CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

No studies were located regarding the toxicokinetics of isophorone in humans, but there are limited data from animal studies. These data are summarized below.

- Isophorone is absorbed following inhalation, oral, and dermal exposure. However, quantitative estimates of bioavailability have not been determined for any route of exposure.
- Isophorone is widely distributed throughout the body, although percentages of the absorbed dose distributed to each tissue have not been reported.
- Several metabolites of isophorone have been identified in urine. Proposed metabolic schemes for isophorone include several types of reactions, including methyl oxidation, reduction, dismutation, and conjugation.
- Urine appears to be the primary excretory pathway for isophorone and metabolites, although exhaled air and fecal excretion also occur.

3.1.1 Absorption

No studies were located regarding the absorption of isophorone following inhalation, oral, or dermal exposure of humans to isophorone.

Studies in animals show that isophorone is absorbed following inhalation, oral, and dermal exposure. Isophorone was widely distributed to the organs of rats exposed for 4 hours to a concentration of 400 ppm (Dutertre-Catella 1976), indicating that isophorone is absorbed after inhalation exposure. That isophorone is absorbed by the lungs can also be inferred from the systemic toxicity observed in animals following inhalation exposure (see discussion of health effects in Chapter 2). Imbriani et al. (1985) measured a blood/air partition coefficient of 2,349 for isophorone, indicating that isophorone is well absorbed from the lungs.

Preliminary results of a pharmacokinetic study indicate that rats treated orally with ^{14}C-isophorone excreted 93% of the radiolabel in the urine, expired air, and feces in 24 hours (Strasser 1988). The majority was found in the urine indicating that isophorone was well absorbed. The wide distribution of isophorone in the organs of rats and a rabbit 1–5 hours after dosing by gavage with 4,000 mg/kg (Dutertre-Catella 1976) indicates rapid gastrointestinal absorption. In two rabbits given a gavage dose of

1,000 mg/kg isophorone, a blood level of isophorone of 102 μg/L was found within 10 minutes. The level increased to 141 μg/L in 30 minutes and declined to ≤0.05 μg/L in 21 hours. The results indicate rapid absorption and elimination. The detection of unchanged isophorone and its metabolites (see Section 3.1.3, Metabolism) in the urine and the observations of systemic toxicity and carcinogenicity (see Chapter 2) in animals exposed orally to isophorone provide qualitative evidence that isophorone is absorbed after oral exposure.

A report that a high dermal dose resulted in signs of central nervous system depression in 1/4 rabbits indicates that isophorone is absorbed following dermal exposure (Hazleton Labs 1964).

3.1.2 Distribution

No studies were located regarding distribution of isophorone in humans.

Little information on distribution of absorbed isophorone is available. In rats exposed to 400 ppm isophorone for 4 hours and sacrificed immediately after exposure or 1.5 or 3 hours after exposure, levels of isophorone were highest immediately after exposure in all tissues examined (brain, lungs, heart, stomach, liver, spleen, pancreas, kidney, adrenals, testicles, and ovaries) (Dutertre-Catella 1976). Levels ranged from 1.5 to 74 μg/g tissue wet weight. Tissue levels declined rapidly in males but declined very little in females by 3 hours after exposure.

