicate that the reproductive system might be a target organ.

Developmental Toxicity

1. Similar to reproductive health outcomes, the Agency places importance on assessment of developmental toxicity; it is desirable to have such data from inhalation and oral routes prior to developing MRLs.

2. State whether there is sufficient information in humans (or in several animal species) to indicate whether the substance affects development following exposure via all three routes. Do the animal data support the human data? *Remember that the emphasis is on human health significance.*

3. In the absence of route-specific data, state whether pharmacokinetic data may support the substance's potential to affect development across routes of exposure. The end

result may be that qualitatively we would expect similar health outcomes, but the levels (that cause the effects) may or may not be possible to predict.

Immunotoxicity

1. Is there reason to believe that the immune system is a target for this substance, either from empirical data or from references from related substances? For example, were there any effects on lymphoid tissue or blood components (peripheral lymphocytes) in the 90-day study? If the answer is a resounding "no," it may be possible to conclude that no additional information is needed at this time.

2. If the answer above is "yes" (please refer to the section where Immunological and Lymphoreticular Effects are discussed), has a battery of immune function tests been performed?

3. Is there any reason to suspect the effects may be route- or species-specific?

Neurotoxicity

1. Is there reason to believe that the nervous system is a target for this substance, either from empirical data or from inferences from related substances? Specifically, is there behavioral, histopathological, neurochemical, or neurophysiological information? If not, it may be possible to conclude that no additional information is needed at this time.

2. Is there any reason to suspect the effects may be route- or species-specific or age-dependent?

3. If there a substance is an adult neurotoxin, developmental neurotoxicity should be studied.

Epidemiological and Human Dosimetry Studies

1. Describe any human studies that are currently available and their limitations.

2. Is there likely to be an identifiable subpopulation in the general populace and/or in the workplace potentially exposed to the substance?

3. Discuss the type of study that might be proposed, and highlight endpoints for which there is information from animal studies or from case studies suggesting that those endpoints may be of concern.

4. Relate how this information will be useful for establishing cause/effect relationships and future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect

Chapter 1 of *Biological Markers in Reproductive Toxicology* (NAS/NRC 1989) provides a good general discussion of this topic. A copy of this reference is being provided to each contractor. This data need should contain the following two subheadings.

Exposure. A biomarker of exposure is an exogenous substance, or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (e.g., measurement of the parent compound or its metabolite(s), DNA adducts, etc.).

1. Identify known biomarker(s) of exposure for the substance, and state what biological materials should be monitored to determine (a) short-term exposure, (b) intermediate-term exposure, and (c) long-term exposure.

2. State whether the identified biomarkers are specific for the substance (e.g., metabolites).

3. If the parent compound(s) or its metabolite(s) are the only known biomarkers, discuss the usefulness of developing alternative biomarkers to complement this analysis (e.g., sensitivity may be a problem, and you may wish to refer the reader to Chapter 7, Analytical Methods).

4. Keep in mind that the purpose for developing a biomarker is often to facilitate future medical surveillance, which can lead to early detection and possible treatment.

5. Identify the data needs and why they are needed.

Effect. For the purpose of this data need, a biomarker of effect is a measurable biochemical, physiological, or other alteration within an organism that, depending on the magnitude, can be recognized as an established or potential health impairment or disease.

1. Identify known biomarker(s) of effect (i.e., enzyme levels, lymphocytes, aberrations) for the substance, and state what biological materials should be monitored to

determine effects resulting from (a) short-term exposure, (b) intermediate-term exposure, and (c) long-term exposure. State whether the biomarker can be used for dosimetry or is only indicative of effect.

2. Identify the data needs and why they are needed.

Absorption, Distribution, Metabolism, and Excretion (ADME)

This data need should discuss these parameters by route and duration of exposure; the subsequent data need should describe toxicokinetics across species.

1. Is information available to assess relative rates and extent of ADME regarding the three routes of exposure?

2. Are there differences in ADME regarding time or dose, i.e., do saturation phenomena come into play?

Comparative Toxicokinetics

This data need should examine toxicokinetics across species; the preceding data need (ADME) should describe route- and duration-specific pharmacokinetic needs.

