Research to Support the Determination of Spacecraft Maximum Acceptable Concentrations of Potential Atmospheric Contaminants

Final Report
Southwest Research Institute Project 12-5326

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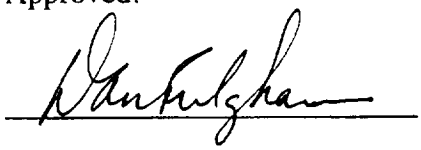
Approved:



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Introduction

In many ways, the typical approach to the handling of bibliographic material for generating review articles and similar manuscripts has changed little since the use of xerographic reproduction has become widespread. The basic approach is to collect reprints of the relevant material and place it in folders or stacks based on its dominant content. As the amount of information available increases with the passage of time, the viability of this mechanical approach to bibliographic management decreases. The personal computer revolution has changed the way we deal with many familiar tasks. For example, word processing on personal computers has supplanted the typewriter for many applications. Similarly, spreadsheets have not only replaced many routine uses of calculators but have also made possible new applications because the cost of calculation is extremely low.

Objective

The objective of this research was to use personal computer bibliographic software technology to support the determination of spacecraft maximum acceptable concentration (SMAC) values.

Specific Aims

The specific aims were to produce draft SMAC documents for hydrogen sulfide and tetrachloroethylene taking maximum advantage of the bibliographic software.

Methods

Software Versions

The BiblioLinks software was version 3.02, the Pro-Cite was version 2.1.1, and the wordprocessor used was Microsoft Word for Windows version 6.0a. The personal computer used was an IBM compatible with an Intel 33 MHz 486 processor using Microsoft Windows version 3.11.

Computerized Literature Searches

The Dialog computer database system was used to search the TOXLINE, MEDLINE, AEROSPACE, NTIS, and CA SEARCH databases. The basic search terms used were the chemical names and their Chemical Abstracts identification numbers as shown in the table below. Health effects and risk related terms were joined with the AND operator to produce the set of tagged format records which were listed to a PC and captured in a series of text files with approximately 50 entries each. The records were listed in blocks because the ASCII files have no error correction. If a garbled transmission occurred, then only the block of 50 records needed to be retransmitted.

SYSTEM:OS - DIALOG OneSearch
File 156:TOXLINE 1965-1992/DEC
File 155:MEDLINE 1966-1993/MAR (9303W3)
File 108:AEROSPACE 62-93/ISS01
File 6:NTIS 64-93/9302B2
File 399:CA SEARCH 1967-1992 UD=11726
Set Items Description

SELECT response set to SHORT
S1 3915 TETRACHLOROETHYLENE
S2 10198 RN=127-18-4
S3 23515 HYDROGEN()SULFIDE
S4 25583 RN=7783-06-4
S5 15795 HEALTH EFFECTS
S6 29885 HEALTH()EFFECT? ?
S7 8124 HEALTH()RISK? ?
S8 1091580 TOXIC?
S9 3021264 ANIMAL
S10 5884056 HUMAN
S11 123200 PHARMACOKINETIC? ?
S12 1150 (S1ORS2)AND(S5ORS6ORS7ORS8ORS11)AND(S9ORS10)
S13 628 (S3ORS4)AND(S5ORS6ORS7ORS8ORS11)AND(S9ORS10)
S14 1759 S12ORS13
S15 813 RD S12 (unique items)
S16 470 RD S13 (unique items)

The Dialog database search was run a second time in February 1994 to bring it up to date and new entries were added to the database.

Conversion to PC Database

The ASCII files containing 50 record blocks from the Dialog search were concatenated together into one large file for import. The importation went smoothly with minor adjustments to the BiblioLinks settings. The importation was not perfect, however, and some manual cleanup was performed. This step could probably have been eliminated with more skilled operation of BiblioLinks, but by the time the errors were discovered, many acquisition numbers had been added and it was decided to do a manual cleanup rather than reimport the data.

The records were obtained from several different databases and some databases use all capital letters. Pro-Cite technical support indicated that there was no alternative to retyping in the current version, but the new version for MS-Windows would have an option to capitalize the first letter in a field or each word.

Document Physical Acquisition

Triage

A printout of the entire database with abstracts and descriptors was used to select the articles for acquisition. These marked lists were then submitted to the SwRI library for acquisition.

Accession Number

A sequential accession number was assigned upon receipt and this number was entered in the Notes field in the form /AXXXX/ where XXXX is a 4-digit number.

