Spaceflight Recovery Considerations for Acute Inhalational Exposure to Hydrazines

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INTRODUCTION: Inhalation of hydrazine or hydrazine-derivative (for example, monomethylhydrazine) vapors during spaceflight operations remains a risk to crew and ground support personnel. Here we sought to provide an evidence-based approach to inform acute clinical treatment guidelines for inhalational exposures during a noncatastrophic contingency spaceflight recovery scenario.

METHODS: A review of published literature was conducted concerning hydrazine/hydrazine-derivative exposure and clinical sequelae. Priority was given to studies that described inhalation though studies of alternative routes of exposure were additionally reviewed. Where possible, human clinical presentations were prioritized over animal studies.

RESULTS: Rare human case reports of inhalational exposure and multiple animal studies provide evidence of varied clinical sequelae, including mucosal irritation, respiratory concerns, neurotoxicity, hepatotoxicity, hemotoxicity (including Heinz body development and methemoglobinemia), and longitudinal risks. In an acute timeframe (minutes to hours), clinical sequelae are likely to be limited to mucosal and respiratory risk; neurological, hepatotoxic, and hemotoxic sequelae are unlikely without recurrent, longitudinal, or noninhalational exposure.

CONCLUSIONS: Acute clinical management should focus on likely clinical concerns as supported by existing data; recovery medical personnel should be prepared to manage mucosal irritation and respiratory concerns, including the potential need for advanced airway management. There is little evidence supporting the need for acute interventions for neurotoxicity and there is no evidence that acute hemotoxic sequelae would drive the need for on-scene management of methemoglobinemia, Heinz body development, or hemolytic anemia. Training that overemphasizes neurotoxic or hemotoxic sequelae or specific treatments for such conditions potentially raises the risk for inappropriate treatment or operational fixation.

KEYWORDS: hypergolic, monomethylhydrazine, aerozine, pyridoxine, methemoglobinemia, neurotoxicity.

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Hydrazines are hypergolic fluids used as propellants in the aviation and space industries. In spaceflight operations, these chemicals present occupational health hazards to astronaut crewmembers as well as ground recovery teams. Many spacecraft vehicles use hypergolic fuels for onboard reaction control systems; after atmospheric reentry, off-gassing of reaction control systems can be a source of hypergolic inhalation during recovery operations. Inhalational exposure of hypergolic propellants [including hydrazine (HZ) and hydrazine-derivatives (HZ-D)] and oxidizers has been a source of injury to both ground support teams and astronaut crewmembers in spaceflight-related operations.[60,61,71]

Adverse health effects from HZ and HZ-D [such as monomethylhydrazine (MMH) or 1,1-dimethylhydrazine, which is also known as unsymmetrical dimethylhydrazine

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(UDMH)] can range from distracting mucosal irritation to life-threatening respiratory, hematologic, and central nervous system (CNS) dysfunction.[53,59,82] Due to a limited number of human exposure cases documented in the medical and scientific literature, much of the evidence driving regulatory and medical treatment standards is anecdotal or extrapolated from animal studies. While reassuring that few human cases of HZ/HZ-D toxicity have been recorded, this has led to variable guidelines regarding exposure concerns and appropriate medical response and clinical treatment guidelines relative to potential exposure scenarios. The timeline for the development of HZ/HZ-D-related toxicity, expected clinical manifestations and emergent medical needs, and appropriate treatment guidelines for acute spaceflight-related exposures remain unclear. While prior literature has focused on unique or rare clinical events that follow HZ/HZ-D exposure, there is need for improved understanding of expected acute and emergent clinical sequelae from acute, one-time exposures, particularly regarding what types of clinical events may manifest during a spaceflight recovery or rescue operation and prior to transport to a definitive medical care facility.

While hypergolic propellants, including HZ/HZ-D, certainly carry a risk of acute catastrophic event (e.g., explosion, fire), a more plausible survival scenario driving acute clinical needs may be subcatastrophic exposures, particularly inhalation. Indeed, such an event occurred during the Apollo-Soyuz test flight, when ingestion of nitrogen tetroxide into the capsule volume during pressure equalization following atmospheric reentry led to crewmember inhalational exposure with subsequent clinical sequelae requiring medical treatment.[23,60,71] Rescue and recovery forces adhere to occupational exposure guidelines and, in nominal circumstances, would test for the presence of hypergols prior to vehicle approach. Despite this hazard control measure, crewmembers and ground personnel remain at risk of exposure during off-nominal and contingency scenarios. Scenarios with a specific risk of hypergol exposure to crew include loss of capsule pressure vessel integrity and depressurization, occult leaks postlanding where exposure occurs prior to recognition and mitigation, capsule gaseous ingestion, or off-gassing events. Such acute exposures (in this context we expect "acute" exposure to be on the order of minutes) can drive clinical sequelae that could directly impair a crew or first responder's ability to perform critical duties in the postlanding operational environment.

Here we sought to address the risks of HZ/HZ-D inhalational exposure in noncatastrophic spaceflight recovery operations (excluding vehicular explosion or similar compromise). We sought evidence of clinical signs, symptoms, and outcomes at variable exposure concentrations that might indicate a need for particular clinical proficiencies, medical treatment needs, or specific skillsets required for acute management of inhalational HZ/HZ-D toxicity in spaceflight operations.

