Developmental toxicity: web resources for evaluating risk in humans

Janine E. Polifka a,*, Elaine M. Faustman b

a Department of Pediatrics, TERIS Project, University of Washington, PO Box 357920, Seattle, WA 98195-7920, USA
b Department of Environmental Health, Institute for Risk Analysis and Risk Communication, Center for Child Environmental Health Risks Research, University of Washington, Seattle, WA 98105, USA

Abstract

This review presents a brief overview of Internet resources that provides information on developmental toxicity. The advantages and limitations of these resources for evaluating human risk and where each one is useful for informing various stages of the risk assessment process (i.e. hazard characterization, dose-response assessment, exposure assessment and risk characterization) are reviewed. How these Internet resources can be utilized to obtain information on and evaluate the developmental risk associated with exposures during pregnancy will be illustrated using toluene. Translating information derived from laboratory and human population studies into clinical management prescriptions for individual patients is difficult. With the increasing availability of Internet resources that provide information relevant for developmental risk assessments, health care professionals will be better equipped to make more accurate estimations of potential risk for their patients. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Teratology; Developmental and reproductive toxicity; Risk assessment; Information resources; Toluene

1. Introduction

In its report ‘Risk Assessment in the Federal Government: Managing the Process’ the National Research Council (NRC) committee formally describes a process for conducting human health risk assessment (NRC, 1983). This general approach to risk assessment was later modified in 1991 for purposes of evaluating potential developmental toxicants (US EPA, 1991). Risk assessment is the systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations (NRC, 1983; Faustman and Omenn, 2001) and involves a four-step process: (1) hazard characterization, (2) dose-response assessment, (3) exposure assessment and (4) risk characterization (US EPA, 1991; Moore et al., 1995). Although initially developed for regulatory purposes to identify environmental health risks in the human population, health care professionals often find themselves engaged in the practical application of the risk assessment process when their patients express concerns about exposures to potential de-
velopmental hazards during pregnancy. In the clinical setting, elements of the risk assessment process can be used to determine the developmental risk associated with a particular exposure in the individual patient (Scialli, 1992; Paul, 1993). That is, the clinician has the task of determining whether or not a particular substance that a patient has been exposed to has been found to produce adverse developmental effects in laboratory animals or humans. And if so, what types of effects were produced, during what stage of development, and at what doses? The clinician must then evaluate the particular circumstances of the patient’s exposure and how likely the patient’s exposure will result in an adverse developmental outcome.

In the past, gathering information necessary to assess developmental toxicity risks associated with a particular exposure could be a formidable task for the clinician. Often the clinician lacked easy access to resources, as well as the time required to conduct a comprehensive review of the literature. With the creation of the Internet, the process of information gathering has become much easier and quicker. In addition, information on the Internet is more up-to-date than that found in books and other traditional resources.

However, appropriately using this information to assess developmental risk in a patient requires careful review and interpretation of the data. This is because much of the risk output from developmental toxicity websites is population-based and should not be applied to an individual case without taking into account all of the idiosyncrasies of that individual, or without taking into account the exposure and risk context for a specific risk scenario. Particular care must be taken by health professionals when communicating the risks derived from population-based studies to their patients. In addition, the framework for risk assessment is agency-dependent; and therefore, an understanding of the framework that is used by an agency or organization to assess risk is essential if the information is to be correctly used to counsel patients. For example, many of the web resources are targeted at scientists and public health managers; hence they are less readily useful for a more general audience.

Another limitation of developmental toxicity websites is that much of the exposure data reported by these websites is insufficient and not very robust for adequate risk assessment. This is particularly true for commercial products that are mixtures, for which exposure data are even more limited. Finally, use of many websites for risk assessment is limited because they lack original reference links and give no indication as to whether or not the information is peer-reviewed. This makes it difficult to assess the quality of the evaluation provided as well as the data on which it is based.

This review will critically evaluate a number of Internet resources that provide information on developmental toxicity. How these resources can be utilized to obtain information and evaluate the developmental toxicity risk associated with exposures during pregnancy will then be illustrated using the chemical toluene. Many of the Internet resources were developed to provide developmental toxicity information on drugs and chemicals for use in formal risk assessments and regulatory activities. To help the health care professional and appropriately utilize these Internet resources, we will provide a risk assessment context to our review. That is, each resource will be evaluated as to whether or not it provides information relevant for hazard characterization, dose-response assessment, exposure assessment, and/or risk characterization. When appropriate, we will also describe the risk assessment defaults or rating systems that the Internet source may employ in its evaluations. The four-step risk assessment process for evaluating potential developmental toxicants is explained below. When discussing the Internet resources in the context of risk assessment, it is not the authors’ intent to discuss risk assessment in the regulatory format, but rather as a tool for identifying and characterizing potential developmental toxicants and their effects.

2. Hazard characterization

The initial step in the developmental toxicity risk assessment is to determine if and under what exposure conditions the agent in question has
been found to produce adverse developmental effects in animals and/or humans. These effects include those that may result from exposure prior to conception, during prenatal development, or postnatally up to the time of sexual maturation (Kimmel, 1996). Internet resources that provide hazard characterization information usually provide evaluations of published animal and human data to determine what kinds of effects have been observed, at what doses, and during which stages of pregnancy the effects were produced. The major manifestations of developmental toxicity are death of the developing organism, malformation, growth retardation, functional disorder, or a combination of these (Wilson, 1977). Generally, the following default assumptions are made when evaluating animal studies: (1) adverse effects observed in animal studies may indicate a potential risk for humans, (2) all manifestations of developmental toxicity are of concern, (3) the types of abnormalities seen in animal studies may not be similar to those typically seen in humans, (4) the most appropriate or sensitive animal species is used to estimate risk in humans, and (5) a threshold is assumed for the dose-response curve. These are assumptions that may be supported or refuted as more specific data become available (US EPA, 1991).

Due to the methodological limitations of experimental and human studies, no single study is sufficient to predict developmental risk in humans. In Internet resources that provide hazard characterization information, evidence from both human and animal studies is critically analyzed in order to determine the strength of association (Kline et al., 1989). Furthermore, this evidence must be viewed within dose-response relationships and the context of biological plausibility (Brent, 2001; Faustman and Omenn, 2001). Replication of an association by different studies under different conditions strengthen the association and reduce the probability that the observed association is spurious (Kline et al., 1989). The stronger the association, the more likely a causal inference can be drawn.

Several types of information may be used for hazard characterization of developmental effects in humans. Exposures that are developmentally toxic in humans are usually identified through case reports or as a result of epidemiological investigations. Case reports are clinical observations of adverse developmental effects that have occurred in the children of one or several women who were exposed to a particular agent prior to or during pregnancy. Human developmental toxicants can sometimes be identified through case reports if the adverse developmental effect produced is extremely rare or severe as in the case of phocomelia in infants whose mothers took thalidomide during the first trimester of pregnancy. Case reports can also alert clinicians that an agent may be developmentally toxic in humans if the maternal exposure is rare and associated with a typical effect. For example, an association between the use of the antiseizure medication, valproic acid, during pregnancy by epileptic women and spina bifida in some of their infants was first identified in case reports. Generally, case reports are very limited in their ability to predict human developmental toxicity because chance associations are common, particularly when the maternal exposure or the adverse outcome or both are common (Friedman and Polifka, 2000). Causal associations can rarely be determined on the basis of case reports since they are anecdotal in nature and no comparisons with an unexposed group can be made.

Formal epidemiological studies are the preferred source of information in hazard characterizations to assess the relationship between maternal exposures and adverse pregnancy outcomes because they are designed to measure the strength of association between exposures in pregnant women and the abnormalities observed in their offspring. The two types of epidemiological studies primarily used in developmental toxicology are cohort and case-control studies. In cohort studies, the frequency of an adverse pregnancy outcome in a group of women exposed to a putative developmental toxicant is compared with the frequency of that outcome in either the total population or in a group of women who were not exposed to the agent. Cohort studies can be designed as prospective or retrospective evaluations. In case-control studies the frequency of maternal exposure to a particular agent is compared among
children with or without a specific developmental abnormality. The advantage of many cohort studies is that they are prospective, and therefore, not subject to recall bias. Also, their prospective nature allows many different outcomes following a specific exposure to be assessed, although spurious associations can occur when a large number of comparisons are made and adjustments are not made for such multiple comparisons. The disadvantage of cohort studies is that a large number of women are needed for the study in order to detect an increased frequency of adverse developmental effects in the population studied, particularly if the adverse effect of interest is rare. For example, to detect a relative risk of 3.0 for anencephaly, which has a baseline prevalence of 1/8000, the approximate number of subjects required in each exposed and non-exposed group is over 58,000 (based on a two-tailed test, 0.80 power, and $\alpha = 0.05$), whereas for each group only approximately 7300 subjects are needed to detect a relative risk of 3.0 for cleft lip/palate, which has a baseline prevalence of 1/930 (Source of incidence data: March of Dimes Perinatal Data Center, 2000, published on the Internet at: http://www.modimes.org/HealthLibrary2/InfantHealthStatistics/bdtable.htm.

For other pregnancy outcomes that occur more frequently in the population (such as early miscarriages), having a large sample size is not as critical. Case-control studies offer the advantage, then, that the relationship between maternal exposure and rare pregnancy outcomes can be assessed without the requirement of a large number of women. However, because case-control studies are retrospective, they suffer from problems of recall bias and ascertainment bias. In prospective cohort studies, identification of maternal exposure is less difficult because the women are asked about the exposure before they are included in the study. Case-control studies, however, must depend on the ability of the mother to remember exposures that took place during pregnancy. Certainly women who have had an adverse pregnancy outcome are more likely to remember exposures that occurred during pregnancy than are women who had uneventful pregnancies. Ascertainment bias occurs when an infant is included in the study that has the same developmental abnormality as the one of interest, but it is known that the infant’s abnormality is unrelated to the maternal exposure. A more detailed discussion of the epidemiological approaches traditionally used to evaluate human developmental toxicity can be found in the book, Scientific Frontiers in Developmental Toxicology and Risk Assessment by the NRC (2000) and in the Guidelines for Developmental Toxicity Risk Assessment developed by the US EPA (1991). The online versions of these resources can be found, respectively, at: http://www.nap.edu/books/0309070864/html/ and http://www.epa.gov/ncea/raf/pdfs/devtox.pdf.

