N92-22355

HUMAN EXPOSURE LIMITS TO HYPERGOLIC FUELS

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ABSTRACT

Over the past four decades, many studies have been conducted on the toxicities of the rocket propellants hydrazine (HZ) and monomethylhydrazine (MH). Numerous technical challenges have made it difficult to unambiguously interpret the results of these studies, and there is considerable divergence between results obtained by different investigators on the inhalation concentrations and exposure durations required to produce a given toxic effect. To determine the safe maximum acceptable concentrations (MACs) for each toxic effect inducible by exposure to hypergolic fuels in spacecraft atmospheres, NASA undertook a critical review of published and unpublished investigations on the toxicities of these compounds. The quality of the data from each study was assessed based on current state-of-the-art practices for similar studies. While many questions remain unanswered, MACS were determined using the best available data for a variety of toxic endpoints for potential continuous exposure durations ranging from 1 hour to 180 days. Spacecraft MACs (SMACs) were set for each compound based on the most sensitive toxic endpoint at each exposure duration.

INTRODUCTION

Payload and utility chemicals to be used or generated on manned space flights are evaluated by toxicologists at NASA for their potential health effects on crew members. For each mission, toxicologic information summaries and brief hazard assessments for each chemical flown are published as a "Blue Book". In addition, SMACs are established for individual priority airborne chemicals by NASA and contractor toxicologists after in-depth toxicological evaluations of the chemical. The SMAC documents include summaries of the chemical, physical, pharmacokinetic, and toxicological properties of each chemical and document the rationale used to establish the SMAC values. The SMAC values are used as guidelines to determine the levels of containment needed for each chemical flown and the health impact of a chemical release into the cabin atmosphere.

NASA has a policy to comply with maximum exposure limits for the workplace (ground based operations) established by other nationally recognized groups such as the American Congress of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV®) Committee. The ACGIH, for example, promulgates recommended exposure limits (TLVs) for airborne chemicals in the workplace atmosphere, based on the typical occupational exposure pattern, i.e. 8 h/day, 5 d/wk, for a working lifetime. This exposure pattern is quite different from that experienced by astronauts, i.e. continuous exposures for periods of up to one week, typically, and eventually up to 6 months or longer. The TLVs, thus, are applicable for many ground-based NASA operations. The recent announcement by the ACGIH's TLV committee proposing to lower the TLV for HZ from 0.1 ppm to 0.01 ppm generated interest within NASA and the U.S. Air Force due to the difficulty of rapidly measuring 0.01 ppm. The stated basis for lowering the TLV ten fold was a study[1] which showed an increase in nasal tumors at 50 ppb. However, the authors of the cited study stated in their report that this result was not statistically significant. At this same time, JSC toxicologists were preparing SMAC documents on both HZ and MH. Based on their review of the literature on HZ, some felt that the scientific literature did not support lowering of the TLV value. While safety should never be compromised, we must also take into account the fact that limited resources would be wasted if MACs for hypergolic fuels were set at unnecessarily low values. A preliminary review of the impact of lowering the current standards for safe levels of these fuels indicates that important NASA and Air Force operations could be restricted due to the need to:

1) revise current operating procedures for determining and certifying that the work environment contains less than 10 ppb of either hydrazine,

2) develop instruments with enough sensitivity to measure very low concentrations of fuels in real time, and

3) improve engineering controls to restrict exposure of workers.

The following is a description of the process that the JSC toxicologists used to evaluate the toxicological data available in the literature for HZ and MH and to establish SMAC values for these compounds.

PROCEDURE FOR SETTING SMAC VALUES

The information gathering phase of the SMAC setting process involves a comprehensive review of the published literature on the toxicity of the compound. This includes a search of the computerized databases (e.g. Toxline, Toxlit, Medline, etc.) for all articles on the toxicity and/or chemistry of the compound. Abstracts of all relevant articles are obtained and reviewed. The key articles are identified and complete copies of the original articles are obtained whenever possible. A toxicity table is compiled containing a summary of the toxicity findings for inhalation exposures, including species exposed, exposure durations and chemical

concentrations, and toxic effects observed. If insufficient data is available from inhalation exposures, toxicity data from other routes of exposure must be used.