METHODS

A review was conducted to identify currently available information and published literature of human and animal studies involving acute inhalation exposure to HZ/HZ-D compounds, including HZ, MMH, and UDMH. Search terms included hydrazine, monomethylhydrazine, unsymmetrical dimethylhydrazine, aerozine, hypergol, toxicity, toxin, toxicology, propellant, occupational exposure, spaceflight, aviation, fuel, respiratory, mucosal, irritation, irritant, hepatotoxicity, liver function, neurological, seizure, and similar terms. Databases included the National Library of Medicine, PubChem, Ovid, Medline, Web of Science, and the Defense Technical Information Center. NASA archives and documentation from regulatory bodies, including the Center for Disease Control (CDC), Environmental Protection Agency (EPA), the National Institute of Occupational Safety and Health (NIOSH), the National Research Council (NRC), and the Occupational Safety and Health Administration (OSHA), were searched for the same criteria. Titles obtained from these search criteria were reviewed for relevance. Studies published in a language other than English without available translation were discarded. Studies that identified inhalation toxicity or sequelae related to inhalation of HZ/HZ-D compounds were prioritized and reviewed in their entirety. Studies that focused on other routes of exposure and/or intermittent/recurrent exposure were reviewed and included when used as the basis of understanding for standard of care, generally when inhalation data were unavailable. References of all reviewed manuscripts were also searched to identify additional applicable studies. Both animal and human studies were considered for inclusion, though relevant human exposures took precedence with support from animal data.

RESULTS

Applicable Exposure Limits and Use of Personal Protective Equipment

The primary toxicities related to HZ/HZ-D exposures can be broadly categorized as mucosal irritation, respiratory irritation, neurotoxicity, hepatotoxicity, hemotoxicity, and mortality risk. Given the known toxicity of HZ/HZ-D compounds, various regulatory bodies have imposed guidelines or permissible limits for occupational and acute exposures to HZ/HZ-D compounds. These guidelines for HZ, MMH, and UDMH are presented in **Table I**, **Table II**, and **Table III**; limits are specific to health concerns, exposure scenario, and occupational requirements.

While NASA develops Spaceflight Maximum Allowable Concentrations (SMACs) for chemicals in air, such limits apply only to spacecraft while in flight.[57] Exposure limits during ground support and spaceflight recovery activities are instead guided by occupational limits. These occupational limits in turn drive utilization of personal protective equipment (PPE) and operational protocols.

Table I. Hydrazine Exposure Guidelines.

GUIDELINE	INTENT	10 min	30 min	1 h	2 h	4 h	8 h	16 h	24 h	7 d
EPA AEGL-1[17] (Nondisabling)	Level at which temporary or nondisabling effects may occur	0.1 ppm	0.1 ppm	0.1 ppm		0.1 ppm	0.1 ppm			
EPA AEGL-2[17] (Disabling)	Level at which disabling, but not life-threatening effects, may occur	23 ppm	16 ppm	13 ppm		3.1 ppm	1.6 ppm			
EPA AEGL-3[17] (Life threatening)	Level at which life-threatening effects may occur	64 ppm	45 ppm	35 ppm		8.9 ppm	4.4 ppm			
NRC SPEGL[11]	Short-term public emergency exposure limits			0.12 ppm	0.16 ppm	0.03 ppm	0.015 ppm	0.008 ppm	0.005 ppm	
NASA SMAC[57]	NASA-established limits imposed on spacecraft operations during flight			4 ppm					0.3 ppm	0.04 ppm
OSHA IDLH[11]	Level at which exposure is immediately dangerous to life and health		50 ppm							
NIOSH REL[11]	Recommended upper limit for occupational exposure to avoid adverse health effects				0.03 ppm (2-h ceiling)					
OSHA PEL[11]	Legally enforceable regulatory ceiling limit, imposed to protect workers against exposure-related health effects						1 ppm			
ACGIH TLV[11]	Exposure at or below this level does not create unreasonable risk of injury. NASA-adopted consensus standard.						0.01 ppm			

Hydrazine exposure limits and guidelines as established by various regulatory and scientific agencies. While included for completeness, Spacecraft Maximum Allowable Concentration (SMAC) values only apply to space vehicles while in flight.
ACGIH—American Conference of Governmental Industrial Hygienists; AEGL—Acute Exposure Guideline Level; EPA—Environmental Protection Agency; IDLH—Immediately Dangerous to Life and Health; NASA—National Aeronautics and Space Administration; NIOSH—National Institute of Occupational Safety and Health; NRC—National Research Council; OSHA—Occupational Safety and Health Administration; PEL—Permissible Exposure Limits; REL—Recommended Exposure Limits; SPEGL—Short-term Public Emergency Guidance Level; TLV—Threshold Limit Values.

Table II. Monomethylhydrazine (MMH) Exposure Guidelines.

GUIDELINE	INTENT	10 min	30 min	1 h	2 h	4 h	8 h	16 h	24 h	7 d
EPA AEGL-1[16] (Nondisabling)	Level at which temporary or nondisabling effects may occur	NR	NR	NR		NR	NR			
EPA AEGL-2[16] (Disabling)	Level at which disabling, but not life-threatening effects, may occur	5.3 ppm	1.8 ppm	0.90 ppm		0.23 ppm	0.11 ppm			
EPA AEGL-3[16] (Life threatening)	Level at which life-threatening effects may occur	16 ppm	5.5 ppm	2.7 ppm		0.68 ppm	0.34 ppm			
NRC SPEGL[12]	Short-term public emergency exposure limits			0.24 ppm	0.12 ppm	0.06 ppm	0.03 ppm	0.015 ppm	0.01 ppm	
NASA SMAC[57]	NASA-established limits imposed on spacecraft operations during flight			0.002 ppm					0.002 ppm	0.002 ppm
OSHA IDLH[12]	Level at which exposure is immediately dangerous to life and health		20 ppm							
NIOSH REL[12]	Recommended upper limit for occupational exposure to avoid adverse health effects			0.04 ppm (2-h ceiling)						
OSHA PEL[12]	Legally enforceable regulatory ceiling limit, imposed to protect workers against exposure-related health effects						0.2 ppm			
ACGIH TLV[12]	Exposure at or below this level does not create unreasonable risk of injury. NASA-adopted consensus standard.						0.01 ppm			