Database Issues

Multicompound Database

This project used one database for both the hydrogen sulfide and tetrachloroethylene citations. One could, of course use separate parallel systems for each compound, but the combined approach was used to simulate an integrated SMAC document support system. There was only a slight overlap between the hydrogen sulfide and tetrachloroethylene literature, for example, standard references and texts. If both the compounds were of the same chemical category, for example halogenated hydrocarbons, the degree of overlap could be much higher.

A practical aspect of using single database is that the accession numbers could be entered without determining for which compound the citation was relevant. This could be an important issue because in this database approximately 10% of the articles obtained were not classifiable as hydrogen sulfide of tetrachloroethylene based on a full-text search of the bibliographic citation. For these citations, it was necessary to inspect the physical manuscript and add an additional entry into the Notes field.

Accession Numbering

Each document was assigned an accession number when received. This number was in the form /AXXXX/ as the first entry in the Notes field where XXXX is a 4-digit accession number. Because less than 1000 documents were acquired, only the last three digits of the accession number were required to identify an article. The search term /A0*, where * is a wild card symbol, successfully selected all articles with an accession number in the appropriate format.

The accession number was written on the first page of each document for convenience in identification. In order to use the manuscript searching capability of Pro-Cite to assemble the bibliography, it is necessary to insert information in the manuscript text. The most accurate was to cite articles by their Pro-Cite record number which is different from their accession number. The Pro-Cite record number is a function of when the record was

added to the database and the acquisition number is determined by the arrival on an article. For example, to cite the article with acquisition number A0115, it is necessary to insert [#6440] in the text. A bibliographic printout of the database in acquisition number order was used as the cross reference to put the Pro-Cite record number on articles in addition to their acquisition number. A prefix of "A" was used to identify the acquisition numbers and a prefix of "#" was used to identify Pro-Cite record numbers.

Mechanical Storage Units

The documents were stored in a set of three plastic hanging file folder boxes. Hanging folders with numbers in increments of 10 were used to hold the documents. This system permitted unambiguous refiling. The system also made it possible to audit the files to confirm that all the documents listed in the database as acquired were physically present by identifying any numbers missing in the acquisition sequence.

Literature Acquisition Monitoring

Database listings marked with the citations selected for acquisition were used to both drive and monitor the acquisition process. In retrospect, it would have been a good idea to mark each record selected for acquisition in the Notes field with a code such as REQ. One could then use the database to print the set of citations which had a Notes entry of REQ but not /AXXXX/ (the accession number) and obtain a listing of items which were selected for acquisition but had not yet been acquired.

Target Searches

Because of variations in nomenclature and spelling, it was necessary to develop search terms which would capture all the manuscripts for a given chemical as shown in the following table.

Chemical Search Term Table

Search	Search Term
Hydrogen Sulfide	((sulfide* or H2S or hydrogen* or sulphide*) and #42 = /A0*)
Tetrachloroethylene	((tetra* or per* or halo* or solvent* or organic or volatile or chlor*) and #42 = /A0*)

A set of Pro-Cite topic area searches was constructed and stored as files. The intersection of a chemical search and a topic search gives the set of articles which are potentially relevant.

Topic Search Table

Class	Type	Search
ADME	Pharmacokinetics/ Metabolism	and (pharmacokinetic* or toxicokinetic* or half-life or metabol*)
Duration	Acute	and acute
Duration	Chronic	and chronic
Duration	Subchronic	and subchronic
Effect	Cancer	and (carcin* or cancer or neoplas*)
Effect	Genotoxicity	and (genetic* or DNA or chrom* or genotoxicity)
Effect	Irritation	and irritat*
Effect	Mutagenicity	and mutagen*
Effect	Reproduction	and (repro* or fertilit* or infertilit* or abortion)
Effect	Teratology	and (teratolo* or "birth defect")
Other	Mechanism	and mechanism*
Other	Synergistic Effects	and synergistic*
System	Blood	and (blood or hemato*)
System	Bone	and (bone or skelet*)
System	Cardiac	and (cardi* or heart* or EKG or ECG)
System	Glands	and (gland or adrenal* or pancrea* or salivary* or endocrine*)
System	Immune System	and immun*
System	Kidney	and (kidney or nephro*)
System	Liver	and (liver or hepato*)
System	Lung	and (respir* or pulmon* or lung)
System	Nervous system	and (nerv* or brain or cogniti* or arousal or alertness)
System	Sensory Systems	and (sensory or eye or ear or vestibular or balance or hearing or vision)
System	Skin	and (skin or derma*)