The evaluation phase involves a determination of the biological endpoints of most concern and a critical review of the quality of the available data. The criteria used to rank the toxic endpoints include the severity of immediate effects on crew performance, which could jeopardize mission-related activities, and the severity of long term health effects on crew members. The criteria used to judge the quality of the studies include such factors as:

- Was the chemical pure and was its concentration determined analytically at frequent intervals during exposure?
- Was the exposure chamber operated according to accepted guidelines?
- Were there confounding exposures to other agents?
- Were a sufficient number of subjects exposed?
- Were there sufficient numbers of appropriate controls which were properly sham exposed?
- Were all the subjects & controls healthy (other than treatment-related effects)?
- Were relevant endpoints examined after appropriate exposure periods?

Based on these criteria, the highest quality, relevant studies are identified and used as starting points to derive SMAC values.

The extrapolation phase of the SMAC setting process involves extrapolation of data from the key studies to relevant human exposure conditions to obtain MACs for each endpoint of concern at exposure durations of 1 hr, 24 hr, 7 days, 30 days and 180 days. Thus, each exposure duration may have multiple MACs, each based on one biological endpoint such as carcinogenesis, irritation, central nervous system effects, lethality, cardiovascular effects, etc. The use of adjustment factors is often required to account for differences in species, routes of administration, exposure duration, and effects of microgravity. Extrapolation to untested exposure durations is often based on the unproven, but widely used assumption that the toxicity of a compound is a linear function of the product of the exposure duration, t, and the concentration of the compound, c. If the product of c times t for various exposure scenarios is equivalent, then equivalent toxic effects can be expected. This method of extrapolation is not universally applicable, however, and must be used with caution.

The value of the MAC for the most sensitive endpoint is selected for each exposure duration to establish SMAC values. The rationale used to set these "INTERIM" SMAC values is documented along with the information used from the key studies.

The review phase of the SMAC setting process involves sending the INTERIM SMAC document to the National Research Council's Committee on Toxicology for comments. After return of the document by the NRC's COT, it is revised as needed and an OFFICIAL SMAC established.

The following descriptions illustrate how the process described above was applied in establishing SMAC values for HZ and for MH.

HYDRAZINE

A computerized search of several toxicology-related databases identified numerous articles dealing with HZ and related compounds. Of these, abstracts were reviewed for 65 articles whose titles indicated they would be of relevance to setting SMAC values. Full copies were obtained for 29 of these articles. Two of these articles proved to be key articles on which the SMAC values were based.

HZ vapor is extremely irritating to the eyes, nose, and throat. Quantitative worker exposure information, however, is not available and/or cannot be estimated from the existing published data[2]. The median concentration of HZ detectable by odor is 3-4 ppm[3]. Inhalation can cause dizziness, anorexia[4] and nausea. HZ can be absorbed through the skin[5] or orally and can induce contact dermatitis[6,7,8], neurological impairment[9, 10], and at a dose of 10 mg/kg injected intraperitoneally for three days in rodents, HZ induces kidney, lung, and liver damage[11]. Accidental human exposures to high, but unspecified doses induced temporary blindness, and tremors[12] and, in one case involving 6 months of occupational contact exposure, conjunctivitis, tremor, cough, fever, vomiting, diarrhea, and death[13] A two hour exposure to 1.0 to 2.0 mg/l (7600 to 15200 ppm) of HZ vapors has been reported to induce convulsions, respiratory arrest and death in mice and rats[10]. The toxicity of multiple lower doses was cumulative, but surviving animals recovered and lived normal lifespans if exposure was discontinued. The LC_{50} for a four hour exposure to HZ was 750 mg/m^3 for rats and 330 mg/m^3 for mice[3]. Exposure to 1.0 ppm of HZ for 90 days was highly lethal to rats and mice and moderately lethal (20%) to monkeys[14]. HZ was fetotoxic in rats and mice at 5 mg/kg administered intraperitoneally and was teratogenic in mice at 12 mg/kg. HZ was mutagenic in several test systems[15, 16, 17] and induced sister chromatid exchanges *in vitro* [18].