MMH exposure limits and guidelines as established by various regulatory and scientific agencies. Note that AEGL-1 limits for MMH are not recommended due to inadequate data and little apparent margin between exposures causing minor effects and those resulting in serious toxicity. Additionally, while included for completeness, Spacecraft Maximum Allowable Concentration (SMAC) values only apply to space vehicles while in flight.
ACGIH—American Conference of Governmental Industrial Hygienists; AEGL—Acute Exposure Guideline Level; EPA—Environmental Protection Agency; IDLH—Immediately Dangerous to Life and Health; NASA—National Aeronautics and Space Administration; NIOSH—National Institute of Occupational Safety and Health; NR—not recommended; NRC—National Research Council; OSHA—Occupational Safety and Health Administration; PEL—Permissible Exposure Limits; REL—Recommended Exposure Limits; SPEGL—Short-term Public Emergency Guidance Level; TLV—Threshold Limit Values.

Table III. 1,1-Dimethylhydrazine [Unsymmetrical Dimethylhydrazine (UDMH)] Exposure Guidelines.

GUIDELINE	INTENT	10 min	30 min	1 h	2 h	4 h	8 h	16 h	24 h	7 d
EPA AEGL-1[16] (Nondisabling)	Level at which temporary or nondisabling effects may occur	NR	NR	NR		NR	NR			
EPA AEGL-2[16] (Disabling)	Level at which disabling, but not life-threatening effects, may occur		6.0 ppm	3.0 ppm		0.75 ppm	0.38 ppm			
EPA AEGL-3[16] (Life threatening)	Level at which life-threatening effects may occur		22 ppm	11 ppm		2.7 ppm	1.4 ppm			
NRC EEGL[10]	Short-term public emergency exposure limits			3 ppm	0.12 ppm	0.06 ppm	0.03 ppm	0.015 ppm	0.01 ppm	
NASA SMAC[57]	NASA-established limits imposed on spacecraft operations during flight			0.002 ppm					0.12 ppm	0.03 ppm
OSHA IDLH[10]	Level at which exposure is immediately dangerous to life and health		15 ppm							
NIOSH REL[10]	Recommended upper limit for occupational exposure to avoid adverse health effects			0.06 ppm (2-h ceiling)						
OSHA PEL[10]	Legally enforceable regulatory ceiling limit, imposed to protect workers against exposure-related health effects						0.5 ppm			
ACGIH TLV[10]	Exposure at or below this level does not create unreasonable risk of injury. NASA-adopted consensus standard.						0.01 ppm			

UDMH exposure limits and guidelines as established by various regulatory and scientific agencies. Note that AEGL-1 limits for UDMH are not recommended due to inadequate data and little apparent margin between exposures causing minor effects and those resulting in serious toxicity. Additionally, while included for completeness, Spacecraft Maximum Allowable Concentration (SMAC) values only apply to space vehicles while in flight.
ACGIH—American Conference of Governmental Industrial Hygienists; AEGL—Acute Exposure Guideline Level; EEGL—Emergency Exposure Guidance Level; EPA—Environmental Protection Agency; IDLH—Immediately Dangerous to Life and Health; NASA—National Aeronautics and Space Administration; NIOSH—National Institute of Occupational Safety and Health; NR—not recommended; NRC—National Research Council; OSHA—Occupational Safety and Health Administration; PEL—Permissible Exposure Limits; REL—Recommended Exposure Limits; TLV—Threshold Limit Values.

Odor Detection

The U.S. NRC Toxicology Subcommittee on Acute Exposure Guideline Levels (AEGLs) indicated that the Level of Distinct Odor Awareness (LOA) for hydrazine is 63 ppm; this is defined as the concentration at which more than 50% of exposed persons should be able to identify an odor related to HZ inhalation.[58] An additional study indicated reliable detection and identification of MMH at slightly higher concentrations, with 6 of 7 subjects (85.7%) able to identify a faint, nonirritating to minimally irritating odor at 10-min exposures to concentrations of 90 ppm MMH.[51] Another study demonstrated 66.7% of subjects able to identify an odor associated with 0.2 ppm MMH single inhalation (30 cc aerosolized by facemask) exposure, with naïve subjects more likely to detect the odor.[38] Other sources report odor detection at far lower concentrations, as low as 2–5 ppm.[17,59] This suggests that individual perception of odor may vary and some may be able to olfactorily identify MMH presence at far lower concentrations than others. However, perception of odor does not directly correlate with symptoms or clinical sequelae; further, odor detection may occur at concentrations above recommended exposure levels and is not operationally reliable as definitive confirmation of exposure.

Acute Mucosal Irritation

Mucosal irritation is frequently reported prior to, or in conjunction with, more significant clinical sequelae of HZ/MMH exposure, though symptoms are highly variable.[33,49,73] In humans, the study noted above (in Odor Detection) in which subjects were exposed to 10 min of 90 ppm MMH reported only mild ocular irritation and conjunctival injection after exposure,[51] where the olfactory study of subjects after a single 30-cc inhalation of 0.2 ppm MMH by face mask reported 12 of 42 subjects (28.6%) with noticeable mucosal irritation and subsequent events, including mucosal blistering, minor bleeding to more impactful nasal hemorrhage, localized nasal inflammation, and desiccation of mucosa.[38] Even so, none of the affected subjects required medical treatment or hospitalization and none reported longitudinal symptoms or sequelae.[38]

An early study of nonhuman primate (NHP) exposure to HZ and UDMH at ≥ 0.4 ppm for 90 d demonstrated notable ocular irritation after 24 h of exposure.[39] With the application of an interspecies uncertainty factor, this study drove the concentration-based (duration independent) limits for the AEGL-1 values of 0.1 ppm as an acute tolerance threshold for HZ/HZ-D.[58] Additional studies have further identified chemical conjunctivitis and photophobia in dogs after prolonged (multiday) exposure to 5 ppm MMH;[33] however, study of multiday inhalational exposure at 2 ppm MMH,[33] or in dogs and NHP at 1 ppm MMH,[22,35] demonstrate minimal to no evidence of mucosal irritation.