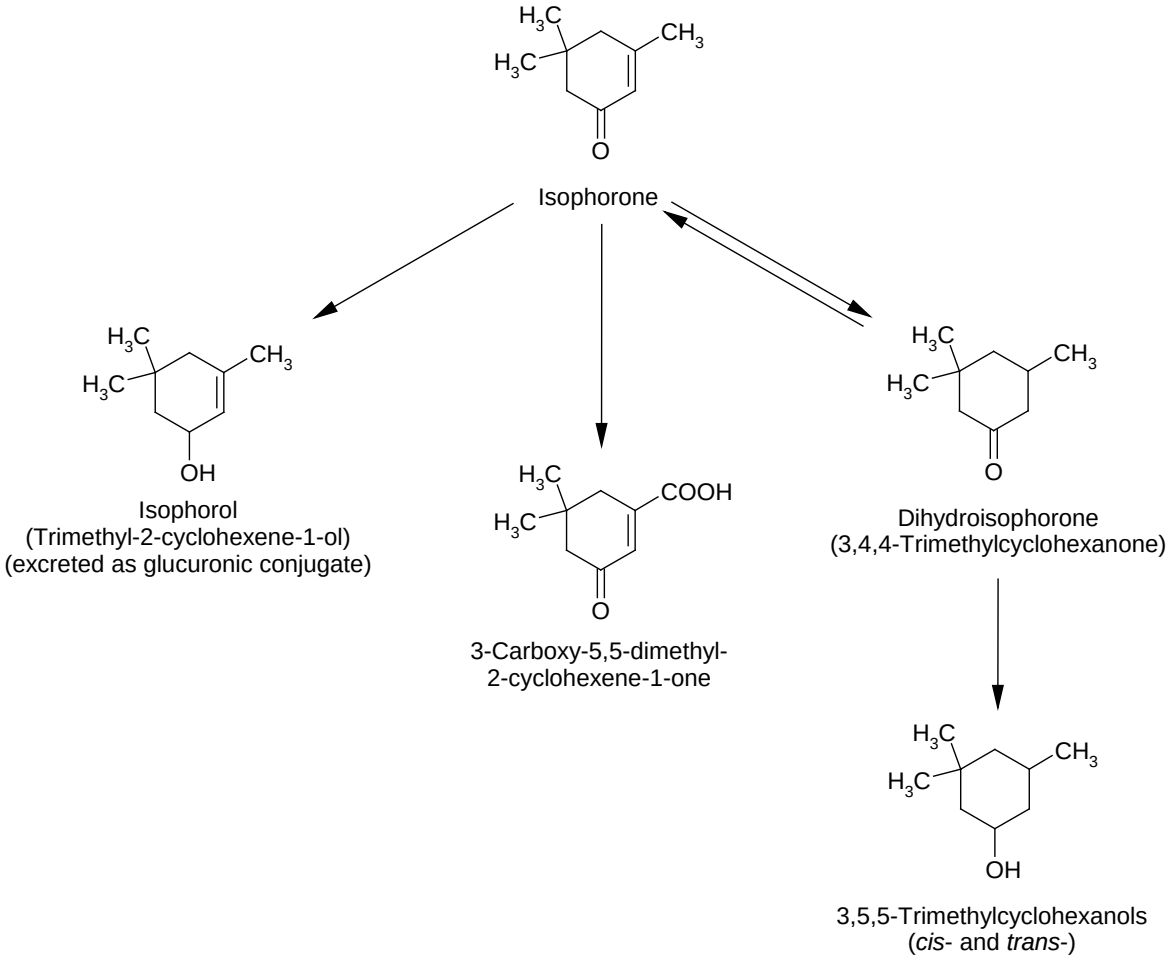
An oral exposure study of ^{14}C-isophorone in corn oil administered to male rats showed that ^{14}C was widely distributed, with highest levels in the liver, kidney, preputial gland, testes, brain, and lungs (Strasser 1988). Isophorone also was widely distributed to the tissues of rats and a rabbit following treatment with isophorone at a gavage dose of 4,000 mg/kg (Dutertre-Catella 1976). The rats died within 1–5 hours and the rabbit died within an hour after dosing, at which times tissues were sampled for analysis. In rats, tissue levels of isophorone in μg/g tissue wet weight were as follows: stomach 6,213; pancreas 2,388; adrenals 1,513; spleen 1,038; liver 613; brain 378; lung 383; heart 387; kidney 465; testes 275, and ovaries 471. In rabbits, tissue levels in μg/g tissue wet weight were as follows: stomach 5,395; adrenals 1,145; ovaries 3,000; spleen 545; liver 515; kidney 295; heart 260, and lungs 50.

3.1.3 Metabolism

No information regarding metabolism of isophorone in humans was identified.

Metabolites of isophorone have been identified in urine of animals administered oral isophorone. In rabbits and rats treated with oral isophorone, the following metabolites were identified in the urine: trimethyl-2-cyclohexene-1-ol (isophorol) and its glucuronic conjugate; 3-carboxy-5,5-dimethyl-2-cyclohexene-l-one; 3,4,4-trimethylcyclohexanone (dihydroisophorone); and cis- and trans-3,5,5-trimethylcyclohexanols (Dutertre-Catella et al. 1978; Truhaut et al. 1970). Rat urine contained more dihydroisophorone and less isophorol than did rabbit urine. Dutertre-Catella et al. (1978) proposed that metabolism of isophorone involves methyl oxidation to 3-carboxy-5,5-dimethyl-2-cyclohexene-l-one, reduction of the ketone group to isophorol, reduction of the ring double bond to dihydroisophorone, and dismutation of dihydroisophorone to cis- and trans-3,5,5-trimethylcyclohexanols. The metabolic pathways are presented in Figure 3-1.