There are conflicting reports on HZ's carcinogenicity. The National Institute of Environmental Health Sciences finds that there is sufficient evidence for the carcinogenicity of HZ in experimental animals, but inadequate evidence for its carcinogenicity in humans[19]. Inhaled HZ has been reported to induce alveolargenic carcinomas in three of eight mice exposed at 0.2 ppm[20], nasal and bronchial tumors in rats at 1 ppm[21] (see Table 1 below), and nasal tumors in 16 of 160 hamsters exposed at 5 ppm[21]. Unequivocally toxic doses (up to 50 mg/l), however, administered in drinking water for the lifetime of rats were only weakly carcinogenic[22]. In male rats (the most sensitive species and sex) exposed by inhalation, tumors (which were predominantly benign) appeared only late in life in animals showing many other chronic toxic effects including a greatly increased inflammatory response of the upper airways[21]. An additional study would be extremely helpful. Only scanty epidemiological data is available on HZ-related cancers in humans[2]. No excess risk of cancer has been found in workers occupationally exposed to HZ vapors, but the number of workers having substantial exposure has been too few to detect anything other than gross hazards[23, 12].

Of the many toxic effects of HZ exposure, the ones of most concern, for which quantitative data are available include hepatotoxicity, carcinogenicity, and lethality. These effects were evaluated and MACs were set for each endpoint at the various exposure durations.

Hepatotoxicity:

Liver effects induced by airborne HZ include focal liver cell

hyperplasia in female rats exposed at 1 ppm HZ for 2 yrs and "fatty changes" in the liver in several species after 90 days continuous exposure to 0.8 ppm HZ[25, 14]. MAC values for liver toxicity were calculated for 180 d, 30 d, and 7 d. The use of the "concentration times time" rule to extrapolate to exposure times of 24 hrs or less (a two order of magnitude extrapolation) was deemed inappropriate for a compound such as HZ which has such a steep dose-response curve.

Carcinogenicity:

HZ has been found to be carcinogenic in animal model systems[21, 25, 17]. The oncogenic changes were mostly benign and observable only at the microscopic level, producing little or no impairment of respiratory function and no effect on life expectancy. The non-oncogenic toxicities of HZ exposure in animals were more severe in producing debilitation and lethal effects. There are, moreover, no known reports of HZ-induced human tumors. Most human exposures to HZ have been accidental or job-related and dose-response data are not available. Although the data for a carcinogenic effect of HZ are not compelling, prudence requires that carcinogenicity be considered in determining a MAC for HZ. MACs were calculated using the linearized multistage model method described by the NRC[27] as illustrated below.

Based on the data of MacEwen et al., the NRC Committee on Toxicology (COT) calculated that the lower 95% confidence limit on the inhalation dose that would produce a 1% lifetime tumor incidence in rats is 0.055 ppm for a 6 hr/day, 5 day/wk, 52 wk/yr, 1 yr exposure. This extrapolates to 0.005 ppm for a continuous 2 yr exposure:

$$0.055 \text{ ppm} \times (6 \text{ hr} / 24 \text{ hr}) \times (5 \text{ hr} / 7 \text{ hr}) \times (1 \text{ yr} / 2 \text{ yr}) = 0.005 \text{ ppm}$$

Extrapolating the 1% tumor incidence from a continuous 2 year exposure at 0.005 ppm to a 24 hr exposure at the same 0.005 ppm concentration, the NRC COT estimated[28] the tumor risk for rats should be no more than 10^{-2}.

The NRC has stated[29] that the linearized multistage model is sufficiently conservative so that an additional species extrapolation factor is unnecessary. Therefore, the following equation, based on Crump and Howe's linearized multistage model[27], was used to calculate the exposure concentrations, D, which would yield a tumor risk of 10^{-3} for exposure durations of 1 h, 24 h, 7 d, 30 d, and 180 d.:

$$D = (d)\ (25{,}600)^k\ (10^{-3}/\text{risk}) \div \{25{,}600 - ((365)(\text{age}))^k\} - 25{,}600 - ((365)(\text{age}) - \text{exp})^k$$

where

d is the the concentration during a lifetime exposure (0.005 ppm in this case)
25,600 is the # of days in a 70 y human lifetime
k is the number of stages in the model (3 in this case)
10^{-3} is the acceptable risk level
age is the minimum age of an astronaut, in years (30 in this case)
exp is the exposure duration, in days (0.042, 1, 7, 30, or 180)
risk is the risk of tumor for lifetime exposure to d (10^{-2} in this case)

This equation yields the following values, rounded to one significant figure:

300	ppm for	1 hr
10	ppm for	24 hr
2	ppm for	7 d
0.4	ppm for	30 d
0.07	ppm for	180 d