Population-based surveillance studies and registry studies are special types of epidemiological studies that are becoming more common in developmental toxicology research. Population-based surveillance registries are established in order to monitor rates of congenital anomalies detected during pregnancy, at birth, or diagnosed up to one year of age. The quality of data from population-based surveillance registries differs depending on how active or passive the system is. For example, in an active surveillance trained registry staff members actively seek cases in hospitals, clinics, or other health-care facilities by systematically reviewing medical records (Edmonds, 1997). Passive systems, on the other hand, depend on identification from vital records departments or reports from local health care professionals. Under reporting of outcomes is a major problem with passive systems. In 1994, Congress provided funds to the Centers for Disease Control (CDC) to assist state health departments improve their birth defects surveillance capabilities (Erickson, 1997). During 1998, the CDC awarded 3-year cooperative agreements to surveillance programs in 18 states to address problems, which hinder the surveillance of birth defects. Links to some of the birth defects surveillance programs in the United States can be found at the National Birth Defects Prevention Network website: http://www.nbdpn.org/NBDPN/links.html.

Pregnancy registries collect postmarketing data on pregnancy exposures to particular products or agents and outcomes of these pregnancies. Pregnancy registries have been typically established by
pharmaceutical companies who are interested in keeping track of any reported reproductive effects of prescription drugs already on the market (Honein et al., 1999). One such pregnancy registry, the Antiepileptic Drug (AED) Pregnancy Registry, is supported by six manufacturers of anticonvulsants and recruits pregnant women throughout North America who are taking AED (Holmes and Lieberman, 2001). Recently, a number of teratology information services (TIS) in the United States have collaborated to prospectively collect data on particular pregnancy exposures and to follow up on pregnancy outcomes. Currently, they are studying the use of asthma medications during pregnancy and have also established a new registry on maternal exposure to leflunomide, a drug used for the treatment of rheumatoid arthritis (Leen-Mitchell et al., 2000). These multicenter studies are designed to allow for evaluation of a spectrum of adverse pregnancy outcomes ranging from spontaneous abortion to functional deficit. Pregnant women who contact participating TIS’s for information regarding the effects of a drug that has been selected for study are asked to participate in the research. Pregnant women who contact the TIS for information on a drug that is known to be nonteratogenic at therapeutic doses (e.g. acetaminophen or amoxicillin) comprise the nonexposed control group. When a drug that is used for the treatment of a chronic disorder is being investigated, a third matched control group, comprising of pregnant women who have the disease but who do not take the study medication, is also used. Although TIS research protocols have varied in the past, a standard framework for conducting collaborative research among TIS has recently been developed (Chambers et al., 2001). Registry and TIS studies can provide valuable outcome data, particularly on newly marketed drugs for which little developmental toxicity information is known. However, because pregnancy registries and TIS depend on voluntary reporting, the results that are obtained are subject to selection or referral bias. Selection of appropriate control groups can minimize this problem. Also, most pregnancy registries compare the observed rates of birth defects to those of population-based surveillance systems. Since methods of data collection and follow-up differ between registries and surveillance systems, such comparisons may not be appropriate (Honein et al., 1999).

A national longitudinal cohort study, led by the National Institute of Child Health and Human Development (NICHD), the CDC and the US EPA, has been proposed to identify and evaluate the effects of chronic and intermittent chemical, biological, physical, behavioral, and social influences on child health and human development. The study will be prenatal to adulthood in scope (Kimmel, 2001). The proposed aims of the study will be to: (1) determine the long term effects of potential developmental toxicants in the environment, such as pesticides, water disinfection by-products, and other classes of substances, (2) determine the influence of environmental factors and exposures on the cause and genetic expression of significant diseases and conditions of children, and (3) determine how patterns of exposure to environmental factors, such as aggregation of exposure, accumulation of exposures or the timing with respect to vulnerable periods (windows), differ with regard to biologic mechanisms and ultimately how these differences affect child health and development. More information about this proposed longitudinal study can be found at: http://www.nichd.nih.gov/about/despr/cohort/index.htm.

3. Dose–response assessment

Dose–response assessment involves characterizing the relationship between the magnitude of an exposure and the incidence of an adverse effect in both animals and humans. Dose–response relationships for developmentally relevant endpoints may be complicated as interaction between endpoints manifested can impart individual endpoint dose–response curves. For this reason, dose–response relationships for individual endpoints, as well as combinations of endpoints should be evaluated (US EPA, 1991).

In animal studies, the dose–response relationship is frequently determined by identifying the lowest effective dose or concentration that pro-
roduces an adverse effect (LOAEL), as well as the highest dose of an agent that does not produce a significant increase in adverse effects (NOAEL). The NOAEL approach focuses on a single dose (NOAEL) and provides no information on the dose–response curve below the observable range or the variability in the data (Omenn and Faustman, 1997). As a result, the NOAEL will be higher in studies that use small sample sizes and possibly lower (more conservative) in studies that use widely spaced evaluation doses. Due to the limitations of the NOAEL, there has been an interest in replacing the NOAEL and LOAEL approaches with a modeling approach that results in a benchmark dose when sufficient data are available (Crump, 1984; Kimmel and Gaylor, 1988). The benchmark dose approach uses a mathematical model to describe the dose–response relationship for a specified response rate (usually 5 or 10%) and lower confidence limit on dose.

The NOAEL, LOAEL, or benchmark dose can be used to calculate a ‘reference dose’ (RfD) or ‘reference concentration’ (RfC), which is an estimate of the dose or concentration in humans at which an adverse health effect is unlikely. The RfD is determined by dividing the NOAEL, LOAEL, or benchmark value by uncertainty and/or modifying factors. For food additives and contaminants, the US Food and Drug Administration (FDA) has set ADIs, or acceptable daily intake values, which involves extrapolating from NOAELs or LOAELs in a similar fashion. Adding safety factors to derive RfDs and RfCs as well as cancer slope factors for a number of pesticides and industrial chemicals can be found in EPA’s Integrated Risk Information System (IRIS) database available online at http://www.epa.gov/iris/index.html. This may mean that the user will have to go back to the hazard characterization information to follow specifics about the dose response assessment.

4. Exposure assessment

Exposure assessment involves determining the type and rates of exposure for the patient and determining the dose, duration, and timing of the patient’s exposure in relationship to the stage of pregnancy. In many cases, the Internet resources that were reviewed and which did provide exposure information provided exposure information in one of the following ways. These include providing exposure levels as comparisons to regulatory reference levels, providing reference to chemical reactivity levels, and reference to typical exposure scenario levels. Occupational exposure limits may be given for reference, such as the TLV (threshold limit value), PEL (permissible exposure limits), STEL (short-term exposure limits), TWA (time-weighted average), etc. For other exposures, such as for water or food, MCL (maximum contaminant levels) or ADI (acceptable daily intake) values, respectively, may be given. Reference to odor or volatility thresholds for a particular chemical or mixture may also be useful ‘first-cut’ exposure information. Similarly, reference to eye irritation levels may provide the reviewer with
some exposure references based on chemical reactivity. Some Internet resources provided ‘typical’ exposures for commonly evaluated exposure scenarios. For example, in the NIEHS Center for the Evaluation of Risks to Human Reproduction (CERHR) documents on phthalates, a scenario of high and average exposure estimates and ranges are given for exposure pathways of interest.

When the exposure is a drug where therapeutic dose information and pharmacokinetics are usually well understood, then determining patient estimates may be ‘relatively’ straightforward. On the other hand, occupational exposures are much more difficult to characterize. The amount of radiation absorbed by a patient administered a radiopharmaceutical agent for a diagnostic procedure, for example, can be better quantified than that absorbed by a nurse or pharmacist who prepares radiopharmaceutical agents for hospital use. Chemical occupational exposures are usually even more complicated to estimate than radiation. Occupational exposures vary widely among individuals even within the same occupational setting, depending on the amount of time spent performing a certain task, physical distance of the employee from the agent in question, and availability and use of protective equipment. Thus, quantitative estimates of maternal and conceptional exposures can be difficult to determine. In some cases it may be possible to measure ambient concentrations of an agent in the workplace but it is still unclear how much of the agent is actually absorbed by the individual. This information can be best provided by laboratory tests, which measure the amount of an agent or its metabolites in the blood or urine of an individual directly (biomarker of exposure) or measure a biomarker of effect.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends Biological Exposure Indices (BEIs) for workplace toxicants that are amenable to biological monitoring. For example, in a patient whose inhalational exposure to a workplace agent is below the TLV, an excessive biological value for that agent can implicate an additional exposure route (dermal) that should be evaluated. In cases where such a BEI is available and if it is not detected, then the patient can be reassured that the risk of a teratogenic effect associated with the exposure is unlikely. Unfortunately, appropriate laboratory tests of exposure are usually not available. Even if they are, it is not always possible to determine if the levels of an agent measured in blood or urine of a pregnant woman pose a risk to the developing embryo or fetus, since both peak as well as total exposure levels can be important in determining risk. Usually, such kinetic information is available for only therapeutic agents.

5. Risk characterization

In risk characterization, the information obtained in the steps above are integrated to estimate the magnitude of risk that the maternal exposure will result in an adverse pregnancy outcome. In addition, a patient’s ethnicity, race, age, lifestyle, occupation, genetic history, nutritional status or medical condition may modify her risk from that normally associated with a particular exposure.

6. Risk management

Clinical risk management refers to the process whereby the clinician uses the scientific information from the risk assessment process and risk estimates to identify clinical options for reducing and preventing hazards to the embryo or fetus. If a woman’s medical condition requires that she continue drug therapy during pregnancy, then the use of safer medications should be considered. Whenever possible physicians should use as few medications as possible to treat pregnant patients. Patients also need to be informed of the risks to their embryo if they choose not to continue with medical therapy. In some cases, an untreated medical condition may be more hazardous to the developing embryo than the medication used to treat the condition.

When exposures on the job are a concern, clinicians may be able to work with employers or industrial hygienists to ensure that exposures to potential reproductive and/or developmental toxic-
cants are adequately controlled through engineering or work practice controls. In some cases it may be necessary for the patient to be temporarily reassigned to another job position if she has anxiety regarding her exposures during pregnancy, or if the patient’s medical history or other risk factors suggest that her risk of an adverse pregnancy outcome is high.

Discussing developmental toxicity risks with a patient involves more than just identifying and characterizing the risk. The magnitude of risk must be communicated to the patient in a way that allows the patient to make informed decisions concerning the management of the pregnancy. The patient may need clarification frequently regarding population-based risks versus individual-specific risk assessments. Understanding risk is very difficult for most people, particularly when there is a great deal of scientific uncertainty. But lack of data is not the only factor that influences how patients perceive and accept risks. Clinicians need to be aware of the information and misinformation their patients bring with them to the counseling session and how it affects their perception of risk. Moreover, the clinician must try to understand the significance of that risk for the patient and her family. Women, who for personal or religious reasons oppose pregnancy termination, may experience considerable anxiety when faced with the possibility of an affected pregnancy, no matter how small the probability. Problems in communicating developmental toxicity risks can occur when the clinician fails to take these factors into account and to address the concerns of the patient (Polifka et al., 1997).

