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Risk Assessment for Developmental Toxicity: Airborne Occupational Exposure to Ethanol and Iodine

Donald R. Mattison*

Introduction

It has been estimated that 40% of the work force (more than 45 million) are women.\(^1\) Approximately 75% are between 16 and 44 years old, and half of them are fertile.\(^2\) The challenge to define the impact of a chemical exposure on a woman and/or her fetus during pregnancy is therefore common.\(^3\)

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1 OFFICE OF TECHNOLOGY ASSESSMENT, REPRODUCTIVE HEALTH HAZARDS IN THE WORKPLACE (1985).


Yet, it is complicated by several factors. One is the assumption that the processes involved in fetal development are the most exquisitely vulnerable of all biological processes. This has led some employers to exclude women from certain jobs and creates the concern that gender bias may drive what is portrayed as attempts to protect the fetus. The only way to approach this type of question is to clearly define the actual vulnerability of the fetus, placenta, pregnant women, nonpregnant women and men to all workplace exposures.

Clearly, definition of the biological process most sensitive to a chemical exposure in an occupational setting is important. However, workplace occupational exposures should be regulated to protect all workers and all biological processes. Therefore, it is critically important that rigorous scientific principles are followed in characterizing the potential for harm.

In addressing the impact of occupational exposure on pregnancy or fetal development it is important to understand how to characterize chemicals that represent potential risks. Similarly, it is important to identify chemicals that do not represent a risk. The purpose of this report is to review the steps used in risk assessment for developmental toxicity. Two chemicals for which airborne occupational exposure can occur, ethanol and iodine, are used to illustrate the process and furnish a basis for discussing approaches to the management of risks for developmental toxicity in occupational settings.

Problems Facing Occupational Health Professionals

Approximately 90,000 chemicals are in use in the U.S. Between 3,000 and 4,000 of them have been tested for developmental toxicity.

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4 Mattison, Exclusion of Fertile Women From the Workplace: Bad Medicine, Worse Law, 86 J. ARK. MED. SOC'Y 491 (1990).
5 OFFICE OF TECHNOLOGY ASSESSMENT, supra note 1.
toxicity. Therefore, for many occupational exposures, no data is available.

Of the chemicals for which data are available, between 100 and 1,000, depending on the rigor of data analysis and interpretation, are teratogenic in animals. If the ratio of developmental hazards among tested chemicals remains the same among chemicals not tested (between 1/30 and 1/3), then it can be estimated that between 3,000 and 30,000 of the chemicals in use may be developmental toxicants in experimental animals. Of interest with respect to prediction of human risk, approximately 30 chemicals are thought to be developmental toxicants in humans. If that ratio of risk for developmental hazard persists over all chemicals, then about 1% of the chemicals in use (approximately 900) may be human developmental toxicants. To the extent this reasoning is correct there are two conclusions; (1) most chemicals in use have little potential for human developmental toxicity, and (2) chemicals not yet identified as developmental toxicants may prove to be such.

6 J. Schardein, Chemically Induced Birth Defects (1985); T. Shepard, Catalog of Teratologic Agents (5th ed. 1986); Steering Committee on Identification of Toxic and Potentially Toxic Chemicals for Consideration by the National Toxicology Program, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council, Toxicity Testing: Strategies to Determine Needs and Priorities (1984) [hereinafter Toxicity Testing].


How Should Occupational Exposures to Chemicals not Characterized for Developmental Toxicity be Managed?

The above estimates suggest that approximately 900 chemicals in commerce have the potential to be human developmental toxicants. How should occupational exposures to chemicals which have not been characterized for developmental toxicity be managed? Several different options are available. One option would simply acknowledge the fact that in absence of data characterizing the development toxicity of a chemical, no male or female capable of reproducing should be exposed to the chemical in a workplace setting. The exclusion of both men and women of reproductive ages from exposure to uncharacterized chemicals may appear to be the only rational method for protecting human reproductive and developmental health.

Why exclude men of reproductive age from untested chemicals? There is evidence demonstrating that reproductive and developmental harm can result from paternal exposure. Therefore, in the absence of data defining male or female reproductive effects, or developmental effects of the chemical, the only rational approach for the management of the potential for risk is to exclude all workers of reproductive age if anyone is to be excluded.

An alternative approach might be to manage occupational exposures to chemicals which have not been tested adequately for reproductive toxicity based on systemic toxicity. For example, if the dose associated with systemic toxicity has been characterized and occupational exposures are kept below the levels associated with systemic toxicity, then it is reasonable to assume that toxicity to reproduction and fetal development would be minimal.

Therefore, management of potential reproductive or developmental risks resulting from occupational exposures to chemicals whose impacts

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on reproduction or development have not been characterized might reasonably be approached by preventing systemic toxicity.

What is a Developmental Toxicant?

A developmental toxicant is a drug, chemical, virus, bacteria, physical agent or deficiency state that alters morphology or subsequent function of a developing organism. Developmental toxicology is the science which deals with the causes, mechanisms, manifestation and prevention of developmental deviations of a structural or functional nature which are produced by developmental toxicants.

Some developmental toxicologists think that any chemical, given in large enough amounts can alter embryonic or fetal development. However, existing data suggests that not all chemicals are developmental toxicants. As previously indicated, these data suggest that between 1/30 and 1/3 of the chemicals tested are developmental toxicants in experimental animals.

Of special interest is data suggesting that reproductive and development endpoints are not always the most sensitive. Koeter reviewed data from 37 chemicals tested for systemic, reproductive and developmental toxicity. For about 1/3 of the chemicals, reproduction was the most sensitive endpoint. For another 1/3 systemic toxicity occurred in concert with developmental effects. Among the compounds


11 Karnofsky, Drugs as Teratogens in Animals and Man, 5 ANN. REV. PHARMACOLOGY 447 (1965).

12 J. SCHARDEIN, supra note 6; T. SHEPARD, supra note 6; Frankos, supra note 8; Jelovsek, Mattison & Chen, supra note 8.

tested, 1/2 had no effect on reproduction or development at the minimal effect level. Therefore, although reproduction and development are critical endpoints for toxicological evaluation, not all chemicals will adversely effect reproduction or development.

