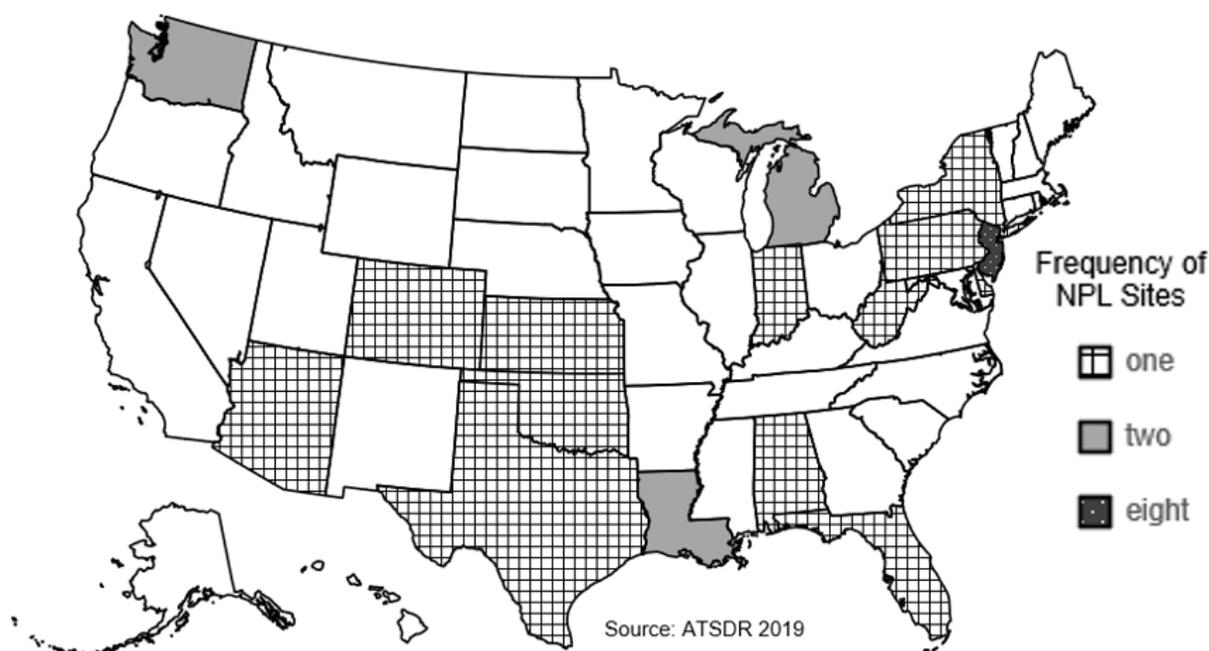


CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Diphenylhydrazine has been identified in at least 26 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which 1,2-diphenylhydrazine has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with 1,2-Diphenylhydrazine Contamination



- The general population is not likely to be exposed to 1,2-diphenylhydrazine because dye manufacturers in the United States no longer produce benzidine based dyes, which was the former principal use of 1,2-diphenylhydrazine.
- The only current use of 1,2-diphenylhydrazine in the United States is in the production of anti-inflammatory pharmaceutical agents for veterinary use.
- 1,2-Diphenylhydrazine is reversibly oxidized in the environment under aerobic conditions, with a half-life in water as short as 15 minutes. This oxidation also occurs in air and soil.
- The fate, transport, and distribution of 1,2-diphenylhydrazine in the environment are influenced by its rapid oxidation to azobenzene.

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5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL**5.2.1 Production**

1,2-Diphenylhydrazine is produced in the stepwise reduction of nitrobenzene by the action of iron or zinc powder in caustic solution (e.g., caustic soda, alcoholic alkaline) first to azoxybenzene, then azobenzene, and finally 1,2-diphenylhydrazine (Sandridge and Staley 1978). A batch process is used in which a caustic soda solution is added to a heated vessel charged with nitrobenzene and iron borings. Additions of iron in caustic soda solution are made to continue the reaction. When the reaction is complete, separation of the 1,2-diphenylhydrazine from the iron sludge is accomplished by solvent extraction or by alternative methods, such as stopping the reaction at the azobenzene step and performing the final reduction in a zinc-alcoholic alkali solution followed by filtration and washing of the sodium zincate mass.

Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of 1,2-diphenylhydrazine in 2016 (TRI18 2020). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use 1,2-Diphenylhydrazine

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
OH	1	100	999	12
TX	1	1,000	9,999	12

^aPost office state abbreviations used.