Because the search is working on the full text of all records, the rate of false alarms is very high. In most searches, most of the citations retrieved are not relevant to the SMAC document. The high false alarm rate of non-relevant citations is exactly the situation desired when working on SMAC documents because the high false alarm rate means that the rate of hits on relevant documents will be high. A very practical approach has been to use the printouts of the results of searches including abstracts as a "pull list" when working on a given topic area in the SMAC document. There are over 560 documents which have been acquired. These documents were selected from an initial literature search of over 1300 citations. The topic searches are used to locate the documents potentially relevant to a topic area.

Topic Areas Search Numbers

The table below shows the number of citations in the topic searches for the two compounds. In any given category, there are a large proportion of citations which are not useful for producing a SMAC document and there is often a high degree of overlap between categories. This is appropriate at the level of searching acquired documents because they have already been selected for acquisition on the grounds of moderate to high potential relevance from their titles, abstracts, or citations in review articles. As a practical matter, when using the Pro-Cite generated pull-list reference lists, which are best if printed with the abstracts, it is easy to narrow the search in the process of pulling the documents from the file folders.

Target Search Citation Counts

Class	Type	Tetrachloroethylene	Hydrogen Sulfide
ADME	Pharmacokinetics/ Metabolism	148	38
Duration	Acute	23	18
Duration	Chronic	28	6
Duration	Subchronic	3	1
Effect	Cancer	128	6
Effect	Genotoxicity	94	7
Effect	Irritation	6	2
Effect	Mutagenicity	46	1
Effect	Reproduction	32	6
Effect	Teratology	10	1
Other	Mechanism	25	10
Other	Synergistic Effects	1	1
System	Blood	99	39
System	Bone	8	1
System	Cardiac	23	14
System	Glands	11	2
System	Immune System	36	10
System	Kidney	38	6
System	Liver	99	13
System	Lung	77	55
System	Nervous system	68	34
System	Sensory Systems	20	3
System	Skin	24	6

Results

Overall Concept

Experience on this project shows that current personal computer hardware and software can be used to facilitate all aspects of literature review for the generation of safe exposure levels such as SMAC values. From the interface to the files from the mainframe computerized literature searches through acquisition monitoring and document physical acquisition and storage, the combination of hardware and software has proved useful in managing large amounts of scientific literature. In the generation of the review documents, the hardware/software system has performed extremely well. The searches within the database for pull-lists of documents in various topic areas has been extremely helpful. It is much more effective to have the use of a pull-list and consider a subset of topic relevant documents than to put them in piles or folders by dominant topic. In a sense, the computerized bibliography pull-lists are virtual piles of documents with a copy of each document in each pile where it is relevant. The Windows environment makes it practical to have both the word processing program and the Pro-Cite resident and operational at the same time. To switch between the two programs, it is only necessary to press simultaneously the Alt and the Tab keys. This makes it easy and practical to conduct ad hoc searches and have the abstract for most entries readily available. Because articles are cited in the review by their Pro-Cite record number, it is convenient to be able to check citations and look up the accession number. Finally, the ability of Pro-Cite type programs to process the review document and generate a bibliography in any of a number of citation formats is a feature which removes drudgery and improves reliability.

As described below, the process of computerized review support can be improved and new classes of tools to enhance and improve the approach are becoming available, but it is now practical to take advantage of this type of support.

Acquisition lag

The documents used for this project were obtained primarily through interlibrary requests through the SwRI library. This has the advantage that the cost is extremely low. The difficulty encountered with this approach was the unpredictable lag in the acquisition of the selected manuscripts. Articles from a given request would arrive with an exponentially declining frequency with a half-life of approximately 2 months. After several months, articles still outstanding were requested again and the exponential arrival process was repeated.

A more expensive but faster alternative would be the use of a commercial reprint company such as "The Genuine Article" service from the Institute for Scientific Information in Philadelphia, PA. The cost is $10.25 for the first 10 pages and 2.75 for each additional 10 pages. A variety of delivery services are available (at extra cost) including express overnight delivery and facsimile response within 30 minutes. In retrospect, it would have been much faster to have planned to use such a service.