Acute Respiratory Risk

Early studies of inhalational exposure to HZ, MMH, and UDMH focused primarily on the potential respiratory

sequelae of exposure. Acute, high-concentration inhalational exposures (primarily animal and one study of multiroute human exposure, including inhalation plus ingestion/submersion[6]) of >50 ppm for greater than 30 min are associated with severe mucosal irritation of the eyes, nose, and throat, followed by respiratory distress, pulmonary edema, and pulmonary hemorrhage.[6,18,42] There have additionally been rare case reports of severe aerozine (1:1 HZ and UDMH mixture) inhalational events of unknown quantity/concentration leading to respiratory concerns including dyspnea, reactive airway, and pulmonary edema.[26,65] While the concentration of aerozine was unknown in these events, it was sufficient to promote immediate recognition of a strong odor and, in one of these cases, the exposed person's clothing continued to smell strongly of aerozine nearly 2 h after evacuation,[26] suggesting a concentration of exposure much higher than the odor threshold (LOA = 63 ppm).[58]

However, lower concentrations have not been associated with respiratory sequelae. Human volunteer inhalational exposures to 90 ppm MMH for 10 min were not associated with respiratory symptoms or concerns.[51] Volunteer exposures to a single 30-cc inhalation of 0.2 ppm by face mask similarly did not result in any respiratory sequelae.[38] In animal studies, there were no respiratory sequelae in rats, dogs, or NHPs after 1 ppm MMH inhalational exposure for 24 h.[22] Another study exposed rats, mice, dogs, and NHPs to 16–60 ppm MMH for 15–60 min with no evidence of respiratory irritation or inflammation, no evidence of CNS excitation or depression, and no performance decrements noted in NHP subjects.[50] An additional study exposed NHPs to either 1 ppm HZ or 0.5 ppm inhaled UDMH for 90 d with no respiratory sequelae reported.[39]

The potential use of various treatments and interventions has been recommended for the management of respiratory distress after HZ inhalation; in most cases, treatment guidance is based on theory grounded in pathophysiology (often derived from animal studies) or clinical parallels. Makarovsky et al. advocates for the use of beta-2 agonists and corticosteroids for bronchospasm or respiratory inflammation, but cites little data and notes reliance instead on clinical corollaries to other inflammatory respiratory conditions or irritant volatile exposures.[53] Similar treatment guidelines reliant on clinical parallels or theory, or focusing instead on issues related to mucosal burn-related injuries or oropharyngeal/tracheal injury from ingestion events,[24,44,64] are reported in Nguyen et al.[59] There are two case reports where an unknown concentration of aerozine inhalation lead to pulmonary edema and treatment with dexamethasone;[26] in one of the cases, pyridoxine was additionally administered. Both cases reported resolution of symptoms 4–6 h after initiation of treatment.[26] Data are limited regarding the correlation between HZ/HZ-D concentration, exposure time, and clinical sequelae or the time courses in which clinical interventions would be indicated or most successful.

Acute Neurological Risk

There has been substantial focus on acute neurological sequelae following HZ/HZ-D exposure in the literature, as well as on the clinical treatment of such sequelae. As with respiratory sequelae, high-concentration inhalation or (more often) multiroute exposures of >50 ppm for greater than 30 min are associated with neurotoxic sequelae, including CNS depression or excitation and seizures, though data are variable and difficult to interpret.[6,18,42] Case reports of human ingestion of HZ/HZ-D have reported acute delirium, lethargy, and agitation,[31,56,73] loss of consiousness,[64] or hepatotoxicity driving hepatic encephalopathy.[45] Symptoms in these cases manifested most often after longitudinal and repetitive noninhalational exposures.[56,73] In two cases, symptoms started acutely after HZ ingestion.[31,64] Case reports of high-concentration exposure to inhaled HZ/HZ-D have additionally reported hyperreflexia, tremors, and clonus; however, in these cases, exposure concentration was unknown, though patients reported an extremely strong odor at the time of exposure and immediate burning of the mucosa, suggesting a relatively high concentration inhaled well above the odor detection threshold.[26]

Animal studies of subcutaneous,[40,80] intravenous (IV),[1,30] and intraperitoneal (IP)[28,30,79] injections of HZ similarly result in neurological depression or excitation and seizure activity.[19,28,30] Data suggest that lower doses of HZ exposure tend to lead to neurological depression while higher doses are more associated with excitation or seizure.[3,48] However, with the exception of the case reports of tremors and hyperreflexia noted above, there are few reports of acute neurological sequelae from isolated and acute inhalational exposures to HZ/HZ-D. In animal studies, MacEwen et al.[52] reported seizure activity in hamsters after 1 h of inhalation exposure to 1380 ppm MMH, approximately 10 times the 4-h LC_{50} of MMH for hamsters (established as 143 ppm by Jacobson et al.[42]) and above the 1-h hamster MMH LC_{50} of 991 ppm established by the same study. At exposures to 1380 ppm MMH, 90% of animals perished within 24 h and convulsions were seen in animals after nearly the full hour of exposure. Animal subjects additionally demonstrated severe respiratory distress as well as liver and kidney injury. However, inhalation exposures in hamsters to 460 ppm, 620 ppm, 810 ppm, 910 ppm, and 1110 ppm MMH demonstrated no seizure activity at any concentration.[52] Inhalation exposures to 1600–3300 ppm UDMH in hamsters were associated with seizure activity after exposure, while concentrations of 1280–2770 ppm HZ were not associated with seizure activity.[52] Haun et al. exposed rodents, dogs, and NHPs to variable concentrations of inhaled MMH; at concentrations at or above the LC_{50} for the species exposed, neurotoxic symptoms including seizures were witnessed in parallel with other signs of organ toxicity, including acute respiratory distress and pulmonary edema, gastrointestinal sequelae including severe vomiting and diarrhea (often hemorrhagic), and nephrotoxicity occasionally leading to gross hematuria.[37]

