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

3.1 TOXICOKINETICS

No studies were located regarding the toxicokinetics of 1,2-diphenylhydrazine in humans; limited laboratory animal data, summarized below, are available.

- 1,2-Diphenylhydrazine is presumed to be absorbed following oral exposure based on the appearance of urinary metabolites and adverse health effects.
- No information on the distribution of 1,2-diphenylhydrazine was identified.
- The available data suggest that 1,2-diphenylhydrazine is metabolized to aniline in the gut and that it readily forms benzidine in the acidic stomach.
- No information is available on the excretion of 1,2-diphenylhydrazine; one study reported the presence of unidentified urinary metabolites.

3.1.1 Absorption

No studies were located containing specific information regarding absorption after inhalation, oral, or dermal exposure to 1,2-diphenylhydrazine in humans or animals. Pulmonary absorption of 1,2-diphenylhydrazine by rats is suggested by detection of an unidentified metabolite in the urine following intratracheal administration of 1,2-diphenylhydrazine in water suspension and dimethyl sulfoxide (DMSO) (Dutkiewicz and Szymanska 1973). It is not known, however, if any of the dose was ingested.

Gastrointestinal absorption of 1,2-diphenylhydrazine by rodents is indicated by the occurrence of parent compound and metabolites in the urine following oral treatment (Section 3.1.4) and adverse health effects observed following oral exposure (Chapter 2).

3.1.2 Distribution

No studies were located regarding distribution in humans or animals after inhalation, oral, or dermal exposure to 1,2-diphenylhydrazine.