Database Issues

Accession Numbers

The accession numbers performed as intended to organize the documents and the use of the /A characters at the start made the code searchable in the Pro-Cite database. Because the assignment of accession numbers was under operator (as opposed to program) control, it was possible for human error to introduce both duplicate and missing accession numbers into the database.

Verification

In order to check the accession number sequence, the database was sorted into accession number order, printed and manually checked. This revealed two duplicate accession numbers, two skipped accession numbers and one accession number in an incorrect format.

Corrections

The accession numbers were manually corrected and an audit trail left in the Notes field.

Utility

By having all the accession numbers present in sequence, it was possible to print the entire database of acquired documents with an outdented record number which corresponded to the acquisition number. This main bibliography is for both hydrogen sulfide and tetrachloroethylene and contains the abstracts, if available. The topic databases specific to hydrogen sulfide and tetrachloroethylene are printed without the outdented record number but either the hardcopy document or the abstract can be readily accessed through the accession number.

Nontarget Searches

Some of the database searches are devoted to testing the adequacy of the descriptors in the searches to determine if the appropriate materials are located.

Purpose

A series of searches and manual repairs were used to resolve all documents with an accession number into the hydrogen sulfide bibliography or the tetrachloroethylene bibliography or into both bibliographies.

Specialized Searches

The table below shows the searches to find hydrogen sulfide or tetrachloroethylene documents and the non-target search to find articles with an accession number but which were not in the bibliographies of interest.

Search	Search Term
Not-targeted compounds	NOT (((sulfide* or H2S or hydrogen* or sulphide*) and #42 = /A0*) or ((tetra* or per* or halo* or solvent* or organic or volatile or chlor*) and #42 = /A0*)) and #42 =/A0*

Manual Repairs

Approximately 50 documents which were acquired and had some degree of relevance to the project were not initially categorizable by the computer search as relevant to hydrogen sulfide or tetrachloroethylene. These were the citations which were returned when the Not-targeted compounds search was run. The hardcopy corresponding to these citations was accessed and the document was characterized and the database repaired by adding key entries in the Notes field. A notation "h2s" was added for hydrogen sulfide and "per" was added for tetrachloroethylene which is also known as perchloroethylene. If a document, for example a reference work, was relevant to both compounds both notations were added to the Notes field. When this process was complete the Non-targeted compounds search set was empty which meant all the documents with an acquisition number were picked up by either the hydrogen sulfide or tetrachloroethylene search terms.

SMAC Document Bibliography Generation

One of the most important features of bibliographic management programs is the capability to read a manuscript and: 1) convert the citation in the manuscript to the specified format (for example, sequential footnote numbers), and 2) generate the corresponding bibliography in the specified editorial style. This is a very useful capability by which it would be, in principle, easy to generate current final formatted manuscripts with current bibliographies. In practice, this is not so practical when it is necessary to use the file format of a previous version of the wordprocessing software for compatibility with Pro-Cite as described below.

Manuscript Entries for Pro-Cite Bibliography Generation

In order to use the manuscript searching capability of Pro-Cite to assemble the bibliography, it is necessary to insert information in the manuscript text. The most accurate was to cite articles by their Pro-Cite record number which is different from their accession number. The Pro-Cite record number is a function of when the record was added to the database and the acquisition number is determined by the arrival on an article. For example, to cite the article with acquisition number A0115, it is necessary to

insert (#6440) in the text. One limitation of this approach is that Pro-Cite does not appear to support the "Other text" feature when citations are done by record number so it is not possible to indicate an individual page number.

A bibliographic printout of the database in acquisition number order was used as the cross reference to put the Pro-Cite record number on articles in addition to their acquisition number. A prefix of "A" was used to identify the acquisition numbers and a prefix of "#" was used to identify Pro-Cite record numbers.

Wordprocessor Version Support

Pro-Cite supported earlier versions of Microsoft Word for MS-DOS (Versions 3-5) than the version of Word for Windows (6.0a) which was used to generate this manuscript and the draft SMAC documents. Word for Windows 6 was used for this manuscript because of its powerful table making capability and enhanced layout view and print preview features. Fortunately, Pro-Cite also supported the Microsoft rich text format (RTF) which preserves formatting information.