Once the nature and magnitude of developmental toxicity risk has been determined, decisions regarding prenatal diagnosis and continuation or termination of the pregnancy can be made. A number of tests are now available for the prenatal diagnosis of congenital anomalies. Ultrasound is a common and noninvasive technique that allows visualization of the fetus. A number of disorders of varying severity can now be accurately diagnosed by ultrasonography in the second trimester. Fetography and amniography are more invasive techniques that utilize contrast dye instilled in the amniotic cavity to visualize the contour of the fetal body. Fetoscopy is another invasive technique that can be used to visualize fetal body parts and obtain fetal tissue samples (Bianchi et al., 2000).

7. Using Internet resources to evaluate the developmental toxicity of environmental agents

Information from the primary literature in the biomedical and toxicological sciences can now be easily obtained online through a search of the National Library of Medicine bibliographic databases, PubMed, TOXLINE, and DART (Developmental and Reproductive Toxicology)/ETIC. PubMed was developed by the National Center for Biotechnology Information (NCBI) at NLM and can be accessed at http://www.ncbi.nlm.nih.gov/PubMed/ or the Toxnet home page at http://toxnet.nlm.nih.gov/. Its bibliographic citations are derived from MEDLINE and other sources. It also has links to the integrated molecular biology databases included in NCBI’s Entrez search and retrieval system. These databases include nucleotide sequences, 3-D protein structure data, population study data sets, and assemblies of complete genomes. MEDLINE contains more than 11 million bibliographic citations from the fields of medicine, nursing, dentistry, veterinary medicine, the health care system and preclinical sciences, dating back to 1966. TOXLINE is an extensive collection of bibliographic citations covering the biochemical, pharmacological, physiological, and toxicological effects of drugs and chemicals. It can be accessed at the Toxnet home page at http://toxnet.nlm.nih.gov/. DART/ETIC is another bibliographic database on the NLM system, specializing in developmental and reproductive toxicology. It contains some 100 000 references from the primary literature and can also be accessed at http://toxnet.nlm.nih.gov/.

No single resource exists that provides all of the information necessary for developmental toxicity risk assessment. A number of Internet resources are currently available, each of which varies in its approach to risk assessment, coverage, applicabil-
ity to clinical assessment, manner of presentation, and the audience it addresses. Some of these resources, such as the US EPA Chemical Fact Sheets and Summaries are a good starting place for toxicological information on chemicals (http://www.epa.gov/docs/chemfact/). This review will describe a sampling of Internet resources that have been developed and which can be useful in assisting the clinician in evaluating developmental toxicity risk. It uses as a model a recent report by the NRC that describes many of the information resources on developmental and reproductive toxicology (NRC, 2001). In addition to the information provided by the NRC report, the advantages and limitations of these resources for evaluating risk and the stage of the clinical risk assessment process that they are useful for will also be reviewed.

8. Internet resources which provide detailed evaluations relevant to developmental toxicity

The following section describes several Internet resources, listed alphabetically, which provide detailed and critical evaluations of data relevant to developmental toxicity.

8.1. California environmental protection agency hazard identification documents on reproductive and developmental toxicity

8.1.1. Description
Under the Safe Drinking Water and Toxic Enforcement Act of 1986, otherwise known as Proposition 65, the governor of California is required to produce a list of chemicals known to cause cancer or reproductive and/or developmental toxicity. The agency for implementing Proposition 65 is the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency. Chemicals can be added to the list if they have been identified to be cancer or reproductive/developmental toxicants in one of three ways: (1) by panel of scientists from outside the State government, including the Developmental and Reproductive Toxicant (DART) Identification Committee of the OEHHA Science Advisory Board, (2) by an authoritative body, such as IARC, US EPA, US FDA, or the National Institute for Occupational Safety and Health (NIOSH) or (3) by a state or federal agency that has formally required that the chemical be labeled or identified as causing cancer or reproductive/developmental toxicity. OEHHA staff reviews the available reproductive/developmental toxicity literature and data on the selected chemical and drafts a hazard identification document. These documents are made available on the OEHHA website for public review and input (http://www.oehha.org/home.html). The DART Identification Committee considers these documents and serves as the State’s qualified experts for rendering an opinion as to whether a chemical has been clearly shown through scientifically valid methods to cause reproductive or developmental toxicity.

OEHHA was required to develop, by 1 July 2001, a list of up to five chemicals identified as Toxic Air Contaminants (TACs) that may cause infants and children to be especially susceptible to illness. Summaries for chemicals reviewed by the state’s Scientific Review Panel (SRP) on Toxic Air Contaminants and considered priority candidates for the list can be found at: http://www.oehha.org/air/toxic_contaminants/sb25priorf.html. Draft documents for chemicals in drinking water that are undergoing preparation and which are planned for release for public review can be found at: http://www.oehha.org/public_info/public/ph-gannounc.html.

8.1.2. Type of risk assessment information provided
The Hazard Identification Documents review all of the available human and animal reproductive and developmental toxicity data for a given compound. Information regarding the chemical structure, physical characteristics, pharmacokinetics, and general toxicity of the compound is also provided. The amount and type of information contained in the documents vary. Some documents provide limited dose-response evaluation, exposure assessment, or determination of allowable or safe exposure levels, whereas others
provide extensive information. For example, for lead the OEHHA conducted a meta-analysis of cohort studies conducted in children older than five years in order to provide an estimate and range of risk for neurodevelopmental effects associated with each 1 mcg/dl increase in blood lead levels.

8.1.2.1. Usefulness in reproductive risk assessment and management

Advantages. The Hazard Identification Documents can provide a comprehensive review and evaluation of the reproductive and developmental toxicity data for an agent, and therefore, are useful for hazard characterization and exposure assessment. In some cases (e.g. lead), the documents are useful for all aspects of the risk assessment process.

Limitations. At the time of this review, locating the Hazard Identification Documents on the OEHHA website required considerable time and effort. The authors were unable to find any comprehensive published list of all agents that have been evaluated by the DART Identification Committee and for which Hazard Identification Documents exist. As the documents undergo lengthy governmental, scientific and public review, the information contained in them is not always up-to-date. It is not known when and how often these documents will be updated. Also, the choice of agents listed is governed by regulation.

Quality Control. The Hazard Identification Documents are prepared by panels of experts in reproductive and developmental toxicity from the California EPA Reproductive Cancer Hazard Assessment Section. Drafts of the documents are evaluated by the DART Identification Committee and then made available to the public for review and comment. Final review documents are then used by the DART Identification Committee to determine whether an agent should be placed on the state’s Proposition 65 list of reproductive and developmental toxicants.

8.2. IEHR evaluative process for determining human reproductive and developmental toxicity of agents

8.2.1. Description

The Evaluative Process was developed by the Institute for Evaluating Health Risks (IEHR) (Moore et al., 1995). This process used scientists with expertise in developmental and/or reproductive toxicology to evaluate the scientific data and to determine if the experimental animal or human data, either alone or in combination, were sufficient to judge an environmental agent’s potential to cause human developmental or reproductive toxicity. The evaluative process was intended for primary use by environmental, occupational, and public health officials and as a reference for physicians involved in medical counseling. The expert committee produced documents that assess the potential reproductive and developmental toxicity of lithium and boric acid (Moore, 1995, 1997). The Institute has been dissolved and no additional reviews will be forthcoming. However, the methodology of the IEHR evaluative process is currently used as the basis for the assessment process of the NIEHS CERHR (discussed below). The IEHR evaluative process is discussed in detail in the book, Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity (NRC, 2001), which has been made available online by National Academy Press: http://stills.nap.edu/books/0309073162/html/.

8.2.2. Type of risk assessment information provided

The evaluative process consists of five sections: the section 1 reviews the reproductive and developmental toxicity data on an agent; section 2 reviews and summarizes the basic toxicity information that is available for a given agent, including absorption, distribution, metabolism, and excretion of the agent; section 3 evaluates the developmental and reproductive toxicity data from both animal and human studies for evidence of concordance or inconsistency and judges the relevance of the toxicity data for predicting potential risk in humans; section 4 describes the pattern and degree of human exposure to the agent in question as a function of its use or uses; section 5 discusses the critical data that are needed to increase certainty in the judgment that a particular agent is a potential risk for humans. The final
phase of the evaluative process is a summary incorporating the scientific judgments and conclusions formed in each of the five previous sections.

8.2.2.1. Usefulness in reproductive risk assessment and management

Advantages. The evaluative process is a comprehensive assessment of human risk potential based on a weight of the evidence approach, and therefore, is useful for all aspects of the risk assessment process. The risk evaluation process is clearly delineated (Moore et al., 1995).

Limitations. The evaluative process is a thorough but lengthy process and only a few documents were produced. This process, however, now serves as the basis for the NIEHS CERHR.

Quality control. The evaluative process used a broad range of scientists from the government, academic, and private sectors who had expertise in developmental and/or reproductive toxicology, exposure assessment, and risk analysis. The documents underwent extensive peer review prior to publication.

8.3. NIEHS Center for the Evaluation of Risks to Human Reproduction (CERHR) documents

8.3.1. Description

The CERHR was established by the NTP/NIEHS in 1998 to provide scientifically based assessments of the potential for environmental agents to cause adverse effects on human reproduction and development. The assessment process used by CERHR is modeled after the IARC (International Agency for Research on Cancer) comprehensive reviews of carcinogens and is based on the evaluative process developed by Moore et al. (1995) for reproductive and developmental toxicants (see above). Chemicals to be reviewed are selected on the basis of several factors: production volume of the chemical, extent of human exposures, public concern about hazards posed by the chemical, and published evidence of reproductive or developmental toxicity. Center Reports on the evaluated chemicals are publicly available on the CERHR website (http://cerhr.niehs.nih.gov).

8.3.2. Type of risk assessment information provided

Center Reports are comprehensive assessments of the potential for a selected chemical to cause genetic, reproductive, and/or developmental toxicity in humans.

8.3.2.1. Usefulness in reproductive risk assessment and management

Advantages. The CERHR Report on a selected agent reviews all the data relevant to developmental and reproductive toxicology in humans, weighs the scientific evidence and assesses the likelihood that a given exposure to the agent poses a hazard to reproduction and the health and welfare of children. The reports, then, serve as an excellent resource for all aspects of the risk assessment process.