**Risk Assessment for Developmental Toxicity**

The process of risk assessment for developmental toxicity incorporates four interrelated activities. The first is hazard identification: Can the chemical produce adverse developmental effects in experimental animals or humans? If so, what type of effects are produced and what is the period of development during which the embryo or fetus is susceptible? The second step is hazard characterization: What is the dose-response relationship and what is the site and mechanism of action? It is important to recognize that dose-response relationships in developmental toxicity can be complicated by multiple competing endpoints, such as reduced fetal weight, disruption of fetal development and fetal death. The third step is exposure assessment: What was the amount, duration, and timing of exposure, and how much was absorbed and distributed to the fetus or placenta? The fourth step is risk characterization: How likely is the exposure to result in an adverse developmental outcome?

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14 COMMITTEE ON THE INSTITUTIONAL MEANS FOR THE ASSESSMENT OF RISKS TO PUBLIC HEALTH, COMMISSION ON LIFE SCIENCES, NATIONAL RESEARCH COUNCIL, RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS (1983) [hereinafter RISK ASSESSMENT]; J. SCHARDEIN, supra note 6; Sheehan, Young, Slikker, Jr., Gaylor & Mattison, Workshop on Risk Assessment in Reproductive and Developmental Toxicology: Addressing the Assumptions and Identifying the Research Needs, 10 REGULATORY TOXICOLOGY AND PHARMACOLOGY 110 (1989).


16 Schardein, Teratogenic Risk Assessment: Past, Present, and Future, in 1 ISSUES AND REVIEWS IN TERATOLOGY 181 (H. Kalter ed. 1983) [hereinafter Teratogenic Risk
Finally, all of this information must be evaluated with a characterization of the benefits of the exposure to arrive at a rational risk management decision. Unfortunately, this rigorous process of analysis has not been followed routinely in attempts to manage developmental risks in the workplace. For example, little published data is available which has explored the adverse effects which accrue to a woman and her fetus from the loss of a job and subsequent loss of health benefits, including prenatal care. In some occupational exposure settings, the loss of income with subsequent impact on maternal and fetal nutrition and the loss of health care benefits may produce substantially greater harm to the fetus, mother and to the family than the continuing occupational exposures.

**Hazard Identification**

The goal of hazard identification is to identify chemicals which impair development before humans are exposed. Therefore, chemicals are evaluated in experimental animals for their effect on development. If they are developmental toxicants the data are used to set exposures thought to protect human populations from developmental toxicity. However, it may not be possible to identify all developmental toxicants


2 RISK – Issues in Health & Safety 227 [Summer 1991]
in animal models. For that reason, epidemiological studies are also conducted to define human developmental effects of chemical exposures.\textsuperscript{17} This means that it is necessary to consider both animal and human endpoints of developmental toxicity.\textsuperscript{18}

Developmental toxicity in animals is defined as the adverse effect of a chemical on the conceptus. The adverse effects may be manifested prenatally or postnatally. Developmental toxicity can include growth retardation, functional deficits, structural malformation or death.\textsuperscript{19}

Manifestations of developmental toxicity observed in experimental animals should not be expected to mimic those observed in humans exposed to the same toxicant. Similarly, manifestations of developmental toxicity observed in humans are not always reproduced in experimental animals. The absence of uniformity of response is not surprising, however, when the differences between human and experimental animal exposure are considered. For example, differences in dosage, placentation, metabolism, pharmacokinetics, critical periods of development and durations of gestation can be expected to influence the expression of developmental toxicity.

Human developmental toxicity also includes alteration of growth, structure, function and death. It is important to recognize that these endpoints may not be independent. For many developmental toxicants

\textsuperscript{17} M. BRACKEN, PERINATAL EPIDEMIOLOGY (1984); J. KLINE, Z. STEIN & M. SUSSER, supra note 15.

\textsuperscript{18} Teratogenic Risk Assessment, supra note 16; J. SCHARDEIN, supra note 6; Species sensitivities, supra note 16; Fabro, supra note 10; Frankos, supra note 8; Wang & Schwetz, supra note 16; Evaluation, supra note 16; Criteria, supra note 3; Proposition 65, supra note 3; Mattison, Blann & Malek, Physiological Alterations During Pregnancy: Impact on Toxicokinetics, to be published in FUNDAMENTAL & APPLIED TOXICOLOGY. Mattison & Jelovsek, Pharmacokinetics and Expert Systems as Aids for Risk Assessment in Reproductive Toxicology, 76 ENV'T HEALTH PERSP. 107; Jelovsek, Mattison & Chen, supra note 8; Jelovsek, Mattison & Young, supra note 16.

\textsuperscript{19} J. SCHARDEIN, supra note 6; 1985, T. SHEPARD, supra note 6; Wang & Schwetz, supra note 16.
there is a spectrum of adverse outcome. At low doses a toxicant may produce growth retardation. At higher doses disruption of fetal development may occur, and at even higher doses, death. For additional complexity, some investigators have suggested that exposures associated with neural tube defects may prevent spontaneous abortion of the malformed fetus. However, recent data does not lend support to that hypothesis. Therefore, variability of outcome and severity of effect is observed when developmental toxicity occurs. The sources of this variability include differences in: dose, timing of exposure, maternal and fetal susceptibility and interactions with other environmental factors.

It is important to note that structural defects resulting from exposure to a developmental toxicant occur in characteristic patterns. Furthermore, individual defect categories (especially when classified by organ, system or body region) are etiologically and pathogenetically heterogeneous. In addition, many adverse outcomes are measured and classified in different ways in humans and experimental animals. This is especially true for abnormalities of function such as learning and behavior.

The classification of human structural abnormalities is different from that used for the classification of animal abnormalities. Human structural abnormalities are generally classified as malformations, disruptions, or deformations. These may have different pathogenic and etiologic

23 J. Schardein, supra note 6; T. Shepard, supra note 6; J. Sever & R. Brent, supra note 7; K. Jones, supra note 20.
implications than for structural abnormalities observed in animals. Furthermore, some structural defects in humans and animals may be considered to be normal variations with no clinical significance while being important clues to mechanisms of abnormal development.  