Code Searching/Replacement

The decision to use Word for Windows 6 for the manuscript meant that in order to use the manuscript search/update and bibliography capability it was necessary to save the text with the RTF format output filter. For example, if SMAC.DOC is the Word for Windows 6 document file then SMAC.RTF would be the RTF format version. Pro-Cite would be used to search and update SMAC.RTF to generate SMAC-OUT.RTF which is a RTF formatted file with the reference codes replaced by reference numbers. The references themselves would be printed from Pro-Cite into SMAC-REF.DOC in Microsoft Word for MS-DOS (Versions 3-5) format. Both SMAC-OUT.RTF and SMAC-REF.DOC could be directly imported into Word for Windows 6 for further work. In practice, there was also an additional step. Pro-Cite generates a file PROBLEM.REF which contains text which it identified as a possible but bad citation. The conversion to RTF adds end-of-line characters at random points in the text stream. When this occurs in a bibliographic citation and, for example (#13250) becomes (#132 at the end of a line and 50) on the next line, Pro-Cite considers this to be a bad citation. Because of this problem, it was necessary to run Pro-Cite on the RFT file, inspect the PROBLEM.REF text file, load the RFT file into MS Word for Windows using the "Text Only" conversion filter, and correct the broken references. The broken references could be found from the entries in PROBLEM.REF by searching with a search target consisting of an opening square bracket, a pound sign, and the first part of the numeric portion of the citation with a paragraph mark at the end. Removing the corresponding paragraph mark in the document was sufficient to fix the citation.

These extra steps made it impractical to keep the bibliography current with the text at all times, but it was practical to produce a footnoted draft any time one was required. Ideally, the bibliography would be added to the document directly and would utilize the Microsoft Word 6.0 footnote capabilities.

Discussion

BiblioLinks

DOS Biblio Links for Dialog

BiblioLinks (for MS-DOS) was much more effective at converting the Dialog records into the corresponding database than previous attempts for other projects using either the current versions of Reference Manager (Research Information Systems, Inc., Carlsbad, CA) or Papyrus (Research Software Design, Portland, OR). Of course, more recent versions of these products may perform better at importing Dialog searches.

BiblioLink II (Windows)

This version of the computerized search import software was obtained after the data had been imported and was not used on this dataset. Based on an overview of the BiblioLink II manual, it appears that this version of the software is much more user friendly.

Pro-Cite

"Learning Curve"

Pro-Cite skill is acquired slowly and requires quite frequent reference to the manual. This learning curve is a consequence of the complexity and flexibility of the program. A Microsoft Windows compatible version of this program with extensive online help and examples would help with the learning process.

Database

Pro-Cite performed well as an application specific database after a degree of proficiency in its operation was obtained.

Searches

Capability

The searching capability was appropriate to the task at hand. The asterisk (*) wild-card operator which matches any set of characters was extremely useful in searching. The NOT, AND, and OR operators in combination with parentheses were sufficient to perform the desired searches. The string length limitation of 250 characters was not a problem. As described below, it would be useful to have the capability to update and append to some fields in the database. The purpose of this would be to indicate the set of records of which a given record was a member. One way to achieve this capability would be with the IF (search expression is true) THEN (perform this action) ELSE (perform this action) ENDIF structure.

What this package lacks for this type of work is a capability to store values in a field as the result of searches and then to act on those values. For example, suppose it was possible to identify the set of all acute studies and write the keyword ACUTE in a field and then repeat the process for the other searches, each time appending the search category for the citation. Once the set of searches was performed, it would then be desirable to print out the bibliographies corresponding to the searches. The net effect, a set of bibliographies by topic was obtained with the current software but many manual steps were required which makes frequent updating of the topic bibliographies impractical.

Flexibility

The ability to save and restore search strings supported modular searching. One saved search string was used to select articles which had been obtained and were relevant to hydrogen sulfide and a second saved search was used to select those articles which were relevant to tetrachloroethylene. These searches were combined with the topic searches (Acute, Subchronic, Chronic, Blood, Cancer, etc.) to produce the topic bibliographies.

Speed

Search speed with a complex query on a 33 MHz IBM PC 486 compatible computer for a complex search such as the Non-Target search was satisfactory. This search of all the text in all the records took less than a minute.

Export Capability

Citation Formats

Pro-Cite has a wide range of citation formats that it supports. Pro-Cite's native format, the ANSI format for computer databases, was used for the bibliographies in this project.

Output Types

Output in the format for an earlier version of the wordprocessing software, Microsoft Word for DOS Versions 3-5, was not a serious limitation because the wordprocessor used to generate the documents, Microsoft Word for Windows 6.02a, could open or import the Pro-Cite generated Word for DOS files without any problems.