The evaluative process used in the preparation of CERHR reports is a lengthy but very open and transparent process. After a chemical is selected for evaluation, an expert panel, usually consisting of a dozen or more specific experts, meets in a public session, reviews the scientific evidence on the chemical, receives public input, and then prepares the report on the chemical. Finally, the NTP staff prepares a summary CERHR report that integrates the findings of the expert panel, public comments, and a discussion of any recently published studies. Reports on seven phthalate esters have been placed on the website. Additional reports on methanol, ethylene glycol, and 1- and 2-dibromopropane are in various stages of development.

Limitations. The CERHR has only been in existence since 1998. Thorough review and comment processes are involved in these assessments. To date, reports on seven compounds have been completed and an additional four are in the process of being developed. These assessments stop short of actually conducting a final risk assessment for specific exposures.

Quality control. CERHR reports are prepared by expert panels in reproductive and developmental toxicology and reviewed by a committee of scientists from the center, NIEHS, and other institutions. As detailed above, extensive peer review as well as public comments were solicited on each evaluation.
9. Internet resources which provide informational summaries relevant to developmental toxicity


9.1.1. Description

The ATSDR is a federal public health agency that conducts a number of activities to help identify, prevent and/or reduce the harmful effects of exposure to hazardous substances. One of their activities is to prepare toxicological profiles on more than 250 of the most hazardous substances found at Superfund sites. These profiles are currently available on the Internet at http://www.atsdr.cdc.gov/toxprofiles/. Information from the profiles has been abstracted into the ATSDR’s HazDat database which is available on the Internet at: http://www.atsdr.cdc.gov/hazdat.html.

9.1.2. Type of risk assessment information provided

Information contained in the toxicological profiles includes sources of human exposure, levels of exposure that result in harmful health effects, biological monitoring, chemical and physical information, toxicokinetics, developmental, reproductive, and genotoxicity, carcinogenicity, occupational exposures, populations at risk, and other related information. In addition, the profiles identify data gaps in current knowledge that are relevant to developing levels of exposure that may present significant risk of adverse health effects in humans.

9.1.2.1. Usefulness in reproductive risk assessment and management

Advantages. The toxicological profiles summarize and interpret available toxicological information and epidemiologic evaluations for hazardous substances. They provide excellent graphic comparisons on toxicological effects observed after acute, subacute and chronic exposure studies. This information is compared across species and critical endpoints. Useful human exposure information is provided. The toxicological profiles are useful for all aspects of the risk assessment process; however, they do not contain formal quantitative risk assessments.

Limitations. The toxicological profiles are quite lengthy and undergo internal and external peer review. Each profile is revised and republished approximately every three years. They have a general toxicological emphasis but include reproductive and developmental toxicity information. However, they were not designed to focus on these specific endpoints. Abstracted information available on the ATSDR HazDat Database is limited and written more for the lay audience. Nevertheless, as general public health statements they are useful risk communication tools.

Quality control. ATSDR toxicological profiles are reviewed by scientists from ATSDR, EPA, CDC and NTP. Each profile is also reviewed by external peer reviewers and draft reports are made available for public review.


9.2.1. Description

The Environmental Defense Scorecard collects data from more than 300 state and federal databases to profile environmental pollution problems and the health effects of toxic chemicals. It provides information on 6800 chemicals released by manufacturing companies. The Environmental Defense staff consists of more than 200 scientists, economists, analysts, and attorneys.

9.2.2. Type of risk information provided

Every chemical profile contains information on which industries use the chemical, how much of it is released into the environment, and the recognized and suspected health hazards that the chemical poses for humans. Risk assessment values for cancer and noncancer effects of each chemical are also provided when available. The risk assessment values provided by Scorecard as reference values (such as q5s and RfDs for cancer and noncancer effects, respectively) are those developed by governmental agencies, such as the ATSDR, California OEHHA or US EPA. The Environmental Defense Internet site also provides its own toxicity assessment values as ‘toluene equivalencies’.
9.2.2.1. Usefulness in reproductive risk assessment and management

Advantages. The Environmental Defense Scorecard provides useful information regarding the volume of a compound that is released into the environment in the US by media and by compound. This is the toxicity release information data required by EPA regulations. Therefore, it is useful for hazard characterization. It also provides a number of links to other toxicology-related websites.

Limitations. Information on the reproductive and developmental toxicity of chemicals is very limited. Chemicals are labeled as reproductive and/or developmental toxicants by the Scorecard if they appear on California’s Proposition 65 list. No data are provided and the reader must go to the references provided to obtain further information. Also, the non-cancer risk assessment values refer to all non-cancer endpoints and consequently it is difficult to know what these summary values mean for reproductive and developmental toxicity in particular. The risk estimates are compared with a reference compound, toluene, and provide comparisons that are of highly questionable utility.

Quality control. The Scorecard obtains its information from online governmental databases and provides links to them. No information is provided regarding internal or external review of the chemical profiles.

9.3. IPCS/INCHEM Programme: (http://www.inchem.org)

9.3.1. Description

IPCS/INCHEM Programme is a cooperative effort between the International Programme on Chemical Safety (IPCS), the World Health Organization (WHO), the International Labour Organization (ILO), the United Nations Conference on Environment and Development (UNCED) and the Canadian Centre for Occupational Health and Safety (CCOHS). The service consolidates up-to-date health and safety information on chemical substances from monographs produced by these international organizations. Internet users can find chemical safety-related information from the following data sources:

- Environmental Health Criteria (EHC) monographs,
- Health and Safety Guides (HSGs),
- International Chemical Safety Cards (ICSC),
- Pesticide Data Sheets (PDSs),
- Poisons Information Monographs (PIMs),
- Joint Expert Committee on Food Additives (JECFA) monographs and evaluations,
- Joint Meeting on Pesticide Residues (JMPR) monographs and evaluations,
- IPCS/EC Evaluation of Antidotes Series,
- CIS Chemical Information,
- OECD Screening Information Data Sets (SIDS),
- Concise International Chemical Assessment Documents (CICADS),
- International Agency for Research on Cancer (IARC)—Summaries and Evaluations.

9.3.2. Type of risk assessment information provided

Information contained in the various full-text documents includes physical and chemical properties, analytical methods, sources of exposure, kinetics and metabolism, and risks to animal and human health.

9.3.2.1. Usefulness in reproductive risk assessment and management

Advantages. IPCS/INCHEM documents provide a comprehensive and critical review of the toxicological and exposure information on drugs and chemicals commonly used throughout the world. The information provided in the documents is designed for scientists, clinicians, and regulators concerned with chemical safety and management. In the IARC monographs, a clear evaluation process is delineated for assessment of carcinogenic risk, but not for other toxicological endpoints. Although the focus of most of these evaluations is not developmental risk, these documents can provide summary information on key developmental toxicity studies. These evaluations frequently focus on either structurally- or process-related groups of compounds, thus providing very useful exposure and use information. Also, infor-
mation regarding typical exposures in certain occupations (e.g. hairdressers, the rubber industry, etc) can be found in these monographs. The IPCS/INCHEM website is useful for all aspects of the risk assessment process.

Limitations. Information provided in some of the documents can be outdated; thus the user is encouraged to examine the evaluation dates. New assessments may be available frequently for certain topics. Information provided in the CI-CADs and PIMs is up-to-date.

Quality control. The monographs are prepared by the organizations, which collect and validate the information contained in the monographs. The monographs subsequently undergo internal review by IPCS and then peer-review by committees of international experts that have been selected by the organizations.

9.4. Material Safety Data Sheets:
(http://hazard.com/msds/; http://siri.org/msds)

9.4.1. Description

Material Safety Data Sheets (MSDS) are documents prepared by chemical manufacturers that describe the hazardous ingredients, physical and chemical characteristics, acute and chronic health hazards, and exposure controls of their products. If the product name is not known, health care professionals can find product information by going to the MSDS Provider website, and looking for products listed under various manufacturers: (http://www.msdspublisher.net/Site/msdspublisher.nsf/search?openform). Although some form of MSDS has been around since the middle of the 19th century (see Aaron Kaplan’s presentation at the 191st ACS National Meeting at http://www.phys.ksu.edu/area/jrm/Safety/kaplan.html), the Occupational Safety and Health Administration (OSHA) began requiring and setting the standards for MSDS’s for hazardous materials in 1986. The EPA as well as some state and local agencies also require MSDS’s (see the Where to Find Material Safety Data Sheets on the Internet website: http://www.ilpi.com/msds/faq/partb.html # agency).

9.4.2. Type of risk assessment information provided

Each material safety data sheet contains the following key information about a product: product identification, hazardous ingredients, physical data, fire and explosion hazard data, health hazard data, reactivity data, spill or leak procedures, special protection information, and special precautions.

9.4.2.1. Usefulness in reproductive risk assessment and management

Advantages. Material Safety Data Sheets are important sources of information about products that pregnant patients may be exposed to on the worksite. The documents are useful in the hazard identification and exposure assessment portions of the risk assessment process. They also provide the phone numbers of individuals that can be contacted for further information.

Limitations. Material Safety Data Sheets are prepared by individual manufacturers to provide information on the safe use of specific products. The quality of the information varies and most material safety data sheets are very brief and lack adequate information to assess toxicity, such as dose-response information. Very little, if any, developmental or reproductive toxicity information is provided. What information is provided can be misleading to nonexperts. For example, the various congenital anomalies that were observed in animal teratology studies may be listed without an explanation or dose context; hence, relevancy of the findings to humans is lacking. MSD sheets may simply state that a substance is a reproductive toxicant in humans without any description of the supportive toxicological evidence or exposure circumstances under which this statement applies. Legal requirements of reporting often outweigh the scientific utility of these documents.

Quality control. Although employers must keep updated material safety data sheets readily accessible to employees under the Occupational Safety and Health Administration Hazard Communication Standard and state right-to know laws, usually no external review of the information contained in the documents is conducted.
9.5. Organization of Teratology Information Services (OTIS): http://www.otispregnancy.org

9.5.1. Description
OTIS is an alliance of more than 45 teratogen information services located throughout North America. Teratogen information services are hospital- or university-based clinical programs which evaluate and interpret the medical literature regarding pregnancy exposures. Some services provide consultation only to health care professionals while others provide consultation to both professionals and the general public. The purpose of OTIS is to strengthen existing teratogen information services in their ability to provide timely and accurate information.

9.5.1.1. Type of risk assessment information provided. OTIS has developed ‘fact sheets’ for health care providers to distribute to patients and clients on topics such as toxoplasmosis, hyperthermia, chickenpox, and Paxil®. These fact sheets are also available on the OTIS Web page. The fact sheets are written in a question-answer format. A brief evaluation of animal and/or human studies is used to answer questions such as ‘Can taking Paxil during my pregnancy cause birth defects?’ and ‘Can I take Paxil® while breastfeeding?’ Also, a list of teratogen information services and their phone numbers are provided on the website so that health care professionals and their patients can call the nearest service for a consultation regarding a particular pregnancy exposure.