Most studies with manifestations of neurological sequelae feature noninhalation routes of exposure. Injection with HZ/HZ-D in NHP subjects has been associated with performance decrements, attributed to either CNS depression and lethargy or to gastrointestinal upset with severe vomiting disrupting operational performance.[66,79] In these studies, NHPs receiving

2.5–5 mg · kg^{-1} IP injections of MMH demonstrated worsening task performance at 1–3 h, with resolution of symptoms after 3–9 h. One study demonstrated minor improvement of neurological symptoms and task performance with coadministration of pyridoxine, though even NHPs that did not receive pyridoxine had resolution of symptoms <12 h from exposure.[79]

In cases of more severe neurological sequelae, use of pyridoxine, often in combination with or supplemental to benzodiazepine therapy,[65] for management of seizures is frequently recommended.[53,59,82] Neurological toxicity and excitation related to HZ/HZ-D exposure is thought to be a result of interference with gamma-aminobutyric acid (GABA) synthesis, which relies on a pyridoxine-dependent decarboxylation reaction.[59,82] HZ/HZ-D exposure leads to a functional deficiency of available pyridoxine. Studies of successful pyridoxine administration for control of HZ-induced neurotoxicity in humans are primarily case reports, with improvement of condition reported even after delayed (3–4 d after HZ ingestion) administration of pyridoxine.[31,53,56] Animal studies similarly report the benefit of pyridoxine administration, including reduction of mortality, in animals receiving subcutaneous, IP, or IV injections of HZ/HZ-D.[1,30,74] Notably, pyridoxine use alone is generally considered ineffective for HZ/HZ-D exposures and subsequent neuroexcitation.[1,82]

Pyridoxine as a therapeutic agent is not without risk.[31,70] Harati et al. reported the use of pyridoxine 3–4 d after accidental ingestion of HZ and subsequent neurotoxicity; in that case, the patient developed severe peripheral neuropathy attributed to pyridoxine administration.[31] Previous literature reviews documenting the potential for adverse sequelae of pyridoxine treatment generally conclude that use of pyridoxine for neurotoxic sequelae, including CNS depression, excitation, or seizures, offers benefits that outweigh the potential risks of administration.[59,70,82] There are no data supporting the use of pyridoxine for HZ/HZ-D exposure when no neurotoxic effects are present.

Acute Hepatotoxicity

Inhalation exposures to HZ/HZ-D have resulted in subsequent transaminitis or other evidence of hepatotoxicity,[59] though clinical sequelae do not invariably follow. Transaminitis may represent an adaptive or reactive rather than adverse effect of exposure. In a case report of seven exposed individuals to an unknown inhaled concentration of HZ (though notable odor was reported) for approximately 10 min, one patient demonstrated elevated alanine aminotransferase and aspartate aminotransferase 5 h after exposure.[43,59] Enzyme levels returned to baseline after 5 wk and the remaining subjects demonstrated no alteration of laboratory values.[43,59] No exposed individuals were symptomatic after this event. Another report involving four personnel exposed for less than 1 min to an unknown concentration of HZ vapor reported no clinical symptoms, but exposed patients exhibited a measured elevation of alanine aminotransferase, aspartate aminotransferase, and creatinine phosphokinase rising over 36 h following exposure.[5] In this case, enzyme levels normalized by 1 wk after exposure.[5] One additional report of a victim of an HZ industrial explosion noted transaminitis 3 d after the event; however, this individual suffered multiple injuries related to the explosion in addition to an unclear exposure concentration to HZ and, thus, this finding is unclear in significance or etiology.[44]

A case report of recurrent, chronic inhalational exposure to HZ over approximately 6 mo led to mucosal irritation, tremors, renal injury, and pulmonary decompensation ultimately resulting in fatality.[73] This case was additionally associated with microscopic hepatocyte necrosis on autopsy; prior to death, laboratory analysis demonstrated elevated bilirubin (along with a mild decrease of hemoglobin), but otherwise normal liver function tests.[73] Other studies of chronic longitudinal exposure to inhaled HZ/HZ-D in humans[63] and animals, including NHPs, rodents, and dogs, have further demonstrated evidence of liver dysfunction or altered laboratory values.[49,59,62] In mice continuously exposed to 1 ppm HZ inhaled for 6 mo, 55% of mice died with mortality attributed to hepatotoxic sequelae;[35] when repeated in rats and NHPs, the same exposure caused no increase in mortality.[75] However, acute cases of inhalational exposure do not frequently identify hepatotoxicity particularly at nonfatal exposure levels in large animals.[2,22,39] Notably, historical studies demonstrating hepatotoxicity after longitudinal exposure, particularly to inhaled UDMH, may have been confounded by dimethylnitrosamine contamination of UDMH, where dimethylnitrosamine inhalation causes known liver toxicity.[34,75]