Timing of Exposure

A fundamental concept of developmental toxicology is that some stages of embryonic development are more vulnerable than others. The time of exposure to a developmental toxicant determines both sensitivity to damage and the type of defect. Most developmental toxicants produce their effects during specific critical developmental periods, which vary across both compounds and species.

For some animal developmental toxicants, critical periods have not been reliably established because treatment for toxicity testing continues throughout pregnancy. For some however, detailed studies have been conducted at different doses and times during pregnancy. For these chemicals, the critical period, sensitive developmental processes and proposed mechanism of action can be described. Specificity to developmental stage has also been found where human developmental toxicity has been studied in detail.

It is generally thought that exposure during the preimplantation or presomite periods (0–14 days after fertilization) produces little developmental toxicity because the conceptus either dies or regenerates completely. Recent data, however, suggests that this hypothesis may be incorrect. These data suggest that preimplantation exposure to certain

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25 K. JONES, supra note 20; R. HOOD, supra note 9.
26 J. SCHARDEIN, supra note 6; T. SHEPARD, supra note 9.
27 R. HOOD, supra note 9.
28 J. SCHARDEIN, supra note 6; T SHEPARD, supra note 9.
chemicals may indeed be followed by developmental toxicity.

During organogenesis (up to 60 days after fertilization) the human embryo is highly sensitive to developmental toxicity and exposure to a toxicant may produce morphologic and functional disruptions. After organogenesis the fetus is less sensitive to morphologic alterations. However, functional changes can occur in selected organs throughout pregnancy and even after birth.

By the third trimester much of the structure of the fetus has been defined. During this period and indeed after birth, many functional characteristics are being developed. For example, cellular communication is being developed, the cell number is increasing in many organs and the patterns of gene expression are changing. Therefore, the fetus (and the infant) remains vulnerable to cytotoxic or disruptive processes during the third trimester (and after birth).

**Hazard Identification with Incomplete Data**

If there is no animal or human evidence available which addresses the developmental hazard posed by a chemical, it may be impossible to assess the risk of an exposure to a male or female. If, however, there are any human reports or animal studies that suggest a possible hazard or there are physical or chemical properties that would make the compound more or less likely to be a hazard, it is important to proceed further in calculating effect and exposure doses.

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30 Jelovsek, Mattison & Young, *supra* note 16.
If any animal studies have been conducted to characterize developmental toxicity, it is important to establish the pattern of toxicity in each animal species, as well as the highest no-observed-adverse-effect-level for each study. Are there any weaknesses of study design that would lower confidence in the study? If there are human studies, it is important to define the outcome for each and the timing of exposure associated with that outcome. Often, however, lack of complete human data makes interpretation difficult.

Implicit in this first step in risk assessment is the assumption that developmental hazards identified in animals are predictive of developmental hazard in humans. The converse, failure to demonstrate developmental hazard, is also assumed to reflect safety following human exposure. It is important to critically review the accuracy of this assumption.\(^3\)

Frankos reviewed the concordance of animal and human data for 38 drugs reported to be developmental toxicants in humans and 165 reported not to produce developmental toxicity.\(^3\) Of 38 drugs identified as human teratogens, 37 were positive in at least one animal species, and 29 were positive in more than one. Among 165 compounds identified as nonteratogenic in humans, only 47 were negative in all animal species tested.

Recent statistical analysis of the predictive power of developmental toxicity testing in animals\(^3\) has suggested that animal data is useful for identifying human developmental toxicants. However, animal studies are not determinative. A detailed collection of inferential rules used by developmental toxicologists to interpret animal studies and assign hazard

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\(^3\) Frankos, *supra* note 8.

for human developmental toxicity has been assembled. In addition, structure activity relationships are being explored.

Even if a chemical is determined to be a developmental hazard, additional information is needed to define the actual risk. Further steps include hazard characterization and exposure assessment, followed by qualitative or quantitative risk assessment.

Hazard Characterization

At a minimum, hazard characterization requires demonstration of the dose-response relationship for the developmental toxicant. For example, what is the highest dose which produces no adverse developmental effect? In addition, characterization of the smallest dose associated with developmental toxicity is also critical to define the exposure or dose at which no adverse human developmental effect is expected.

Given species differences in development, as well as the tendency for animal studies to have a high false positive rate, it is important to have information on the site and mechanism of action of the developmental toxicant. Like hazard identification, hazard characterization also suffers from the lack of published peer reviewed data. As a result, even the minimal requirement for dose-response information is often not available.

For a chemical identified as a developmental toxicant, it is important

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34 Jelovsek, Mattison & Young, supra note 16.
36 Frankos, supra note 8; Mattison & Jelovsek, supra note 18; Jelovsek, Mattison & Chen, supra note 8.
37 Barlow & Sullivan, supra note 1; Toxicity Testing, supra note 6.
to know if the effect is produced by the parent compound or metabolites. What is the compound’s absorption by likely routes of exposure, the extent of placental transport, and the likely fetal exposure at different maternal doses? In addition, it is important to define different levels of effect such as lowest-observed-effect level, the no-observed-adverse-effect level, and the maternal-toxic-effect level. These help assess the likelihood that a given exposure is above or below the threshold for developmental toxicity.

**Exposure Assessment**

In assessing exposure, it is important to determine if the amount and duration was sufficient to cause an indirect or direct developmental effect. If the exposure was at or near maternally toxic levels, or if the exposed individual manifests toxic effects which result from the exposure, then there is the possibility of an indirect effect whether or not the compound is a developmental hazard. If the compound is a known or suspected hazard, systemic toxicity suggests that the chemical(s) did get into the maternal bloodstream and thus the fetus is presumed to be at greater risk than if maternal toxicity was not observed. The route of exposure and the absorption via that route considering gestational age brings into play our knowledge of the physiology of pregnancy and its likely effects on toxicokinetics. All of this information is used to estimate the amount of chemical which reached the fetus.

Because of unique windows of vulnerability for developmental toxicity, exposure assessment requires accurate determination of dose,

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38 R. Hood, supra note 9.
duration of exposure and the relationship of the exposure to developmental milestones. If, for example, the exposure to and clearance of the parent compound and any metabolites occurred prior to conception, it is unlikely that any excess embryonic or fetal risk would result.