Weaknesses

Must Leave Search Window to Browse

In Pro-Cite (for MS-DOS) one is always at least three key strokes away from the Browse or Edit windows when in the Search Window. The ability to Jump to an alphanumeric field value is helpful, but it is not the same as being able to work in both the Search and

Browse or Edit windows simultaneously. This would be a logical candidate for repair in a Windows version.

Citation Numbers Must be Manually Entered

Pro-Cite (for MS-DOS) does not provide a way to automatically enter a citation in a manuscript from a view of the database. To enter a citation in the manuscript, one must type (#XXXXX) where XXXXX is the Pro-Cite record number of the citation. Notice that this is different from the accession number which is used to access the physical manuscript!

Papyrus, in Version 7, has the capability to use the Windows clipboard to format a citation for pasting into the manuscript. This capability would be a significant improvement for Pro-Cite.

No Cut and Paste in Edit Window

The lack of rudimentary editing capability in the database fields increases the chance of introducing typographical errors if material needs to be moved from one field to another. Because cut-and-paste is quite generic in Windows, this will probably be resolved in a Windows version.

Windows Version

A windows version of Pro-Cite is expected in early 1995 which will probably address many of the comments listed above as well as maintain its many heavy-duty features. The windows versions of Biblio-Link and Pro-Cite should be a powerful combination for the type of research needed to support SMAC documents.

New Software and Hardware to Support SMAC

The prices on scanners have been decreasing and the capabilities of optical character recognition software and document management software have been increasing.

For example, hand-held grayscale scanners are available for approximately $100 and full page color scanners with various features including automatic document feeders are available for between $500 and $1000.

Optical character recognition software such as OmniPage Professional has a list price of approximately $500.

Document management software is available in many cost ranges, but some software such as Docuware Pressman from ALOS Micrographics is inexpensive, approximately $350 including a scanner and claims the ability to store scanned material with user keywords and retrieve full pages of text as well as OCR support to allow direct pasting of text into Windows word processors.

Writable CD-ROM systems are coming down in price, but one could have a CD-ROM made relatively inexpensively.

From where we are now with Pro-Cite, it is only a short technological leap to additional software which would make the full text of all the material to support a SMAC available on a computer readable CD-ROM! By using the accession number as the Docuware Pressman keyword, a direct link could be established between the programs and hence the bibliography and the material referenced.

Legal Problem

The technology seems ready for demonstrating the feasibility of a new level of computer assisted toxicologic assessment document preparation and maintenance, however, the technology is moving faster than the legal relationships between data consumers and vendors. The Pro-Cite database on hydrogen sulfide and tetrachloroethylene, which was primarily downloaded from Dialog, and the physical documents which were acquired by interlibrary request under the "fair use" provisions of the copyright law have questionable status. The current legal advice from our organization is that neither can be delivered to NASA without incurring copyright law violations. This problem would be compounded by a full text system described above.

Conclusion

Despite the various problems and limitations encountered, the hardware/software technology for effective computer assistance in the generation of SMAC documents and similar reviews is at hand. Running with Microsoft Word under Microsoft Windows, Pro-Cite and its companion program, BiblioLinks, were successful at accomplishing the objectives of the project. The BiblioLinks software could convert the mainframe computerized literature search into a useful database without manual retyping. The use of the Notes field to store an accession number and manually entered search classification codes worked well.

Computer assisted toxicologic bibliographic management and bibliography generation appears to be a practical alternative to traditional methods and emerging hardware and software will make this approach even more powerful and practical.

Appendix A

Hydrogen Sulfide Bibliography

Adachi, J.; Tatsuno, Y.; Fukunaga, T.; Ueno, Y.; Kogame, M.; Mizoi, Y. Formation of sulfhemoglobin in blood and skin caused by hydrogen sulfide poisoning and putrefaction of cadaver. Nippon Hoigaku Zasshi. 1986; 40(3):316-322.

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Appendix B.

DRAFT Hydrogen Sulfide SMAC Document.

HYDROGEN SULFIDE

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PHYSICAL AND CHEMICAL PROPERTIES

Hydrogen sulfide is a colorless gas with a characteristic odor of rotten eggs[1]. For convenience in making comparisons, all concentrations of hydrogen sulfide have been converted to ppm, assuming standard temperature and pressure (STP).