Lethality:

Analysis of the lethality data, except for very short exposures, is difficult and frustrating. To set the 1-h MAC, we rely on the LC_{50} data from an old report[8] that, nonetheless, appears to be well done. The LC_{50} for a 4-h exposure was 570 ppm in rats and 250 ppm in mice. The results for the more sensitive species (mouse) were adjusted by the following factors: 250 ppm was divided by 10 for inter-species extrapolation, again divided by 10 to extrapolate from the LC_{50} to a NOAEL, and multiplied by 2 to extrapolate from a 4-h exposure to a 1-h exposure to yield a 1-h MAC for lethality of 5 ppm. A factor of 10 was judged to be adequate to go from the LC_{50} to a NOAEL due to the steepness of the dose response curve[30]. The use of a two-fold rather than a four-fold safety factor to extrapolate from a 4 h exposure to a 1 h exposure is supported by experimental results for a similar compound, MH[30]. The 24-h MAC is calculated similarly, but dividing by 6 to extrapolate from a 4-h to a 24-h exposure to yield a 24-h MAC value of 0.4 ppm. The use of the 'concentration times time" rule for longer exposures is not considered appropriate for the available acute data. To set lethality MACs for the longer periods, we must turn to repeated intermittent exposures available on multiple species.

The scatter in the lethality data for repeated exposures to HZ is large and suggests serious shortcomings in some of the study designs. An early report[31] showed that at a nominal concentration of 20,000 ppm, the recovery of HZ decreases from 26% to 4% simply because of the presence of rat bodies, whereas, if the rats are alive, the recovery is decreased to 2%. This clearly indicates that a large fraction of the airborne HZ adheres to the rat fur, probably about 10 times the amount retained in the respiratory system. Since rats preen, much of their exposure to HZ may have been by oral ingestion, rather than inhalation. The point is that the rodent data are so scattered that the true susceptibility is simply unknown.

In the study above[31], food was removed during exposures, so that it was not contaminated with HZ. In some later studies[32], food was not removed during exposure and the rodents were found to be much more susceptible. For example, an 8% mortality was seen in mice exposed to 1.0 ppm HZ for 6 h/d for 2 wk (60 ppm•h)[32], whereas no mortality was seen in mice exposed to 40 ppm HZ 6 h/d for 4 d (960 ppm•h)[31].

Based on these studies, MACs were calculated for lethality, carcinogenesis, and hepatotoxicity as described in the procedure section.

TABLE 1: **MACs and Endpoints for HZ**

Endpoint	Species Tested	Safety Factors Species	Safety Factors NOAEL	MAC (ppm) 1 hr	24 hr	7 d	30 d	180 d
Lethality [8] *LC_{50}=250 ppm, 4 h*	Mouse	10	10	**5**	**0.4**	*	*	*
Lethality [24] *0.8 ppm, 30 d contin.*	Monkey	10	10	*	*	**0.08**	**0.02**	**0.003**
Carcinogenesis[27] *0.05 ppm, 1 yr, contin*	Rat	1	1	300†	10†	2†	0.4†	0.07†
Hepatotoxicity [24] *0.78 ppm, 90d, contin.*	Monkey Rat, Mouse	10	10	*	*	0.1	**0.02**	0.004

* N/A for use of "concentration times time" rule

† Calculated based on NRC COT's equation[27] derived from Crump & Howe's multistage carcinogenicity model, using a lifetime cancer risk of 10^{-3}.

For each exposure duration, the SMAC was set equal to the lowest MAC value among the three endpoints shown above. The resulting values, in units of both ppm and mg/m^3, are listed along with the most sensitive target toxicity at that exposure duration.

TABLE 2: **SMACS for HZ**

	ppm	mg/m^3	Target Toxicity
1-h SMAC	5	13	Lethality
24-h SMAC	0.4	0.5	Lethality
7-d SMAC	0.08	0.10	Lethality, Hepatotoxicity
30-d SMAC	0.02	0.03	Lethality, Hepatotoxicity
180-d SMAC	0.003	0.004	Lethality, Hepatotoxicity

* Temporary 7-d SMAC was set at 0.04 ppm

These SMAC values, except for 180 days continuous exposure, are all above the 0.01 ppm TLV proposed by ACGIH. As will be shown below, the situation for MH is quite different and highlights the need for better, more definitive toxicological studies on this class of compounds.