In a study of one-time IP injection of 2.5 mg · kg^{-1} MMH in NHPs, one NHP subject died shortly after injection and was found on necropsy to have gross hepatic necrosis; this was labeled an outlier by investigators and no other exposed primates demonstrated liver dysfunction of any kind after identical exposures.[79] In studies of hamsters acutely exposed to above-LD_{50} concentrations of inhaled HZ, MMH, or UDMH for 1 h, hepatotoxicity was observed.[52] However, evidence of clinically significant hepatotoxicity in the absence of other severe adverse effects to other organ systems was not identified in the literature reviewed. Clinically significant hepatotoxicity in the literature is closely associated with severe or lethal multisystem toxicity.[35,63,73]

Hemotoxicity and Enzyme Deficiencies

Exposure to HZ/HZ-D, particularly MMH,[13,29,59] leads to a dose- and exposure time-dependent development of Heinz body inclusions, methemoglobinemia, and splenic sequestration and hemolytic anemia.[2,59] Heinz bodies consist of denatured hemoglobin that has been damaged by oxidative stress while methemoglobin occurs when the heme iron is oxidized;[41] thus, the two are frequently seen in parallel. Historical studies have indicated that there is a species-specific sensitivity to the oxidation and hemolytic sequelae of MMH exposure, with dogs being most sensitive, followed by humans, then rodents, then NHPs.[14,29] Thus, historical studies regarding the hemotoxic effects of HZ/HZ-D may be somewhat skewed by this differential sensitivity.

No studies were identified describing clinically significant hematological sequelae from acute inhalational exposure to

HZ/HZ-D. In a study of seven human subjects exposed to inhaled MMH at 50–90 ppm for 10 min, subsequent laboratory analysis demonstrated no evidence of methemoglobinemia in any subject, though Heinz bodies were measured at 3–5% of red blood cells at 7 d after exposure; this resolved spontaneously by day 14.[51] There was no hemolysis or anemia and no reticulocytosis in any subject at any time.[51,78] Animal studies of inhalational exposure at substantially higher concentrations have been associated with hemotoxicity. In a study of acute inhalational exposures to MMH at or above the LC_{50} for the exposed species, Huan et al. identified Heinz body formation in surviving dogs and NHPs with hemolysis and anemia noted 3–7 d after exposure, resolving without intervention after 2–3 wk.[37] Methemoglobin analysis was not performed in that study, but exposed animals were noted to appear cyanotic and blood samples were discolored, with authors acknowledging suspicion of methemoglobinemia.[37]

Even so, much of the evidence regarding HZ/HZ-D-induced development of Heinz bodies and methemoglobinemia is a result of longitudinal or chronic and repetitive inhalational exposures,[35,49,67] in vitro assessments,[25,27,32] or following acute IV administration of HZ/HZ-D.[14,25] No human case reports of acute inhalational exposures to HZ/HZ-D have identified methemoglobinemia following exposure. No clinically significant cases of development of Heinz bodies or subsequent hemolytic anemia have been reported in humans after acute HZ/HZ-D inhalation.

Despite the paucity of data, methemoglobinemia and hemolytic anemia tend to be highlighted as significant risks associated with HZ exposure,[53,59] with literature and operational training detailing the potential need for dedicated treatments to manage clinically significant sequelae. Methemoglobinemia becomes clinically significant due to impaired oxygen-carrying capacity of the blood at 10–30% methemoglobin concentrations.[4,21,72] Methemoglobinemia at clinically significant levels (>10% methemoglobin) has not been reported in humans following any route of exposure to HZ/HZ-D. Development of clinically significant methemoglobinemia would theoretically prompt management, including supplemental oxygen and possible administration of methylene blue.[15] Methylene blue accelerates the reduction of methemoglobin and improves oxygen-carrying capacity and rapidly reverses the symptoms of clinically significant methemoglobinemia.[72,81] However, individuals with hereditary enzymatic deficiencies, particularly glucose-6-phosphate dehydrogenase (G6PD) deficiency, will be unresponsive to methylene blue treatment as they lack the required enzymatic pathway for the treatment to effectively reduce the oxidized heme iron.[72] In fact, administration of methylene blue in such individuals may prompt worsening methemoglobinemia, worsened oxidative stress, and accelerated hemolytic anemia.[47,69,72]

These considerations were identified by early researchers into HZ/HZ-D toxicity. Multiple studies regarding the effects on HZ/HZ-D on the red blood cell noted the potential for methemoglobinemia development and the heightened risk for G6PD-deficient patients, citing both the methemoglobinemia oxidative pathway and the concern for treatment failure or adverse response to methylene blue in individuals with G6PD deficiency.[27,29,78] Such studies recommend against individuals with G6PD and similar deficiencies working in occupational roles where longitudinal or recurrent HZ/HZ-D exposure may occur.[2] However, such recommendations appear to be based on theoretical risk rather than observation of actual exposure-related sequelae. Further, such historical recommendations were not intended for acute exposure circumstances.

Mortality and Longitudinal Risks

There were no identified case reports of fatality following a single, acute inhalational exposure to HZ/HZ-D without concurrent multisystem trauma. There is one case report of 6 mo of repetitive exposure to HZ, presumably by inhalation (though additional cutaneous or even ingestion exposure may have occurred), that ultimately resulted in fatality.[73,75] Animal mortality has been reported after >50 ppm exposures for >30 min, with large animal (including dog and NHP) mortality more commonly reported after >80 ppm exposures for >60 min.[37,42,75] Longitudinal studies of animal inhalational exposure to UDMH demonstrated approximately 33% mortality of dogs exposed to 25 ppm HZ for >72 h[67,75] and approximately 25% mortality in dogs exposed to 1 ppm HZ continuously for 4 mo.[35,75] However, a study of rodents and dogs exposed to inhaled UDMH at 5 ppm for 6 mo demonstrated no significant increase in mortality.[36,75]

Chronic and repetitive occupational HZ exposures have been linked to lung and colon cancer;[54,68,77] however, longitudinal follow-up demonstrated no association between HZ and increased risk of mortality from neoplastic disease or any other cause of death.[55,75] Carcinogenesis and various neoplastic processes have additionally been noted in animals following chronic and repetitive HZ/HZ-D exposures.[9,46,49] There were no studies identified linking acute, one-time exposure to inhalational HZ/HZ-D and longitudinal mortality or carcinogenesis.