1. Are both human and animal data available, and do they indicate similar target organs?

2. Have toxicokinetic studies been performed in both humans and animals? What do these studies show, i.e., are rats a good model?

3. Have toxicokinetic studies been performed in multiple species? If so, are results similar, and would it be reasonable to expect humans to handle the substance similarly (and have similar target organs)?

Methods for Reducing Toxic Effects

This data need should examine the existing clinical and experimental methods of reducing both short- and long-term toxic effects of exposure.

1. Is the mechanism(s) of absorption of the substance known? If so, are there established methods or treatments for reducing absorption following exposure? Note

that these methods are useful only immediately following exposure to the toxic substance. If the mechanism(s) is not known, state this as a data need. Is the mechanism(s) of distribution of the substance in the body known? If little is known regarding distribution of the substance, state this as a data need.

2. Are there established methods or treatments for reducing body burden of the substance or toxic persisting metabolites? Are these methods sufficient to prevent toxicity following long-term exposure?

3. Is the mechanism of toxic action of the substance known? If not, state this as a data need. If the mechanism of toxic action is known, are there established methods that block this mechanism of toxic action?
4. Are there established methods for mitigation of the health effects that result from exposure? For example, are there treatments to repair damage or improve compromised function?

Ongoing Studies

Identify databases and ways to locate additional information. This is important, because there may be studies in progress that will fill a gap or need.

Chapter 6 Data Needs

Physical and Chemical Properties

1. Do we know enough about the chemical and physical properties (i.e., log K_{ow}, log K_{oc}, Henry's law constant, vapor pressure, etc.) of the substance to permit estimation of its environmental fate?

2. Indicate the need for confirmation when toxicokinetic, physical, or chemical information is used to predict the fate of a substance.

Production, Import/Export, Use, and Disposal

In the absence of information on the number of people potentially exposed to the substance near waste sites and other sources, this data need should serve as a surrogate for evaluating human exposure potential. Include an introductory statement based on the information that supports the potential for human exposure to the substance. For example, if the production volume of the

substance is high and its usage is widespread in the home, in the environment, and in industry, then the risk for human exposure may be substantial.

1. **Production**. Do we know whether the substance is currently produced and, if so, in what quantity? Do we know if this amount is larger or smaller than in the past? Do we know what production might be in the future?

2. **Use**. Do we know whether the substance is widely used in the home, environment, or workplace? Do we know if it is a food contaminant?

3. **Release**. Considering typical releases of the substance in the home, environment, and workplace, which environmental media are likely to be contaminated with significant quantities of the substance?

4. **Disposal**. Are current disposal methods efficient, and is there a need to improve them? Is there information on the amounts of the substance disposed of by each method?

5. **Regulatory information**. Do we know if there are rules and regulations governing disposal of the substance?

Environmental Fate

1. Do we know whether the substance partitions in the environment? If so, in what media? Do we know whether the substance's mobility has been characterized in soil?

2. Do we know whether the substance is transported in any environmental medium? If there is no information on the half-life of the substance, this should be considered a data need. To determine the half-life of a substance in water, soil, and sediment, was field testing or microcosms used? Or is the information from controlled lab experiments? How relevant are the data to real-life situations?

3. Do we know whether the substance is degraded or transformed in each environmental medium? Does it persist in some media? Include the fate of degradation products.

Bioavailability

1. State whether the substance is known to be absorbed following inhalation, oral, or dermal contact.

2. State whether there is any information on absorption (bioavailability) of the substance from contaminated air, water, soil, or plant material. If not, can predictions be made?

For example, if a substance is poorly absorbed from the gut and it has a very large K_{oc} value, can anything be predicted about its bioavailability following ingestion of contaminated soil?

Food Chain Bioaccumulation

1. Do we know whether the substance is bioconcentrated in plants, aquatic organisms, or animals (i.e., elevated tissue levels indicating storage in the organism as a result of exposure to contaminated media)?

2. Do we know whether the substance is biomagnified (increased levels in predators resulting from consumption of contaminated prey organisms)?

Exposure Levels in Environmental Media

1. Has the substance been detected in air, water, soil, plant materials, or foodstuffs? *Remember that the focus is on media surrounding hazardous waste sites.* If not, have any environmental monitoring studies been done? If so, are the data current (within 3 years)? Add the following boilerplate.