Figure 3-1. Metabolic Scheme for Isophorone



Source: Dutertre-Catella et al. 1976

3.1.4 Excretion

The excretion of isophorone in humans has not been evaluated. Studies in animals suggest that urine is the predominant route of excretion. Dutertre-Catella (1976) found that the excretion of isophorone in air was low (110 μg) and declined further to 30 μg at 2.5–3 hours after exposure of rats to 400 ppm for 4 hours. Rats and rabbits excreted unchanged isophorone and metabolites in the urine and unchanged isophorone in the expired air following oral dosing with isophorone (Dutertre-Catella et al. 1978), but the rate and extent of excretion were not reported. Preliminary results of a pharmacokinetic study indicate that following an oral dose of ^{14}C-isophorone, male rats excreted 93% of the radiolabel in the urine, feces, and expired air in 24 hours, with the majority in the urine (Strasser 1988).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models for isophorone were identified.

3.1.6 Animal-to-Human Extrapolations

Due to the limited amount of available toxicokinetic data, it is not possible to evaluate differences in metabolism of isophorone between species or humans. Thus, it is not possible to determine which animal model is most relevant to humans. Similar effects are observed in humans and laboratory animals following exposure to isophorone in air (irritation of the respiratory tract, eyes and skin).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to isophorone are discussed in Section 5.7, Populations with Potentially High Exposures.

No data are available on the toxicity of isophorone in children. It is assumed that the types of effects in children would be similar to those seen in adults, as there is no obvious reason why effects would qualitatively differ from those in adults. However, there is no information to determine if children would be more or less susceptible than adults. Developmental studies in animals suggest that inhalation of isophorone during resulted in reduced body weight of pups, and higher concentrations may possibly cause exencephaly (see study details in Section 2.17). However, no information on developmental effects in humans was identified.

Isophorone produces irritation of the respiratory tract in humans and animals (study details are provided in Section 2.4). Individuals with underlying diseases of the respiratory tract, such as asthma, may be more sensitive to the irritant effects of isophorone.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to isophorone are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for isophorone from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by isophorone are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

The use of isophorone or its metabolites as biomarkers of exposure has not been investigated.

3.3.2 Biomarkers of Effect

There are no specific biomarkers to characterize the effects caused by isophorone.

3.4 INTERACTIONS WITH OTHER CHEMICALS

The possible synergistic interactions of isophorone with other solvents are important because mixed exposures occur in occupational settings and may occur in the environment. The joint toxicity of isophorone with 26 other industrial liquid chemicals based on determinations of the oral LD_{50} values in rats of each chemical alone and in a 1:1 (v/v) mixture was determined (Smyth et al. 1969). The LD_{50} values of the mixtures were predicted based on the assumption of additivity of the LD_{50s} of each component, and the ratios of the predicted values to experimentally determined values were calculated. Greater-than-additive toxicity was observed for the mixtures of isophorone with nine chemicals: tetrachloroethylene, propylene glycol, morpholine, ethyl alcohol, ethyl acetate, carbon tetrachloride, acrylonitrile, acetonitrile, and acetone. Less-than-additive toxicity was observed for the mixtures of isophorone with 17 chemicals: Ucon LB-250, Ucon 50-HB-260, toluene, Tergitol XD, propylene oxide, polyethylene glycol 200, Phenyl Cellosolve, nitrobenzene, acetophenone, aniline, Butyl Cellosolve, butyl ether, diethanolamine, dioxane, ethyl acrylate, ethylene glycol I, and formalin. When the frequency distribution of the ratios for all combinations of all chemicals were adjusted to give a normal distribution, however, none of the ratios for mixtures with isophorone deviated significantly from the mean ratios, indicating, essentially, additive toxicity. In a subsequent study, the additivity of equitoxic mixtures, defined as a mixture of chemicals in volumes directly proportional to their oral LD_{50} in rats, was determined (Smyth et al. 1970). Isophorone showed less-than-additive toxicity with Phenyl Cellosolve and Ucon Fluid 50-HB-260 and greater-than-additive toxicity with propylene oxide. The mechanism for such interactions is not known.