DISCUSSION

Table IV provides a summary of clinical sequelae resulting from acute inhalational HZ/HZ-D exposure and the lowest reported dose and time of exposure that resulted in reported symptoms. Where available, the table additionally provides the highest reported doses and times of exposure where exposed subjects did not report associated clinical symptoms. As demonstrated by this table, clinical symptoms following inhaled HZ/HZ-D exposure are variable. Finally, the table offers clinical treatment recommendations and level of evidence (LOE) supporting such recommendations (LOE categories for therapeutic interventions are as derived from the Centre for Evidence-Based Medicine by Burns et al.[8]).

The most likely symptoms from acute inhalational exposure to HZ/HZ-D compounds include mucosal irritation and respiratory irritation, inflammation, or injury, resulting in variable degrees of respiratory distress. Notably, irritation of

Table IV. Acute Clinical Sequelae of Hydrazine and Hydrazine-Derivative Inhalation.

CLINICAL SEQUELAE	LOWEST REPORTED DOSE / TIME OF EXPOSURE RESULTING IN SYMPTOMS	HIGHEST REPORTED DOSE / TIME OF EXPOSURE WITHOUT SYMPTOMS	TIMELINE TO SYMPTOM ONSET	POTENTIAL TREATMENT CONSIDERATIONS	LOE
Nasal Mucosal Irritation / Breakdown	0.2 ppm; single inhalation of 30-cc MMH by face mask (blistering, hemorrhage) (human)[38]	90 ppm MMH; 10 min (human)[51]	Seconds to hours[38,51]	Supportive management including ocular irrigation and nasal hemorrhage control, unlikely need for extensive intervention[38]	4
Respiratory Injury / Distress	50 ppm HZ; 30 min (rodents, dogs, guinea pigs)[6,18,42]	90 ppm MMH; 10 min (human)[51]	Seconds to hours[6,18,42]	Supportive, consider supplemental O_2, beta-2 agonists, corticosteroids[53]	5
Neurological Sequelae (tremors, hyperreflexivity, seizures)	50 ppm HZ; 30 min (rodents, dogs, guinea pigs)[6,18,42]	>LC_{50} for exposed species (HZ, UDMH); 1 h (hamsters, dogs, NHPs)[36,48,52]	Delayed, likely days to weeks before symptom onset[26,31,73]	Supportive, possible delayed (days to weeks) need for anticonvulsives (benzodiazepines), supplemental pyridoxine for refractory/persistent neuroexcitation[31,53,56]	4
Transaminitis (Note: no human cases of hepatotoxic clinical symptoms following exposure were identified)	> Odor Threshold HZ; 10 min (5-h delay before identified transaminitis)[43]	N/A	Hours to weeks[5,43,73]	Unlikely to have clinical concerns; monitoring, appropriate supportive care as needed	4
Hemotoxicity					
Heinz Body Development	50 ppm MMH; 10 min; Heinz Bodies in 3–5% RBC at 7 d after exposure, no clinical sequelae, spontaneous resolution[51]	N/A	Days to weeks[37,51,78]	No evidence of clinical risk in acute inhalational context	4
Methemoglobinemia	≥LC_{50} MMH for exposed species;- 1 h (dogs, NHPs), discoloration of animal and of blood suggested methemoglobin though no analysis performed; hemolysis and subclinical anemia at 3-7 d, spontaneous resolution by 3 wk[37]	N/A	*Days to weeks[37,53,59]	No evidence of clinical risk in acute inhalational context	4
Symptomatic Anemia	N/A	N/A	*Days to weeks[37]	No evidence of clinical risk in acute inhalational context	4

Where possible, sequelae are presented with correlation to the lowest reported dose of indicated compounds and exposure time that is known to have resulted in symptoms, as well as the highest reported dose and time of exposure known to have been tolerated without onset of such symptoms. Treatment considerations are specific to clinical sequelae of acute inhalational exposures in the timelines as indicated. Level of evidence categories for therapeutic interventions are as derived from the Centre for Evidence-Based Medicine by Burns et al. 2012.[8]

HZ: hydrazine; LC_{50}: concentration lethal to 50% of exposed subjects; LOE: level of evidence; ppm: parts per million; MMH: monomethylhydrazine; NHP: nonhuman primate; RBC: red blood cells; UDMH: unsymmetrical dimethylhydrazine.

*Indicates timeline based on theoretical extraction from analog data from animal exposures.

nasopharyngeal mucosa has occurred after MMH exposure at concentrations equal to the OSHA Permissible Exposure Limit (0.2 ppm);[38] while case reports of injury are self-limited and required no clinical intervention, it is worth noting that such sequelae could be quite distracting and limit operational performance. Management of acute respiratory irritation or more severe respiratory sequelae would be largely supportive, but may require airway support, supplemental oxygen, the potential need for advanced airway and mechanical ventilation, decontamination, and rapid evacuation to a definitive medical care facility.

The remaining clinical sequelae, including neurological excitation, transaminitis, and hemotoxicity are either exceptionally unlikely in the absence of a catastrophic or noninhalational exposure or unlikely to present with clinical symptoms in the acute medical response phase (minutes to hours) following a noncatastrophic exposure. For example, while there are reports of transaminitis associated with HZ/HZ-D exposure, this has not been associated with clinical sequelae or impactful liver dysfunction except in cases of lethality from multiorgan toxicity. Monitoring of transaminitis after exposure may be appropriate, but the need for clinical intervention is unlikely.