Property	Value	Reference
Synonym:	**Dihydrogen Monosulfide**	(2)
Formula:	**H_2S**	(2)
CAS #:	**7783-06-4**	(3)
Molecular Weight:	**34.08**	(4)
Boiling Point:	**-60.33**	(4)
Melting Point:	**-85.49**	(4)
Lower Explosive Limit:	**4.3 % (vol. in air)**	(4)
Upper Explosive Limit:	**46 % (vol. in air)**	(4)
Vapor Pressure:	**20 atm @ 25.5° C**	(5)
Vapor Density:	**1.19 (air = 1)**	(4)
Conversion Factor (STP):	**1 ppm = 1.4 mg/m^3**	(4)
Conversion Factor (STP):	**1 mg/l = 719 ppm**	(1)
Odor Recognition Threshold	**0.13 ppm**	(6)

OCCURRENCE AND USE

EXOGENOUS

Hydrogen sulfide occurs in nature in natural gas formations, coal mines, sulfur springs, and volcanic gases; and as a by-product of industrial processing of sulfur containing compounds. In addition, liquid manure systems from high density animal husbandry occupations are a source of hydrogen sulfide which is associated with potential occupational exposures of half a million persons[7]. Hydrogen sulfide is used for a wide range of industrial processes ranging from the preparation of animal hides for tanning[8] through the process for the production of kraft paper[9] to the production of sulfur-containing chemicals such as carbon disulfide, sulfuric acid, and elemental sulfur[1]. Hydrogen sulfide is used as a solvent for the extraction of deuterium oxide for use as moderator in nuclear reactors[1].

ENDOGENOUS

Hydrogen sulfide can also be produced by bacterial action in the intestines and be a component of flatus[1], the hydrogen sulfide content of which is dependent on the amount of carbohydrates consumed[10]. Because the hydrogen sulfide gas is readily absorbed from the intestine and can give rise to systemic effects when administered rectally[11,12], it has long been suspected that there were mechanisms for the metabolism of hydrogen sulfide in blood[13] to protect the organism from self-poisoning. Early studies indicated that hydrogen sulfide was rapidly cleared from the blood[13]. More recently, Thiol S-methyltransferase, an enzyme found in microsomes in the gut mucosa, has been suggested[14] as playing an important role in detoxifying hydrogen sulfide generated in the intestines.

Subgingival microbiotas from periodontal pockets generate hydrogen sulfide when incubated with human serum[15], but the contribution of this route to the total endogenous hydrogen sulfide exposure is not known.

Hydrogen sulfide can be produced during the conversion of the amino acid cysteine to pyruvic acid by cystathionine γ-lyase[16]. The metabolism of cysteine conjugates[17,18] in the cells of the kidney, and during the metabolism of dietary methionine[19]. In rats[19] it appears that younger animals produce more volatile sulfur compounds, including hydrogen sulfide, from methionine metabolism.

PHARMACOKINETICS AND METABOLISM

Hydrogen sulfide is readily taken up from inhalation exposure. It appears that skin absorption of vapor is a minor potential route of exposure[9,6]. At a physiologic pH for blood of 7.4, approximately one-third of the hydrogen sulfide is undissociated. Approximately two-thirds is in the form of hydrosulfide anion (HS^-) and only a very small amount exists as the sulfide anion ($S^=$)[1]. Because of the endogenous sources of hydrogen sulfide exposure, it is not surprising that there are existing metabolic

mechanisms and that based on *in-vitro* experiments, it is likely that the life-time of hydrogen sulfide in oxygenated blood is on the order of minutes [20]. Hydrogen sulfide is distributed to the brain, liver, kidneys, pancreas, and small intestine after short-term inhalation exposure. The current concensus[9] is that the major metabolic pathway is oxidation of sulfide to sulfate followed by excretion by the kidney.

Other potential metabolic pathways[9] include methylation and also reaction with metalloproteins. This includes inhibition of cytochrome oxidase which is probably important in the production of the acutely lethal toxic effect of hydrogen sulfide.

Age may be a factor in metabolic differences[21] in the handling of hydrogen sulfide, based on observations on blood from puppies and older dogs.

Little information is available about the multi-tissue distribution of hydrogen sulfide. Since little appears to be published about the kinetics of hydrogen sulfide metabolism, the basis for the differences in tissue concentration is unclear. The differences could be due to differences in biodistribution, binding, or metabolism.