Recognition of the existence of windows of vulnerability for developmental toxicity also has implications for risk management for occupational exposure settings. For example, if it is known that a toxicant effects developmental processes occurring early in pregnancy, one occupational risk management practice might be to remove women attempting pregnancy from the workplace until after the sensitive developmental stages have been completed. At that point work can be resumed. It is also important to recognize that the physiological alterations which occur during pregnancy may also act to minimize the impact of occupational exposures on fetal development.

**Risk Characterization**

The final step of risk assessment, risk characterization, requires an explicit formal method for translating developmental toxicity data in animals and humans, estimates of time and duration of exposure and an understanding of site and mechanism of action into an estimate of excess risk. Methods have been developed for estimating human risk for developmental toxicity from animal studies. However, there is still

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41 Mattison, supra note 40; Transdermal Drug Absorption, supra note 40; Physiological Alterations, supra note 18; Mattison & Jelovsek, supra note 18.

42 Evaluation, supra note 16; Butler & Kalasinski, Statistical Analysis of Epidemiological Data of Pregnancy Outcomes, 79 ENV'T HEALTH PERSPECT. 223 (1989); Faustman, Wellington, Smith & Kimmel, Characterization of a Developmental Toxicity Dose-Response Model, 79 ENV'T HEALTH PERSPECT. 229 (1989); Gaylor, Quantitative Risk Analysis for Quantal Reproductive and Developmental Effects, 79 ENV'T HEALTH PERSP. 243 (1989); Jelovsek, Mattison & Chen, supra note 8; Jelovsek, Mattison & Young, supra note 16; Kimmel & Gaylor, Issues in Qualitative and Quantitative Risk Analysis for Developmental

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2 RISK – Issues in Health & Safety 227 [Summer 1991]
disagreement on the validity of these methods because they are probabilistic techniques which do not consider species differences in development, nor do they consider differences in the site or mechanism of action of developmental toxicants.

At this point the risk assessment and risk management procedures becomes somewhat subjective because of the lack of an explicit consensus for assigning the final risk and managing that risk. It is important for the risk manager to recognize that not all pregnancies end successfully. Even in the absence of exposure, approximately 15% of pregnancies will end in clinically recognized spontaneous abortion and 2% to 5% of pregnancies will end with the birth of a child with a congenital malformation.43 Realization that not all pregnancies end at term with the birth of a normal child is critical in understanding the magnitude of any excess risk, as well as translating that information clearly to employers and effected or potentially effected employees. In addition, the quality and quantity of the data from which the estimates of developmental risk are derived must also be characterized and communicated to those individuals involved in the management of any excess risk as well as effected employees.

Impact of Airborne Chemical Exposure on the Fetus

Using the approach outlined above, two chemicals for which airborne occupational exposure can occur will be evaluated to characterize risk to the fetus. The management of developmental risks from these chemical exposures will be discussed. These two chemicals were chosen because they allow illustration of the impact of several different physiological changes during pregnancy on pharmacokinetics.

Toxicology, 8 RISK ANALYSIS 15 (1988); Kimmel, Perspectives on the Concern For and Management of Prenatal Chemical Exposure and Postnatal Effects, 562 ANN. N. Y. ACAD. SCI. 1 (1989); Overview, supra note 16.

43 J. KLINE, Z. STEIN & M. SUSSER, supra note 15.
In addition, they also point out the complexity of dealing with exposures to substances which also may be a normal part of the nutritional requirements of the body.

Table 1

<table>
<thead>
<tr>
<th>Pulmonary Function</th>
<th>Nonpregnant</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (respirations/min)</td>
<td>14 - 16</td>
<td>14 - 16</td>
</tr>
<tr>
<td>Tidal Volume (ml)</td>
<td>500</td>
<td>700</td>
</tr>
<tr>
<td>Minute Ventilation (L/min)</td>
<td>7.0 - 8.0</td>
<td>9.8 - 11.2</td>
</tr>
<tr>
<td>Volume exchange (L/8 hrs)</td>
<td>3,360 - 3,840</td>
<td>4,704 - 5,376</td>
</tr>
<tr>
<td>(m³/8 hrs)</td>
<td>3.36 - 3.84</td>
<td>4.70 - 5.38</td>
</tr>
</tbody>
</table>

In conducting the computations to determine exposure and dose it is important to note that pregnancy is characterized by many physiological changes including alterations in pulmonary function. As seen above in Table 1, these alterations in minute ventilation can have a substantial impact on the amount of an airborne chemical delivered to the lungs of a pregnant woman.

**Iodine**

*Hazard Identification:* Iodine is an integral part of the thyroid hormones and as such is an essential micronutrient. The recommended

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44 Modified from Mattison, supra note 40.
45 Mattison, supra note 40; Transdermal Drug Absorption, supra note 40; Physiological Alterations, supra note 18.
daily allowance (RDA 1989) for iodine is 175 μg/day. Iodine deficiency and excess are both associated with developmental toxicity. Because iodine and iodides are contained in a range of medicinals (elixirs and expectorants) as well as topical bactericidials, a rather large literature has developed concerning the developmental toxicity of iodine. In general, these compounds have been shown to impact on fetal thyroid function with large doses producing fetal hypothyroidism and fetal goiter. Human epidemiological studies have suggested that there may be some risk for eye and ear malformations. However, that is only a suggested association and has not been validated in other studies.

The target organs for iodine toxicity outside of the fetus include the respiratory system, eyes, skin, central nervous system and cardiovascular system. With inhalation exposure irritation of the eyes, nose, lacrimation and headaches occur. Contact produces burning and is associated with cutaneous hypersensitivity. Vomiting, abdominal pain and diarrhea may also occur. Ingestion produces gastrointestinal burns and tightness of the chest.

**Hazard Characterization:** Use of iodine-containing medications has been associated with fetal goiter in approximately 400 infants. Although other infants may have been affected and not reported. Doses associated with fetal goiter are generally observed following chronic treatment with iodine containing medications. However, it has been recommended that if pregnant asthmatics respond only to iodine containing medications the therapy should be continued during pregnancy. Short courses of iodine (250 to 500 mg intravenously every

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46 J. SCHARDEIN, supra note 6.
47 J. SCHARDEIN, supra note 6; T. SHEPARD, supra note 6.
49 Burrow, Hypothyroidism in Pregnancy, 298 NEW ENGL J. MED. 150 (1978); J. SCHARDEIN, supra note 6.
6 hours for 2 to 7 days) have been used in preparation of hyperthyroid pregnant patients for subtotal thyroidectomy without adverse effect on the fetus. The threshold for thyroid effects with chronic treatment during pregnancy is below 12 mg/day.