^bAmounts on site reported by facilities in each state.

^cActivities/uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI18 2020 (Data are from 2018)

5.2.2 Import/Export

No information concerning the importation or exportation of 1,2-diphenylhydrazine in the United States was located in the literature.

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5.2.3 Use

One of the major former uses of 1,2-diphenylhydrazine was as a starting material in the production of benzidine-based dyes; however, these are no longer produced or used in the United States. 1,2-Diphenylhydrazine rearranges to benzidine upon treatment with strong acid; benzidine was used by the dye industry for the production of benzidine-based dyes including many of the Direct dyes (e.g., Direct Red 28, Direct Black 4, Direct Blue 2) (Ferber 1978; Lurie 1964).

1,2-Diphenylhydrazine is used by the pharmaceutical industry for the production of the drug, phenylbutazone (trade name Butazolodin, an anti-inflammatory agent); phenylbutazone is no longer marketed for human use in the United States, but is still listed for veterinary use (FDA 2016).

1,2-Diphenylhydrazine was also used for the production of sulfapyrazone (trade name Anturane, a uricosuric agent for the treatment of gouty arthritis) (Hughes 1981; Kornis 1982); however, sulfapyrazone has been withdrawn for sale in the United States (FDA 2009). These drugs are/were made by the condensation of 1,2-diphenylhydrazine with malonic acid derivatives to form pyrazolidinedione structures. It is not clear from the literature if the 1,2-diphenylhydrazine used in the condensation reaction is produced by the manufacturers or if it is purchased by them as an isolated product.

5.2.4 Disposal

Very little information was located in the literature concerning the disposal of 1,2-diphenylhydrazine. Dietrich et al. (1985) reported that wet air oxidation (heating waste water under pressure with the addition of an oxygen-containing gas such as air) would remove 99.88% of the 1,2-diphenylhydrazine in the water (initial concentration, 5,000 mg/L). Results of treatment by wet air oxidation are in keeping with the observation that 1,2-diphenylhydrazine oxidizes to azobenzene (Riggin and Howard 1979). Information regarding the amount of 1,2-diphenylhydrazine disposed of in the United States was not located in the literature.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data, presented in Table 5-2, should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥ 10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10

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(except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005).

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Diphenylhydrazine^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
OH	1	0	0	0	0	0	0	NR	0
TX	1	7	0	0	0	0	7	NR	7
Total	2	7	0	0	0	0	7	0	7

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

NR = not reported; RF = reporting facilities; UI = underground injection

Source: TRI18 2020 (Data are for 2018)

5.3.1 Air

Estimated releases of 7 pounds (~0.0032 metric tons) of 1,2-diphenylhydrazine to the atmosphere from two domestic manufacturing and processing facilities in 2018, accounted for 100% of the estimated total

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environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are summarized in Table 5-2.

No information concerning the release of 1,2-diphenylhydrazine to air was located in the literature. Since there are very limited uses of 1,2-diphenylhydrazine, emissions to the atmosphere are expected to be low.

5.3.2 Water

There were no releases of 1,2-diphenylhydrazine to water from manufacturing and processing facilities required to report to the TRI (TRI18 2020) (Table 5-2).

No other information concerning the release of 1,2-diphenylhydrazine to water was located in the literature. If discharged to water, detectable concentrations will probably persist for only a short time, since the half-life of (100 µg/L) 1,2-diphenylhydrazine in wastewater is about 15 minutes (EPA 1982; Riggin and Howard 1979).

5.3.3 Soil

There were no releases of 1,2-diphenylhydrazine to soil from manufacturing and processing facilities required to report to the TRI (TRI18 2020) (Table 5-2).

No other information concerning the release of 1,2-diphenylhydrazine to soil was located in the literature. The manufacturing process for 1,2-diphenylhydrazine generates a sludge containing iron and/or zinc compounds, probably along with small amounts of unextracted 1,2-diphenylhydrazine. Some of this material may be disposed of in landfills, but no information is available concerning the 1,2-diphenylhydrazine disposal practices.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

No information concerning the transport and partitioning of 1,2-diphenylhydrazine in the environment was located in the literature. Based upon its short persistence time and its physical-chemical properties, volatilization from water or soil surfaces, bioconcentration in aquatic organisms, and leaching from soils

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to underlying groundwater are not expected to be important environmental fate processes for 1,2-diphenylhydrazine.