   Reliable monitoring data for the levels of [substance x] in contaminated media at hazardous waste sites are needed so that the information obtained on levels of [substance x] in the environment can be used in combination with the known body burden of [substance x] to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

2. Have any estimates been made for human intake of the substance from various environmental media?

Exposure Levels in Humans

1. Has the substance been detected in human tissues such as blood, urine, fat, or breast milk? *Remember that the focus is on populations surrounding hazardous waste sites.* If not, have biological monitoring studies been done? If so, are the data current (within 3 years)? Add the following boilerplate.

   This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries

1. Are there known populations that may have unusually high exposures to the substance? *Remember that the focus is on populations surrounding hazardous waste sites.*

2. If so, is there a registry of any population that has been exposed to the substance?

Chapter 7 Data Needs

Methods for Determining Biomarkers of Exposure and Effect

Exposure.

1. For the biomarkers of exposure identified in the Data Needs section of Chapter 3, state whether existing methods are sensitive enough to measure (a) background levels in the population and (b) levels at which biological effects occur.

2. Discuss the precision, accuracy, reliability, and specificity of the methods documented. What are the deficiencies in these areas?

3. Identify the data needed and why they are needed.

Effect.

1. For the biomarkers of effect identified in the Data Needs section of Chapter 3, if appropriate, state whether existing methods are sensitive to measure (a) background levels in the population and (b) levels at which biological effects occur.

2. Discuss the precision, accuracy, reliability, and specificity of the methods documented. What are the deficiencies in these areas?

3. Identify the data needed and why they are needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media

1. The purpose of analytical methods is:

    - To identify contaminated areas.

- To determine if contaminant levels constitute a concern for human health.

2. Which media are of most concern for human exposure to the substance?

3. For each medium, are there methods sensitive enough to measure (a) background levels in the environment and (b) levels at which health effects occur?

4. Discuss the precision, accuracy, reliability, and specificity of these methods. What are the deficiencies in these areas?

REFERENCES

1. NAS/NRC. 1989. Biological markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

ATTACHMENT O: GLOSSARY

Absorption -- The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption -- The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) -- is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model -- is a statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers -- are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Case-Control Study -- A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents

(such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report -- describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series -- describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study -- A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study -- A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs -- substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship -- the quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurrs. The terms, as used here, include malformations and variations, altered growth, and
inutero death.

Environmental Protection Agency (EPA) Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology-- refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity -- a specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life -- a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence -- The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects -- are functional changes in the immune response.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

***In Vitro* --** Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo* --** Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects -- represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL) -- An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF) -- A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity -- State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality -- Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen -- A substance that causes mutations. A mutation is a change in the DNA sequence of a cell=s DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy -- The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio-- a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound -- a phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL) -- An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

Pesticide -- general classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics -- is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model -- is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model -- is a type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model -- is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence -- The number of cases of a disease or condition in a population at one point in time.

Prospective Study--a type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Recommended Exposure Limit (REL) -- A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study -- A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk -- the possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor -- An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio-- The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL) -- The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic -- The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF) -- A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic -- any chemical that is foreign to the biological system.

ATTACHMENT P: ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level

ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	trans,trans-muconic acid

MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM-TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA

OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States

UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result

ATTACHMENT Q: STANDARDIZED ABBREVIATIONS TO BE USED IN THE LEGENDS

(C)	capsule
(F)	feed
(G)	gavage, not specified
(GO)	gavage, oil
(GW)	gavage, water
(IP)	intraperitoneal
(IM)	intramuscular
(IT)	intratracheal
(IV)	intravascular
(SB)	subcutaneous
(W)	drinking water
6	indicates that a conversion follows
66	indicates an entire conversion, identical to the preceding one
<	decreased
<<	greatly decreased
>	increased
>>	greatly increased
AB	absorption
ad lib	ad libitum
BC	blood chemistry
BI	biochemical changes
BW	body weight
cardio	cardiovascular
CEL	cancer effect level
cm^2	centimeter squared
CS	clinical signs
d	day(s)
develop	developmental
DI	distribution
DX	developmental toxicity
EA	enzyme activity
EC_{50}	effective concentration, 50% of test animals or systems estimated to respond
EX	excretion
F	female
FI	food intake
FM	fecal metabolites
g	gestation
gastro	gastrointestinal
gen	generation
gn pig	guinea pig
Gd	gestation day
GN	gross necropsy
hemato	hematological