9.5.1.2. Usefulness in reproductive risk assessment and management

Advantages. OTIS fact sheets provide a brief, authoritative summary of the potential reproductive effects of common pregnancy exposures, which make them useful for wide dissemination to the general public. The fact sheets provide risk evaluation, and therefore, are useful in the risk characterization and management portions of the risk assessment process.

Limitations. The fact sheets are written for nonexperts, and therefore, do not provide the reader with detailed information on the animal and human studies on which the interpretation of studies is based. No formal risk assessment process is used to develop the fact sheets.

Quality control. OTIS fact sheets are written by the OTIS Education Committee and undergo internal review by all OTIS members. The OTIS membership is represented by experts in a variety of disciplines related to teratology, such as medical genetics, pharmacology, dysmorphology, toxicology, epidemiology, obstetric/maternal fetal medicine, and radiation biology.


This module is a collection of four commercially available reproductive risk information databases: Reprotex, Reprotox, Shepard’s Catalog of Teratogenic Agents, and TERIS. A description of each database follows. The Reprorisk System® is available through Micromedex, Inc, a subsidiary of Thomson Healthcare. An Intranet version of Micromedex, Inc. is available by subscription. Further information regarding the Reprorisk System® and other available products can be obtained by going to the Micromedex website http://www.micromedex.com/.

9.7. Reprotex®: (http://www.micromedex.com)

9.7.1. Description
This database is a component of the Reprorisk System® of Micromedex, Inc, and therefore, available via the Intranet by subscription only.

9.7.2. Type of risk assessment information provided
Reprotex contains reviews of the reproductive, carcinogenic, and genetic effects of acute and chronic exposures to over 850 commonly encountered industrial chemicals. Information on some drugs, such as cocaine and fluoxetine, is also included. In addition, the monographs contain information on chemicals pertinent to workplace exposures, such as biomonitoring and governmental regulation.
9.7.2.1. Usefulness in reproductive risk assessment and management

Advantages. Reprotext is a comprehensive database that summarizes a wide range of information regarding the health effects of drugs and chemicals. Therefore, it is useful in characterizing agents that have the potential to cause adverse developmental or reproductive effects. The sections on ‘Predisposing Conditions’ and ‘Biomonitoring’ also make it useful for exposure assessment and risk management.

Limitations. A ‘grade-card’ scale that suggests the level of reproductive hazard is included in each agent review. Ratings for reproductive hazards are in the following format:

A+, Human reproductive hazard with no known no-effect dose.
A, Human reproductive hazard with known no-effect dose.
A−, Unconfirmed human reproductive hazard.
B+, Multiple reproductive effects in animals, but no human data.
B, Mixed reproductive effects in animals, but no human data.
B−, Few reproductive effects in animals but no human data.
C, No reproductive data found.
D, Insufficient information to identify.
E, Known not to effect animal reproduction, but no human data.
F, Known not to affect human reproduction.

This system of ranking suffers from the same limitations as other classification systems, such as the one developed by the FDA for physicians (FDA, 1979). Such classification systems lack information regarding dose, route of exposure, potency, and other important parameters necessary to assess reproductive risk in humans. For example, acetaldehyde is given a reproductive hazard rating of A− because it is a metabolite of ethanol, which is known to be involved in the fetal alcohol syndrome. However, under normal occupational exposures via inhalation, acetaldehyde is not considered to be a reproductive risk; therefore, to categorize acetaldehyde as an unconfirmed human reproductive hazard under these circumstances can be misleading. For these reasons, the reproductive hazard ratings should be used with caution in risk characterization and management.

Quality control. Reprotext® monographs were originally written by Betty J. Dabney, Ph.D., an expert genetic and reproductive toxicologist. The Reprotext monographs are currently written and reviewed by various health professionals on the Micromedex TOMES® Editorial Staff. There is no formal external peer review of the monographs.


9.8.1. Description

Reprotox® is a computerized database that was developed by A.R. Scialli, M.D. and associates at the Reproductive Toxicology Center in Bethesda, MD. Reprotox® is a component of the Reprorisk System® of Micromedex, Inc, and therefore, available via the intranet by subscription only. It is also available by subscription through the Reproductive Toxicology Center as a stand-alone product in other electronic formats.

9.8.2. Type of risk assessment information provided

Reprotox® provides up-to-date information on a wide range of environmental agents, including medications, recreational drugs, infectious diseases, chemicals, and other environmental agents. The summaries review developmental and reproductive toxicity data from human, animal, as well as in vitro studies. Bibliographic references follow the summary of data. Information on medications provided by pharmaceutical companies in package inserts is also included in the summaries.

9.8.2.1. Usefulness in reproductive risk assessment and management

Advantages. Reprotox® was developed for use by scientists, health care professionals and governmental agencies. The database summarizes the scientific data on a large number of environmental agents and includes information on every aspect of reproduction, including fertility, pregnancy, paternal exposure, and lactation. Subscribers to Reprotox® can request information on agents not already included in the database. The information
provided in Reprotox is useful for hazard characterization in the risk assessment process.

Limitations. Although there is interpretation of the data for some of the agents, risk assessment is not done in a formal fashion.

Quality control. Reprotox® summaries are written by health care professionals at the Reproductive Toxicology Center. Summaries are reviewed by Dr Anthony Scialli, who is an obstetrician with expertise in clinical teratology. There is no external peer review of the summaries.

9.9. Shepard’s catalog of teratogenic agents: (http://www.micromedex.com)

9.9.1. Description

The Catalog of Teratogenic Agents is a classic reference book written by Dr Thomas H. Shepard (Shepard, 2001). It was first published in 1973 by Johns Hopkins University Press and is currently in its 10th edition. An electronic version of the book is distributed by Micromedex, Inc. as a component of the Reprorisk System®. An electronic version of the Catalog is also distributed as a stand-alone product in conjunction with the TERIS database (see below).

9.9.2. Type of risk assessment information provided

Shepard’s Catalog of Teratogenic Agents provides up-to-date information on the developmental and reproductive toxicologic effects of more than 2900 drugs, chemicals, and infectious agents. Information from human, animal, and in vitro studies are included. Although the emphasis is on teratology studies, information regarding fertility and paternal exposures is sometimes included. No information regarding the effects of environmental agents on the nursing infant is provided. The 10th edition includes newly added information on more than 100 developmental genes that have been found to cause syndromes or congenital defects.

9.9.2.1. Usefulness in reproductive risk assessment and management

Advantages. The Catalog of Teratogenic Agents includes studies from the Japanese and Russian literature. Until recently, Japanese pharmaceutical companies were required by law to publish their animal teratology studies. This information is valuable because sometimes it is the only published information that is available on a particular drug. The Catalog also summarizes the various developmental and reproductive toxicologic effects that have been found to be associated with certain occupations. The information is, therefore, useful for hazard characterization.

Limitations. No interpretation of the data for developmental toxicity risk in humans is provided.

Quality control. Dr Shepard is a pediatrician and widely-recognized expert in clinical teratology. There is no external peer review of the summaries.


9.10.1. Description

TERIS is a computerized database that provides up-to-date, authoritative information regarding the effects of drugs and chemicals on the embryo or fetus. It was developed by Dr J.M. Friedman and includes information on more than 1100 agents. The majority of the agents on the system are pharmaceuticals. An intranet version of the database is distributed by Micromedex, Inc. as a component of the Reprorisk System®. A list of agents available on the TERIS system is available on the Internet and individual agent summaries can be purchased with a small fee through the Clinical Teratology Website http://depts.washington.edu/~terisweb/teris/index.html. Other electronic formats of TERIS in conjunction with Shepard’s Catalog of Teratogenic Agents are available by subscription from TERIS at the University of Washington in Seattle, Washington.

9.10.2. Type of risk assessment information provided

TERIS provides information on the teratogenicity, transplacental carcinogenesis, embryonic or fetal death, and fetal and perinatal pharmac-
logic effects of the most commonly-used medications and includes various environmental agents. Other aspects of developmental and reproductive toxicity, such as alterations of fertility, male-mediated effects and effects on the nursing infant are not included. Dose-effect and temporal relationships are emphasized whenever possible. Factors such as chronic versus one-time use of a particular agent and interaction with other factors are also delineated. Only in vivo mammalian studies are considered.

Each agent on the TERIS system is assigned an aphorism (or short narrative statement) that refers to the risk of teratogenic effects after maternal exposure to commonly-encountered doses. The aphorism rates the risk of teratogenic effects in the children of women exposed to the agent during pregnancy as either None, Minimal, Small, Moderate, or High. Risks rated as ‘Moderate’ or ‘High’ are considered important enough, at least in some instances, to affect pregnancy management. A ‘High’ risk is assigned if the defects produced are severe (e.g. cardiac malformation or profound mental retardation), if the risk of major malformations was great, or both. Exposures to unusually high doses, especially to doses that are toxic to the mother, may be associated with a higher risk. Other adverse effects, such as alterations of perinatal adaptation or transplacental carcinogenesis, are considered separately in the narrative and, if deemed sufficiently important, are also mentioned in the aphorism under ‘Comments’. An aphorism of ‘Undetermined’ is given to agents for which no or very limited human data are available. This aphorism may be modified on the basis of general pharmacology, animal data, or analogy to a closely-related agent that has been studied more thoroughly. In other cases, the aphorism ‘Unlikely’ is used to denote an agent that is unlikely to pose a substantial teratogenic risk with usual exposures, but the data are too limited to state with confidence that there is no risk above the background risk that attends every pregnancy. Each agent’s teratogenic potential is analyzed on the basis of the reproducibility, consistency, and biologic plausibility of available clinical, epidemiologic, and experimental data. Effects seen in animal studies are weighed more heavily if the exposure is similar in dosage and route to that encountered clinically, if the malformations produced are analogous to those reported in humans, and if the species tested are closely related to humans phylogenetically.

As the developmental toxicity data for various agents often differs greatly with respect to types, number, size and limitations of the studies that are available, the TERIS Advisory Board uses a Delphi approach to evaluate the teratogenic risks associated with prenatal exposures to agents. This approach has been widely used in health research and uses consensus among experts to help resolve inconsistencies found in the results of published studies (Jones and Hunter, 1995).