5.4.2 Transformation and Degradation

Air. No studies were located regarding the rates or products of reaction of 1,2-diphenylhydrazine in the atmosphere. Based on its rapid degradation in aerated water, 1,2-diphenylhydrazine will oxidize in air to form azobenzene as well as other products resulting from the abstraction of a hydrogen from a nitrogen by hydroxyl radicals. The reaction rate constant of 1,2-diphenylhydrazine with photochemically generated hydroxyl radicals was estimated as $211 \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ second}^{-1}$ using a structure estimation method discussed in Atkinson (1987). This corresponds to an atmospheric half-life of <2 hours, assuming a hydroxyl radical concentration of $0.5 \times 10^6 \text{ molecules cm}^{-3}$. 1,2-Diphenylhydrazine also absorbs light above 290 nm (NLM 2020) and may be susceptible to photolysis. No information was found concerning the characteristics of this potential reaction.

Water. Riggin and Howard (1979) and EPA (1982) reported the results of a study on the stability of 1,2-diphenylhydrazine in a number of solvents including distilled water and wastewater. In distilled water at pH values of 2, 4.7, 7, and 10 and at 4°C or at room temperature, <10% of the initial 10 µg/L of 1,2-diphenylhydrazine remained in the water after 1 day. At pH 2, 1,2-diphenylhydrazine degraded to benzidine, while at pH 7, it degraded to an unidentifiable oxidizable product. At pH 10, 1,2-diphenylhydrazine degraded to azobenzene, and at pH 4.7, it degraded into two unidentifiable products, which were not azobenzene or benzidine. In secondary municipal sewage effluent, (EPA 1982; Riggin and Howard 1979) reported that 100 µg/L of 1,2-diphenylhydrazine had a half-life of about 15 minutes in the presence of oxygen, and about 60 minutes when no oxygen was present. These results suggest that 1,2-diphenylhydrazine is unlikely to persist in the environment, particularly under aerobic conditions.

Tabak et al. (1981a, 1981b) and Patterson and Kodukala (1981) stated that 5 or 10 mg/L of 1,2-diphenylhydrazine was degraded up to 80% when initially cultured with settled domestic wastewater. This degradation rate, however, was reduced to 40% in the case of the 10 mg/L concentration, after the third subculture. The authors suggested that a de-adaptive and detoxification process was occurring with 1,2-diphenylhydrazine. It is unclear if the analytical methods used by these authors would have been able to detect 1,2-diphenylhydrazine if present. Both dissolved organic carbon and gas chromatography (GC) analyses were performed on the samples. Considering the sample preparation procedures, however, the

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compound detected might not have been 1,2-diphenylhydrazine, but a decomposition product such as azobenzene.

Sediment and Soil. No information concerning the fate of 1,2-diphenylhydrazine in soil was located in the literature. Based on the fate of 1,2-diphenylhydrazine in water and sediment, detectable concentrations probably will not persist for long periods, but this may depend on the initial concentration.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,2-diphenylhydrazine depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens.

Concentrations of 1,2-diphenylhydrazine in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1,2-diphenylhydrazine levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

The rapid oxidation of 1,2-diphenylhydrazine in water to form azobenzene and other compounds makes its sampling and analysis difficult. Storing a sample containing 1,2-diphenylhydrazine for even short periods can result in complete oxidation; in GC, 1,2-diphenylhydrazine is oxidized to azobenzene upon injection onto the chromatographic column (EPA 1982). Therefore, unless sampling and analysis are performed under conditions that will prevent oxidation or unless concentrations of 1,2-diphenylhydrazine in the sample are very high, analyses of environmental samples for 1,2-diphenylhydrazine are inaccurate (Ahuja et al. 1989; Riggin and Howard 1979). It is doubtful that the concentrations measured reflect on the concentrations present in the sample at the time of collection (i.e., measured concentrations would underestimate actual concentrations) (EPA 1982).

Detections of 1,2-diphenylhydrazine in air, water, and soil at NPL sites are summarized in Table 5-3.

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Table 5-3. 1,2-Diphenylhydrazine Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median ^a	Geometric mean ^a	Geometric standard deviation ^a	Number of quantitative measurements	NPL sites
Water (ppb)			No data		
Soil (ppb)	1,000	1,000	1,710	4	3
Air (ppbv)			No data		

^aConcentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

No ambient air monitoring for 1,2-diphenylhydrazine was located in the literature. This may be due to both the rapid oxidation of 1,2-diphenylhydrazine and its low vapor pressure, which limit the amount of 1,2-diphenylhydrazine entering the atmosphere. In addition, no information was located suggesting that any studies sought, but did not find, 1,2-diphenylhydrazine.