Human exposures resulting in neurological excitation (tremors, clonus, seizures) are difficult to quantify, consisting of either acute inhalational exposures of undocumented timeframes and unknown concentrations (reported only as sufficient to give a "strong odor" or immediate severe mucosal and respiratory irritation) or, alternatively, longitudinal, parenteral, polymodal, or catastrophic exposures (with concurrent explosion or burn injuries).[24,26,73] Polymodal exposures (for example, inhalation plus submersion and/or ingestion) have led to more rapid neurological sequelae, and longitudinal/repetitive exposures can present with neurological symptoms. Most cases of isolated inhalational exposure have not resulted in clinically significant neurological sequelae. Onset of severe neurological excitation is most frequently documented after chronic and repetitive exposure, usually via noninhalation routes, and use of pyridoxine in such cases is generally delayed or longitudinal. The need for pyridoxine as an acute, on-scene intervention is likely limited to delayed recovery scenarios (for example, emergency deorbit scenarios and landing in a remote geographic location, with prolonged and unmitigated hypergolic exposure and 24–72-h delay of rescue force arrival). In such circumstances, careful training of medical providers in the clinical indication of pyridoxine administration, including seizures or other severe neurological sequelae, may be warranted and the carrying of pyridoxine by recovery forces may be indicated. In the absence of such circumstances, particularly in cases where recovery and transfer to a medical facility take place in a matter of hours, determination of clinical indication and administration of pyridoxine if appropriate should be deferred to the medical treatment teams, with the guidance of a trained aerospace medicine practitioner, after arrival to a definitive medical treatment facility.

Clinically significant hemotoxic sequelae after HZ/HZ-D exposure have not been identified in human case reports or studies. While one study identified Heinz Bodies in human subjects after MMH inhalation, levels never reached clinical significance and intervention was not required. Development of methemoglobinemia has not been identified in humans after acute inhalational exposure, and in animal studies methemoglobinemia is limited to noninhalational routes (IV, IP) or chronic and longitudinal exposures. There was no evidence identified in human or animal studies of clinically significant hemolytic anemia from methemoglobinemia or Heinz Body development causing hemoglobin reduction to symptomatic levels after HZ/HZ-D acute inhalational exposure. Studies of other toxic exposures driving Heinz Body development, splenic sequestration, and subsequent hemolysis generally follow a timeframe of 3–7 d before onset of clinically notable anemia,[20,76] and timelines for development of subclinical hematological sequelae from HZ/HZ-D exposures in humans and animals similarly follow a multiday delay before laboratory abnormalities were identified. Thus, the need for acute interventions, such as use of methylene blue or administration of blood products, has not been identified; even if methemoglobinemia or hemolytic anemia were to develop, symptoms would not manifest acutely, and management of such conditions would be longitudinal and could be appropriately left to medical teams for treatment as clinically indicated after arrival at a definitive care facility. While aerospace medical professionals should maintain awareness of the potential hemotoxic sequelae of HZ/HZ-D exposure and may need to provide insight to non-aerospace medical practitioners, there is no evidence that acute recovery or rescue personnel would need to manage hemotoxic clinical sequelae during initial recovery and evacuation efforts.

It is worth noting that overemphasis on toxicological manifestations that are unlikely to occur is not without risk. Emphasizing the potential role for pyridoxine or methylene blue in the treatment algorithm of acute inhalational HZ/HZ-D exposure may increase the risk that minimally trained personnel or those with limited aerospace experience may administer such interventions without appropriate clinical indication. As discussed above, such interventions are not without potential adverse sequelae, including peripheral neuropathy resulting from pyridoxine administration or inadvertent hemotoxicity resulting from methylene blue administration in a patient with a previously unrecognized enzyme deficiency (e.g., G6PD deficiency). However, overemphasis or unnecessary highlighting of rare clinical disorders, including G6PD deficiency, can drive unfamiliar medical providers to be hesitant in the administration of treatments or interventions, particularly during field operations where clinical decision support tools or reference materials may not be available.[7] Given the paucity of evidence of acute inhalational HZ/HZ-D exposure leading to clinically significant hemotoxic sequelae, best practice would be to avoid unnecessary emphasis on such sequelae other than flight surgeon proficiency and awareness and to defer management of any hemotoxic sequelae to the definitive medical care facility with guidance as needed by the flight surgeon. Further, practitioners should avoid unnecessary focus or highlighting of

enzymatic deficiencies (like G6PD) to medical responders unless indicated by other medical considerations in order to prevent operational fixation or hyperfocus on concerns with little to no clinical impact.

In conclusion, tailoring of acute medical care specific to HZ/HZ-D exposure during spaceflight medical support operations requires awareness of potential clinical sequelae of the exposure as well as an understanding of the timeframe associated with development of clinical effects. In the absence of catastrophic explosive events, inhalational exposure remains the anticipated exposure route for astronaut crewmembers and ground support recovery teams. Appropriate acute medical care providers should be aware of the risks of hypergolic propellants as well as indications and protocols for use of PPE. While exposure limits established by multiple regulatory bodies should provide some degree of protection by encouraging the use of PPE at significant concentrations, there is some residual risk of clinical sequelae (particularly mucosal irritation) at or below OSHA Permissible Exposure Limits, and there is always risk of inhalational exposure prior to recognition of a vapor leak or the opportunity for atmospheric sampling. However, acute on-site medical care should focus on recognition of toxic exposure, decontamination, and supportive care of likely sequelae. In the case of inhalational exposure without concurrent catastrophic or explosive event, acute sequelae appear to be limited to mucosal and respiratory irritation requiring traditional supportive care. Medical support should be tailored to these clinical needs.

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