HP	histopathology
hr	hour(s)
ID_{50}	dose producing 50% immunodepression
immuno	immunological
kg	kilogram
LC_{50}	lethal concentration producing 50% kill
Ld	lactation day
LD_{50}	dose producing 50% death
LOAEL	lowest-observed-adverse-effect-level
M	male
m^3	cubic meter
mg	milligram
min	minutes
mo	month(s)
musc/skel	musculoskeletal
MX	maternal toxicity
NA	not applicable
NOAEL	no-observed-adverse-effect level
NS	not specified
neuro	neurological
oc	ocular
once	in exposure column, a single dose or exposure
OR	organ function
OW	organ weight
ppd	postparturition day
pg	postgestation
repro	reproductive
resp	respiratory
RM	respiratory metabolites
skel	skeletal
TG	teratogenicity
TM	tissue metabolites
TWA	time-weighted average
UM	urinary metabolites
UR	urinalysis
v/v	volume per volume
WI	water intake
wk	week(s)
wt	weight
w/v	weight per volume
w/w	wet weight
yr	year(s)

Source of conversion factors used in the supplemental document: EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Office

of Health and Environmental Assessment. Cincinnati, OH: Environmental Criteria and Assessment Office. EPA-600/6-87-008.

Attachment R: Literature Search Strategy for Child Health Issues

1. Selection of databases to search.

The suggested databases that should be searched are these:

- Medline,
- Toxline,
- Embase, and
- BIOSIS.

Two additional databases should be searched when issues of exposure through food and carcinogenicity are even remotely suspected:

- CAB and
- Cancerlit.

2. Searches should use both chemical name(s) and CAS registry numbers.

3. MESH headings and keywords.

Medline, Toxline, and Cancerlit use MESH headings, at least since about 1985. Medline has used MESH headings since its inception in 1966, Cancerlit since 1980, and Toxline since 1985. However, Toxline use of MESH headings appears to be incomplete for all of its subfiles– even for more recent citations.

If you use direct search engine on Medline or Toxline themselves, such as those available on CD ROM or other government central servers, then use MESH headings specifically. In the case of using a literature search service, such as Dialog, specifying MESH headings is not critical, because the MESH headings, both major and minor, are accessed through the "Descriptor" field along with other keywords.

A. The following MESH headings and descriptors are recommended for both types of searches – "Dialog" or Medline/Toxline.

- zygote
- embryo
- fetus
- newborn
- child
- adolescence
- infant
- age factor (optional)

Additional descriptor field terms can be used, but they appear to add little to the searches and they are not MESH headings by themselves. This will add unnecessary citations to the searches.

B. An additional search of the following terms in the title and abstract fields should be added to the descriptors presented above in section A.

- wean? [the ? means for the search engine to accept any suffix letters following it]
- offspring
- postnatal

The following terms often are used in titles, abstracts or descriptor fields for citations of interest, but they do not appear to add citations that would not be picked up by the terms listed above. They most likely add unnecessarily to the searches.

Fetal, juvenile, prenatal, neonatal, postpartum, terato?, utero?, boy, girl, teen, infancy, gestation.

4. Limiting the search by one or more following fields may be valuable, under some circumstances:

- Year of publication, e.g., PY=1970-1990.
- Language, e.g., LA=English (not usually recommended).
- Type of publication, e.g., Review articles only.

5. The DART database of the National Library of Medicine is an active database of publications that include developmental and reproductive toxicology topics. It is also a subfile in TOXLINE, but new DART records are only added 2 to 3 times a year to TOXLINE, so there is a slight lag for up to 2000 new records when compared with records from NLM/DART directly. If these end points are critical and new research might be ongoing, and then consider a direct search of DART. Otherwise, it is likely to add very little to the body of literature for a particular chemical.