Povidone-iodine is used as a vaginal disinfectant. Within 15 minutes of the vaginal use of povidone iodine there is a 5 to 15 fold increase in plasma inorganic iodide with levels remaining elevated for 60 minutes after exposure. This suggests that iodine can be absorbed across the skin from organic iodine preparations. However, absorption across vaginal epithelium is likely to be substantially more rapid and complete than absorption across other dermal sites.

**Exposure Assessment:** The OSHA permissible exposure limit for iodine is 0.1 mg/m³ or 0.1 ppm. Assuming that the airborne level throughout an 8 hour work day remains fixed between 0.01 mg/m³ and 0.10 mg/m³ and that all of the inhaled iodine is absorbed, then the dose will be between 53.8 and 538 μg/8 hour work day (Table 2 below). Because of the pregnancy induced increase in tidal volume this is somewhat more than the amount inhaled by the nonpregnant worker (between 38.4 and 384 μg/8 hour work day). Note that all levels of exposure at or below the OSHA permissible exposure limit are below the lowest dose noted to alter fetal thyroid function and produce goiter (12 mg/day). However, exposures to airborne concentrations greater than 0.03 mg/m³ may produce total doses of iodine which are greater than the recommended daily dietary allowance for pregnant women (175 μg/day).

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52 Mattison, *supra* note 4; *Transdermal Drug Absortion, supra* note 40.


2 RISK – Issues in Health & Safety 227 [Summer 1991]
Table 2

Pulmonary Exposure to Iodine During Pregnancy

<table>
<thead>
<tr>
<th>Ambient air concentration (mg/m³)</th>
<th>Iodine Absorbed (µg/day)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonpregnant</td>
</tr>
<tr>
<td>0.01</td>
<td>38.4</td>
</tr>
<tr>
<td>0.02</td>
<td>76.8</td>
</tr>
<tr>
<td>0.03</td>
<td>115.2</td>
</tr>
<tr>
<td>0.04</td>
<td>153.6</td>
</tr>
<tr>
<td>0.05</td>
<td>192.0</td>
</tr>
<tr>
<td>0.06</td>
<td>230.4</td>
</tr>
<tr>
<td>0.07</td>
<td>268.8</td>
</tr>
<tr>
<td>0.08</td>
<td>307.2</td>
</tr>
<tr>
<td>0.09</td>
<td>345.6</td>
</tr>
<tr>
<td>0.10</td>
<td>384.0</td>
</tr>
</tbody>
</table>

†The calculations assume that the ambient concentration remains constant for the 8 hour work day and that the volume exchange is 3.84 and 5.38 m³ per 8 hours in nonpregnant and pregnant women, respectively.

Developmental Risk Characterization: Given that exposure via dermal or pulmonary absorption is small and in the range of that required for normal function of the thyroid, it seems unlikely that excess risk for developmental toxicity will occur at doses up to the OSHA permissible exposure limit. However, because it is possible to monitor iodine levels (or thyroid hormones) in exposed workers, monitoring would be an excellent adjunct to this assessment and is likely to be reassuring.54 Both pregnant and nonpregnant employees could be

monitored to assess the amount of iodine absorbed by all routes.

**Developmental Risk Management:** In this setting the risk manager should explain the characteristic biphasic response for developmental toxicity. Deficiencies in dietary iodine as well as excesses in iodine exposure are both associated with an increased risk for adverse developmental outcome. Iodine is also part of the normal diet and many foods, including seafood, contain quite high levels of iodine. The levels of exposure in this hypothetical occupational setting up to airborne concentrations as high as 0.1 mg/m$^3$ assuming an 8 hour inhalation exposure do produce daily doses that are greater than the recommended daily dietary allowances for pregnancy. They are however, substantially below the threshold for developmental toxicity in humans. This threshold has been suggested for iodine containing medications following the outcome of exposed human pregnancy. In summary, iodine deficiency and excess can be associated with developmental toxicity. The exposures evaluated in this example however, appear to be substantially below the threshold for developmental toxicity observed in humans. These data suggest that continued exposures to airborne concentrations of iodine up to 0.10 mg/m$^3$ throughout pregnancy would not be associated with any increased risk for developmental toxicity.

**Ethanol**

*Hazard Identification:* Studies in animals and humans have identified ethanol as a developmental toxicant.$^{55}$ There is no question that the offspring of alcoholic women who continue to consume large amounts of alcohol during pregnancy are at risk for the Fetal Alcohol Syndrome (FAS). FAS is characterized by altered growth,


2 RISK – Issues in Health & Safety 227 (Summer 1991)
morphogenesis and function including (i) prenatal and/or postnatal growth retardation, (ii) central nervous system involvement, (iii) facial dysmorphology with at least two of the following, microcephaly, short palpebral fissures or poorly developed philtrum, thin upper lip and/or flattening of the maxillary area.

FAS is rare among the general population, varying between 0.04% and 0.15% in different countries. Among women who abuse alcohol during pregnancy, the risk of FAS has been reported to be as high as 32%. However, this may overstate the risk of FAS as the studies from which these estimates are derived are confounded by unsystematic ascertainment and clinical evaluation of the infant.

An early study using data from the Collaborative Perinatal Project compared 23 alcohol abusers with 46 controls. Offspring of alcoholic women were significantly shorter and lighter than controls. Offspring of alcoholics also had an increased frequency of congenital anomalies and lower IQ at age 7. Among these children, the risk of FAS was 32%.

Another study compared 223 infants of alcoholic women with 276 control children. Although the infants in this study were lighter and shorter than controls there was no difference in congenital malformations. A third study evaluated 204 infants of alcoholic women as part of a study evaluating birth outcome in 12,000 pregnancies. This study also demonstrated that these infants were small and light compared to controls. Congenital malformations were increased in these children, and 3% had stigmata of FAS.