METHYLHYDRAZINE

A computerized search of several toxicology-related databases identified a large number of articles dealing with MH and related compounds. Of these, abstracts were reviewed for 173 articles whose titles indicated they would be of relevance to setting SMAC values. Full copies were obtained for 79 of these articles. In contrast to the situation with HZ, the data for MH toxicity available from a study[33] performed at NASA's White Sands Testing Facility proved to be a key article which required the setting of the SMAC at a very low value.

MH can induce a variety of toxic effects. The overt signs of acute MH toxicity in mice, rats, dogs, and monkeys include irritation of nose and eyes, blood discrasias (hemolytic anemia and Heinz bodies in humans, monkeys and dogs) salivation, emesis, diarrhea, hyperactivity, tremors and severe tonic-clonic convulsions, which precede death. In addition, chronic exposure to low concentrations of MH has been shown to induce blood and liver effects in dogs and cancer in mice and hamsters.

Lethality:

A steep dose-mortality response curve was seen for all species, regardless of the length of exposure. Of the species tested, squirrel monkeys were the most sensitive to the lethal effects of MH. Monkey LC_{50} experiments were performed, examining three exposure times: 15, 30 and 60 min. and using 25 monkeys, total. The lower confidence limit was used for calculating the MAC based on the LC_{50}. This yields a value which is lower than that obtained based on the NOAEL, since no confidence limits were calculated for the NOAEL. This anomaly is due to the steepness of the dose-mortality response curve. A safety factor of 100 was used in calculating the MACs for lethality due to the severity of the endpoint.

Nasal Injury:

The most sensitive endpoint for toxicity at concentrations greater than or equal to the odor threshold was nasal injury. Since the data for injury were obtained from human subjects[32], no species conversion was required. Nevertheless, since 75% of the subjects complained of irritating odor and 28% developed significant nasal pathology under the test conditions, the tested concentration of 0.2 ppm must be lowered to a level which would be anticipated to produce no adverse effects. A safety factor of 10 was used to estimate the NOAEL. An additional safety factor of 10 was warranted to account for the fact that a single sniff caused the observed effects, whereas the MACS must be set to protect during continuous, much longer term potential exposures. The resulting level of 0.002 ppm is less than or equal to even the 180 day MACs for all other endpoints. Since the endpoint is injury of the nasal mucosa, and since no epidemiological data were available to indicate that long term exposure to sub-irritating (short-term) levels of MH would lead to cumulative effects, the MAC for nasal injury was set at 0.002 ppm MH for all exposure durations. It must be noted that the results of this NASA study do not correlate with the results reported by others for exposure of humans to MH (see Heinz bodies discussion below). Nevertheless, a careful review of the data and methodology showed that this study appeared to be well done and did not reveal any basis on which this study could be discounted or ignored.

Heinz Bodies:

The low level of Heinz bodies seen in human volunteers exposed to 90 ppm MH for 10 min were not enough to produce any noticeable symptoms of toxicity, and this toxicity was completely reversible(35). MACs were not calculated for exposure times longer than one hour, for the reasons stated in the footnote to the table below.

Carcinogenesis:

The NRC COT[28] used the data of Kinkead et al.[34] as input to the multistage model of Crump and Howe to obtain a 95% lower confidence limit of 0.116 ppm for a lung tumor risk in mice of 0.01, based on a work-week exposure schedule. Using the "concentrations times time" rule to convert to a continuous lifetime exposure yielded the value of 0.01 ppm corresponding to a lifetime tumor risk of 0.01.

Blood Effects:

In continuous, 90 day low dose inhalation exposures of rats, dogs and monkeys at 0.04 pm and 0.1 ppm, dogs showed significant decreases in hematocrit hemoglobin levels and blood cell count, but only at the higher dose[17]. MAC values were calculated by applying Haber's rule and a safety factor of 10 to the (NOAEL) 0.04 ppm level. Microgravity should not affect the crewmembers' susceptibility to the hemolytic effects of MH because microgravity reduces the total red cell mass, but the hematocrit remains at near normal levels because the plasma volume is also reduced.

In order to determine which of these toxic end-points should be used as the basis for setting the SMAC, MAC values were determined for each endpoint at each of five exposure durations. The results, tabulated below, were used to select the value which provided the best protection.