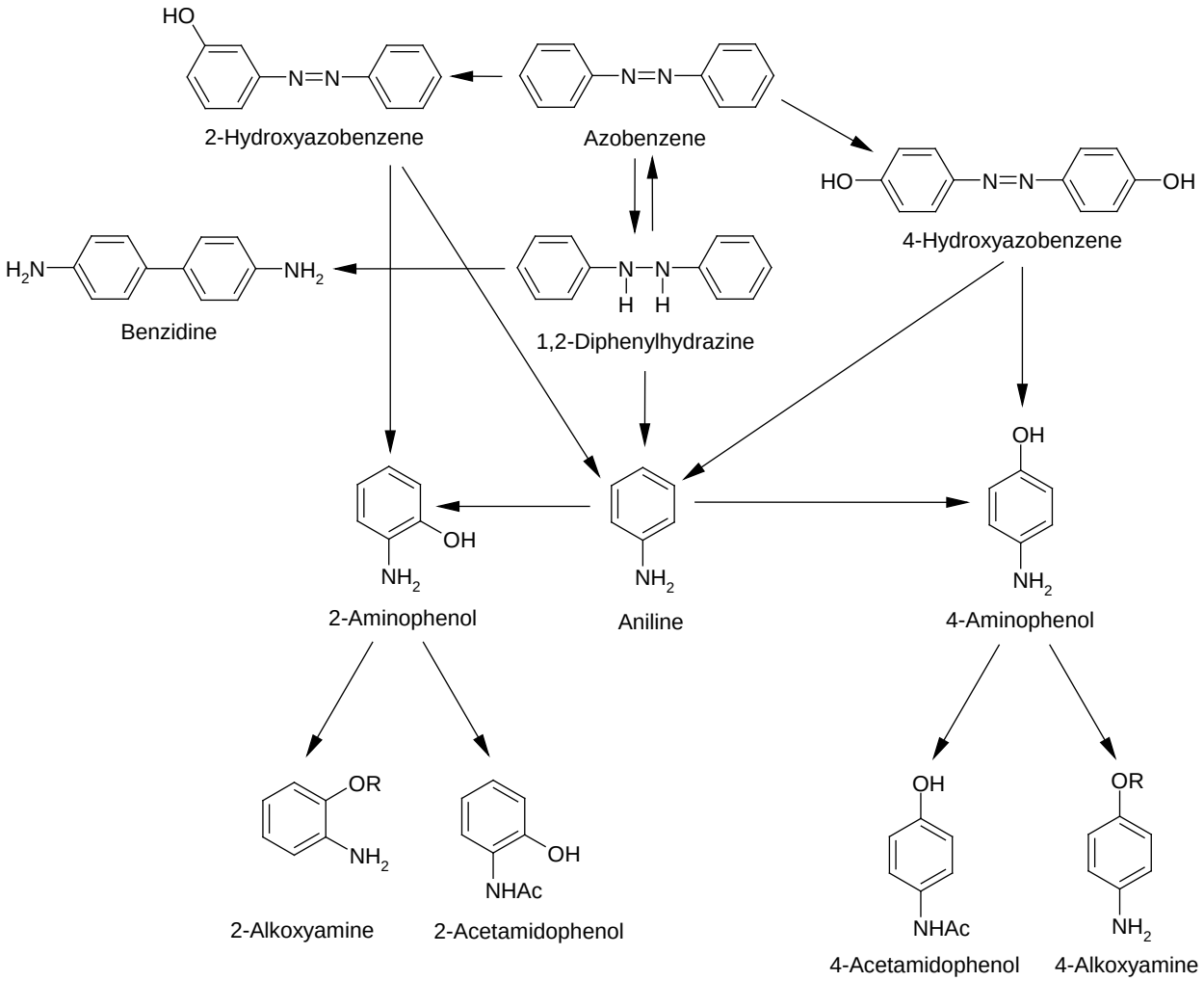
3.1.3 Metabolism

Limited information is available on the metabolism of 1,2-diphenylhydrazine. In the only study involving 1,2-diphenylhydrazine as the parent compound, rat urine was analyzed for metabolites following single oral (200 or 400 mg/kg), intraperitoneal (100 or 200 mg/kg), intravenous (4 or 8 mg/kg), and intratracheal (5 or 10 mg/kg) doses of 1,2-diphenylhydrazine (Dutkiewicz and Szymanska 1973). Unchanged 1,2-diphenylhydrazine was detected following treatment by all routes, and aniline and benzidine were identified following the oral and intraperitoneal treatments. Other metabolites included two unspecified hydroxy derivatives of benzidine (oral route), 2- and 4-aminophenol (intraperitoneal route), and unidentified compounds (oral, intravenous, and intratracheal routes). Amounts of compounds excreted were not quantitated. The validity of the findings of this study is uncertain, however, as the analytical methodology (thin-layer chromatography) may have produced degradation products that were identified as unchanged 1,2-diphenylhydrazine or metabolites. The metabolites identified by Dutkiewicz and Szymanska (1973) are consistent with a metabolic scheme proposed by Williams (1959) (Figure 3-1), which is based on data for azobenzene and aniline. As summarized by NRC (1981), aniline is oxidized by hydroxylation of a ring carbon to form 2- or 4-aminophenol or of the nitrogen to form phenylhydroxylamine, and then is conjugated to glucuronic or sulfuric acid. An oral study of azobenzene with conventional and germ-free rats (Macholz et al. 1985) showed that metabolism of 1,2-diphenylhydrazine to aniline resulted from the reductional and hydrolytic capability of gut flora. *In vitro* metabolism of 1,2-diphenylhydrazine to aniline by rat intestinal microorganisms has been demonstrated (Bolton and Griffiths 1978). Benzidine is formed readily from 1,2-diphenylhydrazine by acid rearrangement. It has been suggested that benzidine may be produced from 1,2-diphenylhydrazine by acidity in the stomach (IARC 1972).

3.1.4 Excretion

No studies were located regarding excretion in humans or animals after inhalation, oral, or dermal exposure to 1,2-diphenylhydrazine. The presence of an unidentified metabolite in the urine of rats following intratracheal and oral administration of 1,2-diphenylhydrazine in water and DMSO suspensions (Dutkiewicz and Szymanska 1973) suggests that some urinary excretion occurs.

Figure 3-1. Metabolic Scheme of 1,2-Diphenylhydrazine



Source: Williams 1959

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 were identified for 1,2-diphenylhydrazine.

3.1.6 Animal-to-Human Extrapolations

There are insufficient data in which to evaluate possible species differences in the toxicokinetic properties of 1,2-diphenylhydrazaine.

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 1,2-diphenylhydrazine are discussed in Section 5.7, Populations with Potentially High Exposures.

No data are available in on the toxicity of 1,2-diphenylhydrazine in children and it is assumed to be similar to adults. No developmental toxicity studies have been identified for this compound. No populations with unusual susceptibility to health effects of 1,2-diphenylhydrazine have been identified. It is possible that people with chronic liver disease or possibly compromised hepatic function might be unusually susceptible to 1,2-diphenylhydrazine, because the liver is a target organ of 1,2-diphenyl-hydrazine in animals.

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 1,2-diphenylhydrazine 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 1,2-diphenylhydrazine 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 1,2-diphenylhydrazine 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

No studies were located regarding biomarkers of exposure to 1,2-diphenylhydrazine. The metabolites of 1,2-diphenylhydrazine were identified in one study (Dutkiewicz and Szymanska 1973); however, the validity of the findings is uncertain because of the analytical methodology used (see Section 3.1.3). No enzymatic changes that could be used as biomarkers of 1,2-diphenylhydrazine exposure are known.

3.3.2 Biomarkers of Effect

No biomarkers of effect were identified for 1,2-diphenylhydrazine exposure. No specific alterations in the organism that could be recognized as biomarkers were found, and the most susceptible organs or tissues were not identified.

3.4 INTERACTIONS WITH OTHER CHEMICALS

A carcinogenicity study was reported in which groups of rats were given weekly subcutaneous injections of 1,2-diphenylhydrazine (20 mg) alone or concurrently with benzidine sulfate (15 mg) for life (Genin et al. 1975). Combined incidences of tumors (injection site, liver, and other sites) were increased and the mean tumor latent period was decreased in the group with combined 1,2-diphenylhydrazine and benzidine sulfate exposure. It is unclear whether these findings provide evidence for an interaction between 1,2-diphenylhydrazine and benzidine or additive effects of two carcinogens. The results of this study were also reported by Shabad and Genin (1975) and Kurliandskiĭ et al. (1976).