Animal studies have demonstrated alcohol dose dependent increases

56 Jones, Smith, Streissguth & Myrianthopoulos, *Outcome of Pregnancy in Chronic Alcoholic Women*, 1 LANCET 1076 (1974); Heinonen, Slone & Shapiro, supra note 47.
in embryo and fetal lethality, resorption, and stillbirth. Malformations have been induced in all species studied with the exception of rabbits. Malformations produced most consistently were craniofacial disruptions resulting from central nervous system, ocular and facial toxicity. The CNS disruptions observed included anencephaly, exencephaly, hydrocephaly, microcephaly, neural tube defects, agenesis of the corpus callosum, agenesis of the olfactory bulbs and hypophyseal dysplasia. Ocular malformations included anophthalmia, microphthalmia, coloboma, retinal disorganization and ablepharia. The facial malformations observed included agnathia, micrognathia, maxillary and mandibular hypoplasia, cleft palate, cleft lip, microtia and low set ears. Other malformations have also been observed.

These data indicate that ethanol is a developmental toxicant in animals and humans. The next step is to explore the dose-response relationship and site and mechanism of action.

Hazard Characterization: Among animal studies, alcohol dose dependent increases in fetal toxicity and malformation have been observed. Analysis of these dose-response studies suggest that blood alcohol concentration is the most useful biomarker of risk for fetal toxicity and malformation (Table 3).

59 Blakley, supra note 54.
Table 3

<table>
<thead>
<tr>
<th>Species</th>
<th>Min. Blood Alcohol (mg/L) Associated with Developmental Toxicity</th>
<th>Perinatal Mortality</th>
<th>Malformations</th>
<th>Intrauterine Growth Retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>730</td>
<td>430</td>
<td>730</td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>610</td>
<td>610</td>
<td>610</td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>1500</td>
<td>1500</td>
<td>1700</td>
<td></td>
</tr>
<tr>
<td>Monkey</td>
<td>1300</td>
<td>2000</td>
<td>1600</td>
<td></td>
</tr>
</tbody>
</table>

The blood alcohol levels associated with fetal toxicity (mortality, malformation, or growth retardation) falls into a range spanning two orders of magnitude (approximately 100 to 1000 mg/L). In general, chronic exposure associated with growth retardation occurs with alcohol concentrations between 600 and 2000 mg/L in mice (Table 3). Concentrations associated with malformations were between 400 and 2000 mg/L. Perinatal mortality has been reported at concentrations between 600 and 2000 mg/L. The other observation these studies have provided is that chronic low dose exposure is associated with greater developmental toxicity than acute or subacute low dose exposure.

Although the data is somewhat conflicting, the proximate teratogen or developmental toxicant is thought to be ethanol, although acetaldehyde, a metabolite of ethanol, may also play a role in

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60 Data from: Pierce & West, Alcohol Induced Microcephaly During the Third Trimester Equivalent: Relationship to Dose and Blood Alcohol Concentration, 3 ALCOHOL 185 (1986); Pierce & West, Blood Alcohol Concentration: A Critical Factor for Producing Fetal Alcohol Effects, 3 ALCOHOL 269 (1986); Blakley, supra note 54; Bonthius & West, Alcohol-induced Neuronal Loss in Developing Rats: Increased Brain Damage with Binge Exposure, 14 ALCOHOL CLIN. EXP. RES. 107 (1990).
developmental toxicity. The mechanism by which ethanol produces its
effect is thought to be by one of several routes including direct
embryonic cell damage, maternal malnutrition, fetal malnutrition,
depression of fetal and placental protein synthesis or fetal hypoxia. It is
also likely that ethanol exerts some of its adverse developmental effects
through paternally mediated toxicity.61

Among humans the estimation of dose effect relationships for
developmental toxicity is somewhat more difficult than for experimental
animals.62 Complicating factors include intermittent binge consumption
of alcohol and the effect of preconception and paternal exposure to
alcohol. As observed in experimental animals, the threshold for fetal
toxicity in humans also appears to depend to some extent on the
developmental endpoint considered. The most sensitive endpoint
appears to be growth, in which fetal toxicity is manifest by a decrease in
birth weight. Although some investigators have suggested that

61 R. HooD, supra note 9.
62 Mills, Graubard, Harley, Rhodes & Berendes, Maternal Alcohol Consumption
and Birth Weight. How Much Drinking During Pregnancy is Safe?, 252 J.A.M.A.
1875 (1984); Ernhart, Sokol, Martier, Moron, Nadler, Ager & Wolf, Alcohol
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Monson, Schoenbaum, Stubblefield & Ryan, The Association of Alcohol
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Stein & Kline, Smoking, Alcohol and Reproduction, 73 AM. J. PUB. HEALTH 1154.
(1983); Zuckerman & Hingson, Alcohol Consumption During Pregnancy: A
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Alcohol Use During Pregnancy and Decreased Infant Birth Weight, 67 AM. J. PUB.
HEALTH 1154 (1977); Hingson, Alpert, Day, Dooling, Kayne, Morelock,
Oppenheimer & Zuckerman, Effects of Maternal Drinking and Marijuana Use on
Fetal Growth and Development, 70 PEDIATRICS 539 (1982); Tennes & Blackard,
Maternal Alcohol Consumption, Birth Weight, and Minor Physical Anomalies, 138
AM. J. OBSTET. GYNECOL. 774 (1980); Streissguth, Barr, Sampson, Darby &
Martin, IQ at Age 4 in Relation to Maternal Alcohol Use and Smoking During
Pregnancy, 25 DEV. PSYCHOLOGY 3 (1989); Jones, Smith, Streissguth &
Myrianthopoulos, supra note 55.
threshold dose. There appears to be no adverse effect of ethanol on fetal growth when maternal consumption is below 1 to 2 oz (30 to 60 ml or 30 to 60 gms) of absolute alcohol per day. This also appeared to be the threshold for premature placental separation.\textsuperscript{63} One study suggested that spontaneous abortion was the most sensitive endpoint with a threshold for ethanol consumption of approximately 1 oz twice per week.\textsuperscript{64} Of interest, a study conducted in Paris\textsuperscript{65} suggested that the increased risk for growth retardation and stillbirth was seen almost exclusively among beer drinkers. However, this effect may be due to other life style factors among beer drinkers compared to women drinking other alcoholic beverages. The more severe endpoints, congenital malformations, spontaneous abortion and FAS appear to require substantially higher alcohol consumption.