9.10.2.1. Usefulness in reproductive risk assessment and management

Advantages. TERIS is intended to assist health practitioners assess teratogenic risks in individual patients. For each agent on the system, TERIS provides two assessments: (1) a risk assessment with an estimate of the magnitude of teratogenic risk to a child born after maternal exposure to the drug or chemical during pregnancy and (2) an assessment of the quality and quantity of the data on which the teratogenic risk estimate is based. The risk estimates are based on published animal and human data identified through a systematic search of the PubMed, Toxline, and DART bibliographic databases. Data from human studies are weighed more heavily than data from animal studies in the derivation of TERIS risk estimates. In the absence of human data, the teratogenic risk of an agent in humans is considered to be undetermined. However, a cautionary comment regarding the potential for a high risk may be added if the general pharmacology, animal data, or analogy to a closely related agent suggest that such a potential might exist. Although not as extensive as the evaluative process, TERIS nevertheless considers all of the relevant data and reaches a determination about an agent’s magnitude of teratogenic risk. Therefore, it is useful for most aspects of the risk assessment process with respect to developmental toxicity, but has limited exposure information for chemicals and other environmental agents.
**Limitations.** The majority of agents on the TERIS system are medications and not all aspects of reproductive and developmental toxicity are considered in the agent reviews. As the TERIS risk estimates are semi-quantitative, they are vulnerable to misinterpretation. For example, a risk of ‘Undetermined’ may be misconstrued to imply that the agent is not a developmental toxicant in humans since no adverse effects have been demonstrated in humans. However, in TERIS a risk estimate of ‘Undetermined’ implies only that the risk in humans is unknown. As stated above, this risk estimate may be followed in some cases by a comment stating that even though the risk is unknown, the general pharmacology, animal data, or analogy to a chemically-related agent suggests that there might indeed be a potential for risk.

**Quality control.** TERIS agent summaries are written by Dr J.M. Friedman and Dr Janine E. Polifka. The summaries are then peer-reviewed by an Advisory Board which is comprised of six (including Dr Friedman) internationally recognized experts in clinical teratology and other related fields, such as medical genetics, pediatrics, epidemiology, toxicology, and dysmorphology. TERIS risk assessments are based on a consensus of the TERIS Advisory Board after each has independently reviewed the summaries. Risk assessments provided by the Board members are ranked and summarized by the TERIS staff. Consensus is derived by excluding the highest rating and the lowest rating if the difference is no greater than two units. An average of the remaining ratings is then taken. Any agent, which has ratings that are two units or further apart are automatically held for discussion and rerating. If consensus is reached, the process ceases and the agent summary (along with its risk aphorisms) is uploaded on the TERIS system. The Advisory Board meets approximately three times per year to discuss those agents for which a consensus could not be initially achieved. The discussion continues until a consensus is reached.


9.11.1. Description
The Teratology Society is a national organization comprised of members from a wide range of scientific fields, including pediatrics, anatomy, epidemiology, pharmacology, toxicology, developmental biology, obstetrics, pathology, genetics, and dentistry. The purpose of the Society is: (1) to promote research that studies the causes of abnormal embryonic development and birth defects, (2) to communicate results of these studies to health care professionals, public health officials, and the general public and (3) provide education and training on the causes, mechanisms, treatment, and prevention of birth defects. The Teratology Society holds an annual meeting for the purpose of exchanging ideas and research results.

9.11.2. Type of risk assessment information provided
The Teratology Society periodically develops position papers on important topics, such as vitamin A supplementation during pregnancy, use of folic acid to reduce the risk of birth defects, and the developmental toxicity of endocrine disruptors to humans. The papers can be viewed on the Teratology Society website ([http://teratology.org/comm/commpub.htm](http://teratology.org/comm/commpub.htm)). These position papers critically examine the scientific evidence for the occurrence and magnitude of human teratogenic effects associated with the agents of concern. Recommendations concerning exposures to these agents during pregnancy are then presented. Public letters regarding important issues, such as use of dietary supplements during pregnancy, are also available on the Teratology Society Website. Full-text review articles on potential human teratogens (teratogen updates) published in the Teratology Journal can be obtained from the Teratology Society Website ([http://teratology.org/members/teratupd.htm](http://teratology.org/members/teratupd.htm)).

9.11.2.1. Usefulness in reproductive risk assessment and management

**Advantages.** Some of the position papers and all of the teratogen updates provide a thorough review of the developmental and reproductive toxicology studies that have been published on a particular agent, and therefore, are very useful for
hazard characterization and exposure assessment. Recommendations regarding the use of these agents during pregnancy presented in the position papers are useful for risk characterization and provide valuable guidelines for risk management.

**Limitations.** Position papers are typically developed for agents that have received a great deal of publicity (e.g. vitamin A, folic acid and alcohol) or for which new evidence exists. No formal risk assessments have been adopted in the development of the position papers or teratogen updates.

**Quality control.** The position papers are written by members of the Public Affairs Committee and approved by the Public Affairs Committee and the Council of the Teratology Society.

9.12. **Toxicology Data Network (TOXNET®):**

**http://toxnet.nlm.nih.gov/**

9.12.1. **Description**

TOXNET® is a collection of toxicology datafiles and bibliographic databases available through the National Library of Medicine (NLM). In addition to bibliographic databases such as TOXLINE, DART/ETIC, PubMed, and EMIC, TOXNET® provides access to the following datafiles:

- **CCRIS**—contains information on test results on carcinogenicity, tumor promotion and inhibition, and mutagenicity.
- **ChemID Plus**—provides information on chemical structures and nomenclature. It contains over 350,000 chemical records.
- **GENE-TOX**—database of mutagenicity test data on over 3000 chemicals.
- **HSDB (Hazardous Substances Data Bank)**—database that provides information on the toxicologic and biomedical effects of more than 4500 chemicals. Data on human health effects, industrial hygiene, emergency handling procedures, environmental fate, occupational exposure standards, and other related areas are obtained from the primary literature, government documents and technical reports.
- **IRIS (Integrated Risk Information System)**—database prepared and maintained by the US EPA that contains carcinogenic and noncarcinogenic health risk information on over 500 chemicals. Each chemical review contains information on oral reference doses (RfDs) and inhalation reference concentrations (RfCs) for chronic noncarcinogenic health effects (including developmental and reproductive effects), hazard identification, oral slope factors and oral and inhalation unit risks for carcinogenic effects. IRIS toxicological reviews are also available online through US EPA at [http://www.epa.gov/irisweb/index.html](http://www.epa.gov/irisweb/index.html).
- **TRI (Toxics Release Inventory)**—contains names and addresses of facilities that release toxic chemicals into the environment, the amounts of certain chemicals released to the air, water, or land or transfer to waste sites.

9.12.2. **Type of risk assessment information provided**

Both HSDB and IRIS briefly summarize animal and human developmental and reproductive toxicity studies and provide information regarding occupational exposure standards. HSDB provides additional information on chemical safety/handling and biomonitoring methods. IRIS reviews data for setting chronic reference doses (RfDs) and chronic reference concentrations (RfCs).

9.12.2.1. **Usefulness in reproductive risk assessment and management**

**Advantages.** The information provided by HSDB and IRIS is particularly useful for hazard identification and exposure assessment. The information provided by HSDB on occupational exposure standards and biomonitoring methods also make it useful for risk characterization. IRIS includes links to online comprehensive toxicological reviews for many new chemicals on the EPA website: [http://www.epa.gov/iris/index.html](http://www.epa.gov/iris/index.html).

**Limitations.** Review of data for setting RfDs and RfCs in IRIS is comprehensive, but use of these in risk assessment requires training in toxicology.

**Quality control.** HSDB is peer-reviewed by the Scientific Review Panel (SRP), a committee of experts in toxicology, occupational medicine, pharmacology and other related disciplines. IRIS was developed by the EPA. Therefore, in accordance with EPA policy, the IRIS documents un-
dergo internal and external peer review, followed by an agency-scientific consensus review.

10. Internet resources which provide primary data relevant to developmental toxicity


10.1. Description

One of the goals of NTP is to determine the developmental and reproductive toxicity of chemicals to which women of reproductive age are exposed by using well-controlled animal studies as a basis for human risk assessment. To achieve this, animal studies are designed to determine a dose-response relationship in addition to the detection of a potential for toxicity. A list of chemicals that have already been studied can be found at http://ntp-server.niehs.nih.gov/htdocs/pub-TT0.html. Individual documents can be purchased through the National Technical Information Service (NTIS) http://www.ntis.gov/search.htm. The full text of the NTP Technical Reports and NTP Toxicity Reports from 1997 onward are currently available by subscription at the website of the Environmental Health Information Service (EHIS): http://ehis.niehs.nih.gov/. Abstracts of past and current reports are available free of charge. The EHIS is a service of the NIH—National Institute of Environmental Health Sciences and the DHHS—National Toxicology Program. Nominations for chemicals to be studied come from the general public, NIEHS, and other government agencies. Generally three categories of study designs listed on the NTP website are of interest for developmental toxicology and these include teratology studies (where chemical exposure occurs during development), continuous breeding studies (where exposure occurs throughout two generations), and short-term developmental and reproductive toxicity screen in rats. These latter studies attempt to identify the physiologic processes, such as development, female and/or male reproduction, and various somatic organs/processes that are the most sensitive to exposure to chemicals of interest. Guidance on internationally harmonized animal study designs for evaluating the developmental and reproductive effects of pharmaceuticals can be found on the FDA website at: http://www.fda.gov/cder/guidance/s5a.pdf. For guidance on testing protocols for food additives and contaminants, see: http://www.cfsan.fda.gov/~redbook/red-toa.html. For pesticides and industrial chemicals, guidance for study designs can be found on the EPA website at: http://www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/.

10.2. Type of risk assessment information provided

NTP is interested in developing studies that are designed to evaluate the effects of exposure to chemicals during critical phases of development, which may result in reproductive and/or developmental toxicity. Long term studies that include exposure of pregnant animals to the chemical of interest, followed by direct exposure to the offspring for as long as puberty are emphasized.

10.2.1. Usefulness in reproductive risk assessment and management

10.2.1.1. Advantages. The ultimate goal is to have a better understanding of the site and mechanism of action of reproductive and developmental toxicants. NTP studies are designed to cover broad
treatment periods. These types of studies are useful for hazard characterization and dose-response assessment.

10.2.1.2. Limitations. Considerable toxicological expertise is required to extrapolate the results from these studies to humans for purposes of risk characterization. For example, exposure of pregnant animals throughout the entire period of organogenesis and beyond with daily repeated administrations may not always have relevance to typical exposures in humans.