TABLE 3: **MACs and Endpoints for MH**

Endpoint		Specie Tested	Safety Factor	MAC (ppm) 1 hr	24 hr	7 d	30 d	180 d
Lethality[30] *LC_{50}, 1 hr = 82 ±16 ppm (2 died/4 exposed)*	Severe	Monkey	100	0.65	0.03	*	*	*
Lethality[30] *NOAEL, 1 hr = 75 ppm (0 died/2 exposed)*	NOAEL	Monkey	100	0.75	0.03	*	*	*
Nasal Injury[33] *12/42 exposed to 0.2 ppm, 30 cc, single sniff*	Mod	Man	1	**0.002**	**0.002**	**0.002**	**0.002**	**0.002**
Heinz Bodies[36] *10 min @ 90 ppm*	Mild	Man	1	15	*	*	*	*
Carcinogen[34] (b) *2 ppm, 1 yr, intermittent*	Mod	Mice Cr&Howe model		*	*	3.5	0.85	0.15
Liver Effects[35] *0.04 ppm, 90 d, contin*	NOAEL	Dogs	10	*	*	0.05	0.012	**0.002**
Blood Effects[35] *0.04 ppm, 90 d, contin*	NOAEL	Dogs	10	*	*	0.05	0.012	**0.002**

* N/A for use of "concentration times time" rule.

Using the equation for the linearized multistage model shown above for HZ, MACs were calculated using a continuous lifetime exposure to 0.01 ppm for which the NRC COT calculated an upper 95% risk of 0.01. Because the model is conservative, no safety factor is used to convert animal test data to human exposure limits. Since it is not anticipated that microgravity will affect humans' sensitivity to the potential carcinogenic effects of MH, no adjustments were made for microgravity-induced physiological changes.

Liver Effects:

In continuous, 90 day low dose inhalation exposures of rats, dogs and monkeys at 0.04 pm and 0.1 ppm, dogs were the only species in which liver pathology was observed, and only at the higher dose[35]. MAC values were calculated using Haber's rule and a safety factor of 10 to the NOAEL level (0.04 ppm).

For each exposure duration, the SMAC was set equal to the lowest MAC value among the endpoints shown above. The resulting values, in units of both ppm and mg/m^3, are listed along with the most sensitive target toxicity at that exposure duration.

TABLE 4: **SMACS for MH**

	ppm	mg/m^3	Target Toxicity
1-h SMAC	0.002	0.004	Nasal Injury
24-h SMAC	0.002	0.004	Nasal Injury
7-d SMAC	0.002	0.004	Nasal Injury
30-d SMAC	0.002	0.004	Nasal Injury
180-d SMAC	0.002	0.004	Nasal Injury/Blood Effects/Liver Effects

**Previous 7-d SMAC was 0.04 ppm.*

CONCLUSION

While one would intuitively expect that the toxicities of HZ and MH would be similar, the SMAC values appear to contradict this. We feel that this situation is an artifact of the quality and type of studies which have been performed to date. For MH, the SMAC values are based on the results of a single study, which showed a much higher toxicity for MH than all other studies we found. In spite of this inconsistency, the study appears to be well done and its results cannot be ignored. For HZ however, no similar test has been performed, to our knowledge. Thus, no data are available in the literature to support lowering the SMAC for HZ to a value comparable to the SMAC for MH. The old scientific refrain, "more work needs to be done", certainly applies to toxicological studies of the hydrazines.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the invaluable discussions, comments, and reviews of their colleagues, Drs. Martin Coleman, Chiu-Wing Lam, and King Lit Wong.

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CONCLUSION

While one would intuitively expect that the toxicities of HZ and MH would be similar, the SMAC values appear to contradict this. We feel that this situation is an artifact of the quality and type of studies which have been performed to date. For MH, the SMAC values are based on the results of a single study, which showed a much higher toxicity for MH than all other studies we found. In spite of this inconsistency, the study appears to be well done and its results cannot be ignored. For HZ however, no similar test has been performed, to our knowledge. Thus, no data are available in the literature to support lowering the SMAC for HZ to a value comparable to the SMAC for MH. The old scientific refrain, "more work needs to be done", certainly applies to toxicological studies of the hydrazines.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the invaluable discussions, comments, and reviews of their colleagues, Drs. Martin Coleman, Chiu-Wing Lam, and King Lit Wong.

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