\textit{Exposure Assessment:} These calculations assume that ambient ethanol concentrations are between 250 ppm and 1000 ppm. Using those assumptions plus information on pulmonary function it is possible to calculate the maximum dose of ethanol from inhalation exposure (Table 4). The calculations assume that exposure is constant and continuous over an 8 hour work day, and all the inspired ethanol is absorbed, not an unreasonable assumption as previous studies have shown efficient pulmonary absorption.

\textsuperscript{63} Sokol, Miller & Reed, \textit{supra} note 57; Association of Alcohol Consumption, \textit{supra} note 61.
\textsuperscript{64} J. KLINE, Z. STEIN & M. SUSSER, \textit{supra} note 15.
Table 4

Pulmonary Exposure to Ethanol During Pregnancy

<table>
<thead>
<tr>
<th>Airborne Ethanol (ppm)</th>
<th>250</th>
<th>500</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ml/L air)</td>
<td>0.250 x 10^{-3}</td>
<td>0.5 x 10^{-3}</td>
<td>1.0 x 10^{-3}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume exchange (L/8 Hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant</td>
</tr>
<tr>
<td>Pregnant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary Ethanol Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant</td>
</tr>
<tr>
<td>Pregnant</td>
</tr>
</tbody>
</table>

Using these assumptions, exposure to an ambient concentration of ethanol of 250 ppm represents a total pulmonary dose of 1.0 ml for the nonpregnant worker and 1.4 ml for a pregnant worker. If the ambient concentrations are higher, 500 or 1000 ppm, the total pulmonary dose increases to 2.7 and 5.4 ml for a pregnant worker, exposed continuously over an 8 hour working day.

Ethanol is distributed into body water, which increases substantially during pregnancy. Ethanol is metabolized by hepatic alcohol dehydrogenase. It is not known if ethanol metabolism changes during pregnancy. However, data from one study suggests that there is little change in the rate of ethanol metabolism during pregnancy.

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66 Mattison, supra note 40.
Using this data, with a one compartment pharmacokinetic model\(^{68}\), it is possible to estimate the blood concentration of ethanol resulting from pulmonary exposure (Table 5). In this calculation, the following assumptions are made:

- the volume of distribution is approximately 0.5 L/kg
- the rate of ethanol intake from ambient air concentrations is determined by the concentration (i.e., assuming 250 ppm that is

\(^{68}\) Mattison, supra note 40; *Physiological Alterations*, supra note 18.

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>Maternal Weight (Kg)</th>
<th>Total Body Water (liters)</th>
<th>Blood Ethanol Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50.0</td>
<td>25.0</td>
<td>1.9, 2.19, 2.64, 2.32</td>
</tr>
<tr>
<td>10</td>
<td>50.6</td>
<td>25.5</td>
<td>3.8, 2.50, 2.84, 2.32</td>
</tr>
<tr>
<td>20</td>
<td>54.0</td>
<td>27.0</td>
<td>7.5, 5.00, 5.67, 4.64</td>
</tr>
<tr>
<td>30</td>
<td>58.5</td>
<td>29.0</td>
<td>10.5, 11.22, 11.88, 10.45</td>
</tr>
<tr>
<td>40</td>
<td>62.5</td>
<td>33.0</td>
<td>9.18</td>
</tr>
</tbody>
</table>

**Ambient Ethanol Concentration**

<table>
<thead>
<tr>
<th>Dose Rate (mg/min)</th>
<th>250 ppm</th>
<th>500 ppm</th>
<th>1000 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
<td>3.8</td>
<td>7.5(^{\dagger})</td>
<td></td>
</tr>
<tr>
<td>2.6</td>
<td>5.3</td>
<td>10.5</td>
<td></td>
</tr>
</tbody>
</table>

\(^{\dagger}\) The dose rate (mg/min) is given for nonpregnant/pregnant women with respiratory rates 7.5 or 10.5 L/min, respectively.
equivalent to 0.250 mg/L of air), times the respiratory rate (approximately 7.5 and 10.5 L/min in the nonpregnant and pregnant woman, respectively)

- if all the ethanol inspired is absorbed through the pulmonary epithelium, the dose rate will be approximately 1.9 and 2.6 mg/min in the nonpregnant and pregnant woman, respectively

- the half-life of ethanol is about 20 minutes (ethanol is generally cleared by zero order metabolism)

- with inhalation exposure, the time to steady state and steady state ethanol concentrations can be approximated by a continuous infusion model.

With a half-life of approximately 20 minutes, approximately 100 minutes of exposure is required to reach steady state concentrations of ethanol in body water. If the ambient ethanol concentration is 250 ppm then steady state concentrations would be 2.2 mg/L in a nonpregnant woman and between 2.5 and 2.8 mg/L in pregnant women. With higher ambient concentrations of ethanol the steady state concentrations would obviously increase (Table 5).

**Developmental Risk Assessment**

It is clear that high concentrations of ethanol will produce developmental toxicity in experimental animals. Consumption of large amounts of ethanol during pregnancy is also associated with human developmental toxicity. Estimation of total ethanol dose, assuming all the ethanol which is inspired is absorbed, gave total ethanol doses between 1.4 and 5.4 ml/8 hour work day. In the human, 2 drinks per day throughout pregnancy (approximately 1 oz or 30 ml of ethanol) is thought to represent the threshold for developmental toxicity. The estimated total dose of ethanol, with the assumptions stated above, is below the threshold for human developmental toxicity. Simply calculating the total dose, however, may be misleading because it is believed that a more critical determinant of developmental toxicity is
blood alcohol concentration.