10.2.1.3. Quality control. NTP study reports are evaluated by a subcommittee of the NTP Board of Scientific Counselors.

11. Using Internet resources to obtain information on and evaluate the developmental risks associated with toluene

Using the Internet resources described above, we have examined the developmental toxicity information related to exposures to toluene during pregnancy, and have discussed its relevance for developmental toxicological risk assessment. Toluene was chosen to illustrate this process because exposure in humans can occur in two ways: in the workplace via inhalation and dermal exposures and through self-abuse of compounds in paint or glue sniffing. Therefore, evaluating the risks associated with these two types of exposures during pregnancy requires different information. In this review, we have chosen not to comment on the factual statements made in these reference sources but rather to provide the reader with an introduction to the range and type of available information via the Internet.

11.1. Toluene evaluation

11.1.1. Hazard characterization

11.1.1.1. General Toxicity

Internet resources: information relevant to the hazard characterization of toluene was extracted from the following web resources.
500–1500 ppm: palpitations, weakness, and impaired reaction time.

Effects associated with prolonged glue sniffing: Irreversible neurological effects, including effects on behavior and intelligence, degeneration of the optic nerve and nerve deafness; metabolic acidosis and kidney damage; sudden death.

**Mechanism of action**

In animals, low concentrations (less than 100 ppm) of toluene produced disturbances in dopaminergic mechanisms of the basal ganglia, probably leading to functional changes in sensory-motor integration.

**Critique of Internet Resources**

Using the websites listed, the user could locate dose-response information on the general toxicity of toluene. This included information on target organs and some information on exposure levels that would be anticipated to affect those specific tissues. Although not emphasized in our summary of data, information was available for both human and animal effects, and some inclination of relative sensitivity of animals versus humans was given. Levels of toxicity were compared with the odor threshold, thus providing some exposure clues for the user.

11.1.1.2. Reproductive and developmental toxicity

**Internet resources:** the following Internet resources were utilized in our evaluation of the developmental toxicity of toluene.

- ATSDR: [http://www.atsdr.cdc.gov](http://www.atsdr.cdc.gov);

**Resource information.**

**Animals**

Toluene is not teratogenic in the offspring of animals exposed via inhalation to toluene during pregnancy at doses <1–50 times the human occupational threshold limit value (Hudak and Ungvary, 1978; Shigeta et al., 1982; Ungvary et al., 1983; Anonymous, 1984, 1985; Ungvary and Tatrai, 1985; Courtney et al., 1986; Klimisch et al., 1992; Roberts et al., 1993; Ono et al., 1995; Wilkins-Haug, 1997; Haas et al., 1999; Hougaard et al., 1999). Some of these animal studies had very robust study designs with 25 or more pregnant animals in multiple exposure assessment categories. Fetal growth and retardation are seen at the higher doses, often in association with maternal toxicity. Toluene was not teratogenic in the offspring of pregnant rats fed 520–650 mg/kg per day of toluene, however, reduced fetal brain weight was observed. This dose was estimated to produce blood levels similar to those obtained by inhalational abuse of the solvent in humans (Gospe et al., 1994, 1996; Gospe and Zhou, 1998).

Behavioral alterations were observed among the offspring of rats and hamsters exposed to toluene vapors throughout pregnancy at doses twice the human occupational threshold limit value (Da-Silva et al., 1990). In other studies, behavioral alterations were seen among the offspring of rats treated with toluene throughout pregnancy only at higher doses that were 24–40 times the human occupational threshold limit value, but not after the lower doses (Jones and Balster, 1997; Thiel and Chahoud, 1997; Haas et al., 1999; Hougaard et al., 1999).

**Humans**

Inhalational exposure to toluene at levels greater than 1000 ppm was associated with impotence in men in several studies.

An association with adverse pregnancy outcome and maternal occupational exposure to toluene at least 3 times a week in early pregnancy was observed in one case-control study of 206 spontaneous abortions among female laboratory workers (odds ratio = 4.7, 95% confidence interval 1.4–15.9) (Taskinen et al., 1994). This has not been verified by two other case-control studies, one of 38 women who had miscarriages while working in pharmaceutical factories and the other of 166 pregnancies of women who were exposed to toluene while working in university laboratories (Axelson et al., 1984; Taskinen et al., 1986). In a cohort study of 55 women with occupational exposure to high levels of toluene (50–150 ppm), an increased rate of spontaneous abortion (12.4%) was observed (Ng et al., 1992). However, the observed increased rate of spontaneous abortion may be due to the abnor-
mally low rates of spontaneous abortion in the comparison groups (2.9 and 4.5%).

An increased frequency of occupational exposure to aromatic solvents was found in one case-control study of the mothers of 301 infants with major congenital anomalies (McDonald et al., 1987). The excess exposure was attributable almost entirely to toluene since exposure to toluene was four times more frequent in cases than controls. No consistent pattern of malformations was observed and the doses of toluene that the mothers were exposed to were low. No association with maternal occupational exposure to aromatic solvents during the first trimester of pregnancy was observed in another case-control study of 36 infants with malformations who were born to female laboratory workers (Taskinen et al., 1994).

More than 30 children whose mothers regularly abused toluene during pregnancy have been reported to exhibit a characteristic pattern of congenital anomalies that resembles the pattern seen in children with fetal alcohol syndrome (Hersh et al., 1985; Goodwin, 1988; Hersh, 1989; Lindemann, 1991; Wilkins-Haug and Gabow, 1991; Arnold et al., 1994; Pearson et al., 1994; Arnold, 1997; Wilkins-Haug, 1997; Jones and Balster, 1998). These anomalies include CNS dysfunction, developmental delay, attention deficit disorder, microcephaly, growth deficiency, short palpebral fissures, deep-set eyes, micrognathia, abnormal auricles, and small fingernails. In another study of 35 pregnancies in women who chronically abused toluene there were three perinatal deaths (Wilkins-Haug and Gabow, 1991; Arnold et al., 1994). Many of the infants were born prematurely, and had fetal growth retardation and neonatal hypertonia. Growth retardation for height, weight, and head circumference persisted at least through the first year of life, and developmental delay was common (Wilkins-Haug and Gabow, 1991; Arnold et al., 1994; Wilkins-Haug, 1997).

Transient neonatal hyperchloremic acidosis has been observed in the infants of women who chronically abused toluene during pregnancy (Goodwin, 1988; Lindemann, 1991; Erramouspe et al., 1996). Renal tubular acidosis with subsequent hyperchloremic acidosis is a well-known complication of chronic toluene toxicity in pregnant women (Wilkins-Haug and Gabow, 1991).

**Critique of Internet resources**

Using the Internet resources listed, reviews of both animal and human developmental toxicity studies were available. For the animal studies, information on study design, i.e. number of animals evaluated, number of dose groups exposed, and individual study results were available. Specific responses and detailed information on endpoints were available. For human studies, usually the number of humans evaluated was given and statistically significant outcomes were reported.

11.1.2 Exposure assessment

11.1.2.1 Internet resources: information relevant to the exposure assessment of toluene was extracted from the following web resources.

- US EPA Website: [http://www.epa.gov/ORD/We bPubs/exposure/](http://www.epa.gov/ORD/We bPubs/exposure/);
- MSDS: [http://msds.pdc.cornell.edu/isssearch/msdssrch.htm](http://msds.pdc.cornell.edu/isssearch/msdssrch.htm);
- ATSDR: [http://www.atsdr.cdc.gov/hazdat.html#A3.1.2a](http://www.atsdr.cdc.gov/hazdat.html#A3.1.2a);

11.1.2.2 Exposure pathways. Human exposure to toluene can occur from drinking water, food, and the air. Many people are exposed to toluene in the workplace, with workers in the petrochemical and chemical industries, dye makers, and painters having the highest exposures. Toluene is a solvent, and therefore, is found in many consumer products, such as gasoline, nail polish, cosmetics, rubber cement, paint brush cleaners, stain removers, fabric dyes, inks, and adhesives. Toluene is also present in cigarette smoke. High, acute exposures (500–5000 ppm) occur during deliberate glue sniffing or solvent abuse (Wilkins-Haug, 1997).
Toluene has been found in about 1% of the groundwater sources at amounts lower than 2 ppb. Larger amounts may be found in surface water supplies and in some industrially-contaminated sites. Toluene levels in the air are typically lower than 1 ppm in nonindustrialized areas. Usual indoor levels of toluene are lower than 1 ppm. Usual levels in food are not known.

11.1.2.3. Absorption, Distribution, Metabolism, and Excretion (ADME) of toluene. Toluene vapor is readily absorbed by inhalation and the liquid by GI tract. Toluene is poorly absorbed from the skin.

Major excretory pathway is rapid oxidation of toluene to benzoic acid, which is conjugated with glycine and excreted as hippuric acid in urine.

In humans, up to 75% of inhaled toluene is metabolized to hippuric acid and excreted in urine within 12 h of exposure. The remainder is excreted unchanged with a small percent being excreted as a sulfate or glucuronide of cresol.

Acute exposure levels of inhaled toluene between 500-12 000 ppm can be experienced by individuals who sniff glue.

11.1.2.4. Biological half-life (inhalation exposure). 0.08 Days.

11.1.2.5. Tests for exposure. Toluene in exhaled air is a good indicator of ambient toluene concentrations. Samples can be collected by personal diffusive samplers, desorbed with carbon disulfide, and quantitated by gas chromatography. The concentration of toluene in expired air which corresponds to an airborne concentration of 377 mg/cu m is 40 mg/cu m.

Urinary levels of toluene itself correlated better with airborne toluene levels than either urinary o-cresol or hippuric acid.

Exposure to high levels of toluene can be monitored by measuring levels of urinary hippuric acid. Levels of 0.5–2.5 g per 24 h or 0.8 g/g creatinine are normal, while exposure to an airborne concentration of 100 ppm produces levels of up to 4 g/l.

The ACGIH has established a Biological Exposure Index (BEI) for toluene of 1.6 g hippuric acid/g creatinine in urine, measured at the end of a shift. The BEI for toluene in blood sampled prior to the last shift of the workweek is 0.05 mg/l and for o-Cresol in urine sampled at the end of the shift is 0.5 mg/l. The determinant is usually present in a significant amount in biological specimens of non-exposed subjects, but such background levels are included in the BEI value.

Smoking and drinking of ethanol reduce the amount of urinary hippuric acid in toluene-exposed workers.

11.1.2.6. Exposure limits

EPA (Environmental Protection Agency) recommendations to protect human health. Limit in drinking water: 1 ppm toluene.

Assuming that adults and children drink on the average 2 and 1 l/day of water, respectively; children should not drink water containing more than 20 ppm toluene for 1 day, or 2 ppm for longer lengths of time (7 years). Adults should not drink water containing more than 7 ppm toluene for longer times.

Occupational Exposure Standards.