5.5.2 Water

Water quality data compiled from the STORET Data Warehouse and the U.S. Geological Survey (USGS) National Water Information System (NWIS) reports are summarized in Table 5-4. These data are comprised of water quality data from water resource management groups across the country.

Table 5-4. 1,2-Diphenylhydrazine Detected in Samples Collected Throughout the United States from 1990 to 2020

Type	Number of samples	Number of positive	Concentration range
Groundwater	2,409	92	0.12–21.00 ppb
Surface water	3,286	14	<0.2–260 ppb
Wastewater	12	0	0.22–7 ppb (detection limit)
Leachate	17	0	2.1–5.00 ppb (detection limit)
Sediment	1,238	3	<340–<1,700 ppb
Subsurface soil/sediment	78	0	58–310 ppb (detection limit)
Soil	128	0	336–3,530 ppb (detection limit)

Source: NWQMC 2020

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Two reported identifications of 1,2-diphenylhydrazine in water samples were located in the literature. EPA (1981) reported that 1,2-diphenylhydrazine was present in drinking water in Cincinnati, Ohio (river water treated by coagulation, sand filtration, and chlorination) at a concentration of 1 ng/L. Since the sample preparation involved aeration and the original sample was chlorinated, it is unclear if the detected material was 1,2-diphenylhydrazine or azobenzene. EPA (1982) found that, in addition to injection onto a GC column, either chlorination or aeration of a sample resulted in total disappearance of 1,2-diphenylhydrazine. Tang et al. (1983) reported 1,2-diphenylhydrazine in coal gasification wastewater at concentrations of 0.149 and 1.786 $\mu\text{g/L}$. Sample preparation in this case involved separation into classes by pH, liquid-liquid extraction, concentration, and GC/mass spectroscopy (MS) analysis. No precautions were taken to reduce the aeration of the sample. Also, the analytical procedure indicates that no 1,2-diphenylhydrazine would have been able to survive the conditions of the sample preparation and the detection may be of azobenzene or of 1,2-diphenylhydrazine from another source (e.g., decomposition of another compound to 1,2-diphenylhydrazine).

Hall et al. (1985) reported that no 1,2-diphenylhydrazine ($<1 \mu\text{g/L}$) was detected in the Nanticoke River near the Chesapeake Bay. The analytical method involved liquid-liquid extraction, concentration, and analysis by GC/MS.

5.5.3 Sediment and Soil

1,2-Diphenylhydrazine has been identified in soil only at hazardous waste sites (see Table 5-3); however, it is not clear if the measurements were for 1,2-diphenylhydrazine or its degradation product.

5.5.4 Other Media

1,2-Diphenylhydrazine has been assayed but not detected in fish samples from the Great Lakes area. Camanzo et al. (1987) reported that no 1,2-diphenylhydrazine was detected in fish samples from 13 Lake Michigan tributaries and Grand Traverse Bay fish. Analyses were made by GC/MS and no detection limits were given. Similarly, De Vault (1985) reported that a GC/MS did not identify any of the peaks present in fish samples from Great Lakes harbors and tributaries as 1,2-diphenylhydrazine.

Phenylbutazone can hydrolyze to yield 1,2-diphenylhydrazine, and this drug may contain some 1,2-diphenylhydrazine (Ahuja et al. 1989; Fabre et al. 1984; Matsui et al. 1983). Phenylbutazone is a drug used for the treatment of inflammatory conditions (e.g., arthritis) in animals.

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5.6 GENERAL POPULATION EXPOSURE

Virtually no information concerning occupational exposure or general population was located in the literature. In the past, general population exposure could come from use of anti-inflammatory medication made synthesized with 1,2-diphenylhydrazine, since these drugs may contain small residual amounts (Fabre et al. 1984; Matsui et al. 1983). However, phenylbutazone and sulfinpyrazone are not currently used as human medications (FDA 2009, 2016).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The only populations with potentially high exposure appear to be people living near hazardous waste sites where 1,2-diphenylhydrazine is present and those in occupations that manufacture or use 1,2-diphenylhydrazine. Very little information concerning these populations, however, is available to clearly understand the extent of these potential exposures.