Most experimental animal studies using chronic ethanol exposure have observed developmental toxicity at blood alcohol concentrations of 400 mg/L or greater (Table 3). Some studies, however, have observed developmental effects at concentrations of 60 mg/L. Lower blood ethanol concentrations are associated with growth retardation in experimental animals, with higher concentrations producing developmental disruption. The animal data is also consistent with a threshold for developmental toxicity, with blood alcohol levels below 60 mg/L showing no developmental toxicity. The simulation, using a one compartment pharmacokinetic model and assuming that inhalation exposure can be approximated by a continuous infusion, gave estimated maximum blood ethanol concentrations at ambient exposures of 250 ppm of about 2.5 mg/L at 10 weeks of pregnancy. If the ambient concentrations are 500 ppm or 1000 ppm, maximum blood ethanol concentrations would be 5 and 12 mg/L, respectively, in pregnant women at 10 weeks gestation. These concentrations are substantially below the lowest threshold concentration required for developmental toxicity in experimental animals.

These data and simulations suggest that there is little if any risk from exposures at an ambient concentration of 250 ppm. Even at a higher airborne concentration (1000 ppm), the blood ethanol concentration would be substantially below that associated with developmental toxicity in experimental animals. If there is concern, however, that these calculations may be incorrect, it would be a simple matter to measure blood alcohol concentrations at the beginning and end of a work period to determine the actual concentration. The use of a biomarker of ethanol exposure (blood ethanol concentration) could be used to refine these risk estimates.69

69 NATIONAL RESEARCH COUNCIL, supra note 53.
Risk Management

In responding to questions about airborne ethanol exposure and formulating a reasonable risk management policy, there are several factors that a risk manager must understand. The first is that ethanol is a known hazard for development and has been associated with developmental toxicity in extensive studies conducted in both animals and humans. These studies suggest that ethanol, rather than a metabolite of ethanol, is responsible for the observed developmental toxicity. The data also suggests that there is a clear threshold for adverse developmental effects.

Characterization of a range of developmental toxic endpoints across species suggests at the present time that blood ethanol concentrations represent the best available biological marker for estimating developmental risk. Although most studies suggest that the blood ethanol concentration associated with developmental toxicity occurs above 400 mg/L, some studies have suggested that developmental toxicity may occur with ethanol concentrations as low as 60 mg/L. Therefore, in these studies 60 mg/L was the threshold chosen for comparing blood alcohol concentrations. Over the range of ethanol concentrations in the air (250–1000 ppm), the maximum blood ethanol concentration varied between 2.5 and 12 mg/L at 10 weeks of gestation. Because ethanol produces cellular toxicity across a range of organs, it is reasonable to minimize ethanol exposures throughout pregnancy. Note that during pregnancy the increase in pulmonary function (vital capacity) increases the dose of ethanol. However, also associated with pregnancy is an increase in total body water. This produces a decrease in blood ethanol concentration over the course of pregnancy. At all ambient air concentrations up to 1000 ppm, over each of four time periods of gestation for which the simulation was calculated (10, 20, 30 and 40 weeks), blood alcohol concentrations were substantially below the
estimated threshold (60 mg/L). These calculations suggest that the excess developmental risk, if any, to offspring of workers exposed to airborne ethanol concentration up to 1000 ppm during pregnancy is very small, if there is any excess risk. Workers should be reassured that exposure under these conditions poses little risk to the fetus. Managers should also be reassured that fetal vulnerability to ethanol exposures in the workplace requires substantially higher levels of exposure.

**Conclusions**

The risk assessment methodology originally suggested for cancer provides an important framework for assessing developmental risks and organizing information for risk management. This risk assessment framework requires three discrete steps to collect and organize data and an additional step to calculate the excess risk. The first, hazard identification, is the collection and organization of data demonstrating the safety or hazard of the chemical or chemicals of concern in experimental animal models and in humans. Although many compounds have no data available for assessing developmental risk, it is important to understand that, based on historical data, not all chemicals are developmental toxicants. For those chemicals that produce developmental toxicity, developmental endpoints are the most sensitive for about a third of the chemicals. In addition, for many chemicals associated with developmental toxicity the relative contribution from maternal or paternal exposure remains to be defined. These are important considerations for the risk manager in dealing with chemicals whose developmental toxicity has not been characterized adequately.

The second step, hazard characterization, attempts to organize data which defines the dose-response relationship between the chemical and all adverse developmental endpoints. In addition, detailed information

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70 Risk Assessment, supra note 14.
about the site and mechanism of action, how the compound affects development and how it produces its effect either as a parent compound or after the formation of a metabolite is important for hazard characterization. This data is critical, as compounds may be metabolized by different routes across species with minimal or no formation of the critical toxic metabolite in humans. Alternatively, humans may form the critical developmental toxic metabolite which is not formed in the animal models used.

The third step, exposure characterization, is essential to define the maximum amounts of chemicals to which humans are exposed during pregnancy. In addition to simply defining the amount and duration of exposure, it is also critical to determine the timing of exposure with respect to the pregnancy milestones because of the unique windows of vulnerability for adverse effects on development during pregnancy. This timing of exposure with respect to pregnancy milestones may also be very useful for management of certain developmental toxicants in an occupational setting.

The final step in the quantitative risk assessment process uses the data gathered and organized in the three previous steps to estimate either quantitatively or qualitatively the developmental hazard resulting from the occupational exposure. This final step results in a qualitative or quantitative assessment of excess risk. In this step, data on site and mechanism of toxicity, associations between dose or blood concentrations and developmental toxicity are used along with human exposure data to estimate excess risk, if any, that might accrue during pregnancy from occupational exposures to the chemical or chemicals of concern.

After all of the above steps in qualitative or quantitative risk assessment for developmental toxicity have been completed, it is necessary for a risk management decision to be made. In the most optimum settings the risk management decision is reached collectively.
by the people who will be impacted by the decision, including employers and employees and perhaps other family members as well. It is critically important to carefully define excess risk which results from the occupational exposures of concern. However, it is also critically important not to lose sight of the benefits which result from employment. Many of these benefits are tangible and quantifiable, including income, purchasing power and health benefits. Other nontangible benefits from work can include the impact on self esteem which results from being a productive member of society. Clear characterization of risk from occupational exposures, as well as a clear understanding of the benefits of continuing work are necessary before an informed risk management decision can be made.

The risk assessment framework provides a structure for data organization, data review and the calculation of any excess developmental risk. It also provides the structure to be followed where a causative association is suggested between an occupational or environmental exposure and developmental toxicity.