Permissible exposure limit in air (8-h, TWA for occupational exposure): 50 ppm (375 mg/cu m).

OSHA standards:
– Permissible exposure limit: 8-h; time weighted average: 200 ppm.
– Permissible exposure limit: acceptable; ceiling concentration: 300 ppm.
– Permissible exposure limit: acceptable maximum peak above the acceptable ceiling concentration for an 8-h shift. Concentration: 500 ppm. Maximum duration: 10 min.

11.1.2.7. Critique of Internet resources. Internet resources were reviewed for information relevant to exposure assessment. These references provided information on typical routes of exposures, environmental and occupational levels, and some estimates for specific exposure conditions (e.g. solvent abuse). Information on ADME of toluene was given as were factors known to alter these rates. Half-lives were also given. Biomonitoring information was provided and a BEI was listed. Exposure limits from various regulatory agencies was listed.
11.1.3. Risk characterization

11.1.3.1. Internet resources: information relevant to the risk characterization of toluene was extracted from the following web resources.

Reprotox: http://www.micromedex.com/;

For risk characterization, two exposure scenarios were evaluated: occupational exposures and solvent inhalational abuse.

11.1.3.2. Occupational exposure. Every infant has a 3–6% risk of being born with a serious birth defect or mental retardation apparent by one year of age, even if no exposure has occurred (Beckman and Brent, 1999). The cause of most birth defects is unknown. Providing pregnancy risk assessments for occupational exposures is difficult for several reasons: (1) studies assessing risks associated with pregnancy exposures to occupational agents are usually limited and often non-existent, (2) occupational exposures typically occur to many agents simultaneously and rarely to just one agent, and (3) the extent of occupational exposure is usually poorly characterized with respect to dose and duration of exposure.

The risk to fetal development produced by an exposure to an occupational agent depends not only on the nature of the agent and the stage of the pregnancy, but also on the nature of the exposure and the individual’s response to it.

One of the first steps in characterizing occupational risks for toluene would be to provide some qualitative and/or quantitative context for workplace exposures. For example, the clinician or exposure assessor would ask how frequently and during what work activity toluene exposures took place. Determining if exposures were episodic or chronic would also add to the characterization profile. Based on general toxicity information and information such as odor threshold, some upper limits on potential occupational exposures could be determined.

Chronic exposures to toluene in the workplace at levels that exceed the threshold limit value (TLV) should be avoided as they may increase the potential for toxicity in employees. Exposures that are high enough to be toxic to workers also have the potential for increasing a pregnant worker’s developmental toxicity risk above the background risk. The TLV refers to the time-weighted average concentration of a substance for a conventional 8-h work day and a 40-h work week to which it is believed that ‘nearly all’ workers may be repeatedly exposed every day without adverse health effects (ACGIH, 1998). Since reproductive endpoints were not used to determine the TLV, it cannot be assumed that levels that do not exceed the TLV are without risk for the pregnant worker and her fetus. Developmental toxicity risk may be modified by the general health of the patient, her genetic background, the amount of toluene to which she was exposed, the duration of exposure, and the stage of pregnancy during which exposure took place.

Although several studies have found an increased risk of miscarriage in women who work with organic solvents, these studies have methodological limitations which make it difficult to infer that a causal relationship exists. For example, in many of these studies, the exposure to toluene is ascertained on the basis of the subject’s job title; therefore, quantitative information regarding the amount and duration of toluene exposure is lacking. Toluene may be just one of many different types of organic solvents that the research subjects are exposed to, so it is difficult to determine the relative contribution of toluene to the observed increased rate of miscarriages. In addition, for those limited studies that did find a quantitative dose-response relationship for workplace exposures, occupational levels were exceeded.

Occupational exposure to toluene at levels less than the TLV during pregnancy is unlikely to pose a substantial developmental toxicity risk.
11.1.3.3. Solvent inhalational abuse. A patient who has been abusing toluene during pregnancy has an increased risk of giving birth to an infant with congenital anomalies not unlike those seen in fetal alcohol syndrome. The developmental toxicity risk associated with chronic abuse of toluene may be modified by variables such as amount, duration, time of exposure, as well as exposure to concomitant drugs or chemicals, such as alcohol or smoking.

Women with a positive toluene screen and/or renal tubular acidosis have a greater risk of IUGR in their children than exposed women who do not experience medical complications.

Developmental delays are common, with 2/3 of children who are exposed to high levels of toluene in utero having persistent development delay despite placement in foster care.

Women who abuse toluene during pregnancy may abuse other agents as well (e.g. alcohol or narcotics). However, studies that have screened for alcohol toxicity have found that concomitant use of alcohol during pregnancy in toluene-abusing women is rare.

If a pregnant patient shows signs or symptoms of toluene abuse, she should be questioned regarding her possible abuse and the frequency of her abuse. Tests for metabolites of toluene in blood or urine are not useful for determining toluene abuse during pregnancy. Due to the rapid elimination of these substances, only recent use would result in positive findings. Also, these tests are not routinely available in most clinical settings.

11.1.3.4. Conditions that alter susceptibility. Inhaled toluene is primarily metabolized in the liver by the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to benzoic acid (Wilkins-Haug, 1997). Genetic variations that result in deficiency of the ALDH2, may result in higher than expected benzaldehyde levels in at-risk individuals who are occupationally exposed to levels of toluene at or below the threshold limit value of 50 ppm. These individuals, then, may have an increased risk of toluene developmental toxicity at lower levels of exposure (Wilkins-Haug, 1997). Similarly, it would be expected that concomitant exposure to drugs that inhibit ALDH, such as disulfiram, might increase the developmental toxicity risk of toluene. Indeed, disulfiram has been found to markedly enhance the effects of alcohol when the two agents are consumed together, resulting in symptoms collectively referred to as ‘the acetaldehyde syndrome’ (Hobbs et al., 1996). The syndrome has been attributed to increased concentrations of acetaldehyde that occur as a result of the inactivation of aldehyde dehydrogenase by disulfiram. When alcohol is consumed with disulfiram, serum levels of acetaldehyde can be more than 5–10 times those seen with alcohol alone (Helmbrecht and Hoskins, 1993). The combination of disulfiram and alcohol has also been found to produce a synergistic increase in the incidence of malformations in animals (Lambert et al., 1980).

In addition to toluene, many commercial solvents contain a mixture of volatile hydrocarbons. Consequently, the teratogenic effects attributed to toluene could be due to the concomitant exposure to other volatile hydrocarbons alone or in combination with toluene.

11.1.3.5. Critique of Internet resources. The Internet resources available included general discussions of developmental toxicity risk (in the context of exposure and dose response) as well as risk characterizations for at least two specific exposure scenarios, occupational exposure and solvent inhalational abuse. Detailed quantitative assessments for evaluation of toluene-induced developmental effects were not available. Likewise, linkage of hazard characterization data, with dose-response assessment and exposure assessment required a specialist with training, despite Internet resource access.

Information on conditions that could change or alter susceptibility were available for both lifestyle as well as therapeutic conditions.

11.1.4. Risk management

Workers who have the potential to be exposed to excessive levels of toluene on the worksite should be advised to request a temporary job transfer or leave. Health care professionals should be sensitive to the patient’s need for job protec-
tion and compensation. If necessary, an industrial hygienist can work with the patient to help her minimize exposure to toluene at work. Specific guidelines are available to educate workers on potential workplace hazards. These documents also provide information on protective actions that can be taken as well as workers’ rights to refuse to work in conditions where there is an imminent danger of injury (see e.g. the document, “Workplace Hazards to Reproduction and Development: A Resource for Workers, Employers, Health Care Providers, and Health & Safety Personnel” produced by the Washington State Department of Labor and Industries at: http://www.lni.wa.gov/sharp/repro_dev.pdf.

Management of pregnancies in which toluene abuse is recognized should be aimed at close surveillance for renal tubular acidosis with hypokalemia, preterm labor, and fetal growth retardation. Referral to a treatment program should be made as soon as possible.

Overall, the Internet resources on risk management approaches for developmental risks were limited to general guidance. In the case of toluene, two specific risk scenarios were available and some limited management approaches and options were discussed. Due to the need for a specific contextual basis for risk management for developmental risks, it is not surprising that the Internet resources are limited in this category of information.

12. Conclusions

Toxicological information, previously inaccessible or difficult to obtain is now widely available to health care professionals. Government agencies are increasingly using the Internet as a platform for the dissemination of health-related information. A vast amount of chemical and toxicology related information can be obtained from websites maintained by governmental agencies such as the Environmental Protection Agency (EPA): (http://www.epa.gov), the Agency for Toxic Substances and Disease Registry (ATSDR): (http://www.atsdr.cdc.gov), and the US Department of Health and Human Services (HHS): (http://www.hhs.gov/). Appropriately utilizing this information to assess the developmental toxicity risk associated with an exposure in a patient presents a challenge to the clinician. The risk assessment process formally developed by EPA can provide the clinician with an important framework for assessing and integrating developmental toxicity information relevant to the patient’s exposure. Still, translating information that is derived from laboratory and human population studies into clinical management prescriptions for individual patients is difficult.

A number of useful Internet resources that provide detailed and peer-reviewed data for health care professionals have been described in this review. Making this type of expert-based information widely available on the Internet along with details on how and what risk information was utilized in their available assessments will enable health care professionals to make more accurate estimates of the risks associated with exposures to potential developmental toxicants.

Acknowledgements

This review was supported in part by the EPA/NIEHS Center for Child Environmental Health Risks Research (R826886 and ESO9601), NIEHS Center for Ecogenetics and Environmental Health (P30-ES07033), the Institute for Risk Analysis and Risk Communication, and the Pediatric Environmental Health Specialty Unit (PEHSU) at the University of Washington. Although, the research described in this article has been funded by the National Institutes of Health and the United States Environmental Protection Agency through grants, it has not been subjected to the Agency’s required peer and policy review, and therefore, does not necessarily reflect the views of the Agency and no official endorsement should be inferred.
References


Anonymous, 1984. Two generation inhalation study on a petroleum-derived hydrocarbon with cover letter dated 021384 and EPA acknowledgement dated 031984. EPA/OTS; Doc # FYI-AX-0284-0294 Initial Sequence A.


NRC (National Research Council) 2000. Scientific Frontiers in Developmental Toxicology and Risk Assessment. Committee on Developmental Toxicology, Board on Environ-

mental Studies and Toxicology, Commission on Life Sciences, National Academy Press, Washington, DC.

NRC (National Research Council) 2001. Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity. Subcommittee on Reproductive and Developmental Toxicity, Committee on Toxicology, Board on Environmental Studies and Toxicology, National Academy Press, Washington, DC.