HYDROGEN SULFIDE TISSUE CONCENTRATIONS

Location	Human[22]	Human[23]	Rat[24]
Blood	0.305	14.2	0.48
Muscle	0.690		0.21 thigh 0.22 abdominal
Liver	1.089		1.67 {0.95 control conc.}
Lung	1.338		.60
Kidney	1.170		1.45 {1.19 control conc.}
Heart	1.366		
Brain	0.875		0.31
Units	µg/ml or ug/gm	mg/l	µg/g
Inhalation Exposure	Accident	Accident	550 to 650 ppm until death

Determination of hydrogen sulfide concentration in tissues, especially those from human fatalities, is problematic. Hydrogen sulfide is produced during putrification[25] and levels in blood, liver, and kidneys can increase with time since death[24].

Thiosulphate concentration in urine has been suggested as a biological marker of hydrogen sulfide exposure which is related to the product of exposure concentration and exposure time[26].

TOXICITY SUMMARY

Because of the long history of occupational exposure and the history of morbidity and mortality, the toxicity of hydrogen sulfide has been reviewed several times[27,1,9,28,29,30,20,31]. Because Spacecraft Maximum Allowable Concentration (SMAC) value recommendations represent specialized exposure scenarios, it was necessary to review the data from the perspective of continuous exposure and space flight. Despite considerable attention to hydrogen sulfide over the years, it was still possible to hypothesize a reasonable mechanism for the knockdown effect which does not appear to have been previously articulated.

NRC TYPES OF HYDROGEN SULFIDE INTOXICATION

A National Research Council (NRC) Subcommittee on hydrogen sulfide endeavored to clarify the various types of hydrogen sulfide intoxication with the following definitions in its review[1]:

Acute intoxication

"Effects of a *single* exposure to *massive* concentrations of hydrogen sulfide that rapidly produce signs of respiratory distress. Concentrations approaching 1000 ppm are usually required to cause acute intoxication."

Subacute intoxication

"Effects of continuous exposure to *mid-level* ...(100 to 1000 ppm concentrations of hydrogen sulfide) Eye irritation ... is the most commonly reported effect, but pulmonary edema in the absence of acute intoxication has also been noted."

Chronic intoxication

"Effects of *intermittent* exposures to *low to intermediate concentrations* ... (50 to 100 ppm) of hydrogen sulfide characterized by "lingering," largely subjective manifestations of illness."

ORGANIZATION BY EXPOSURE DURATION

The NRC definitions of the different types of intoxication are useful because they emphasize the fact that the profile of intoxication seen depends on the exposure situation. One may be rendered unconscious by a high dose acute exposure and have no sequela or one may be exposed to a lower dose for a longer time and develop pulmonary edema. Thus, for hydrogen sulfide it is important to recognize the different types of intoxication. In fact, before the chemistry was understood, sewer workers in Paris recognized two

syndromes which were not known to be related. The "mitte" was inflammation of eyes and mucous membranes and the other was an asphyxia called the "plomb" as described in an early review of the hydrogen sulphide literature[27]. It is now understood that these names referred to subacute and acute intoxication, respectively, as characterized by the NRC.

In the toxicity summary portion of this document, the terms acute, subchronic, and chronic are used to refer to the type of exposure, not the characteristics of intoxication as used by NRC. The toxicity summary is divided into acute, subacute, subchronic, and chronic exposure. The acute category includes some repeated dose studies which are arguably subacute repeated-dose exposures, but they are placed with the acute studies for convenience. The subchronic exposure category includes the remaining repeated-dose studies through 120 days of dosing. Occupational situations are considered as chronic exposures. The different types of intoxication defined by the NRC will be reflected in the different rationales and concentrations at different duration's for the SMAC values developed in this document.

ACUTE EXPOSURE

Human

Hot-spring reservoirs[32] and a poultry feather fertilizer plant[33] are unusual locations, but industrial operations[34] and manure pits[35,36], sewers, and cisterns[37,38,23,22,39] are typical locations of hydrogen sulfide fatalities.

A large scale human exposure situation shows the range of effects possible in acute hydrogen sulfide exposure. Following a brief hydrogen sulfide release from a refining plant, approximately 20 minutes in duration, approximately 300 people sought medical attention[40]. Of the 22 fatalities, 41% were dead on arrival, and another 41% died within 24 hours of arrival. Most of the 320 people exposed were evaluated and released, but 47 were hospitalized and evaluated in detail. The most prevalent symptom was the loss of the sense of smell which occurred in all but one patient who complained of a constant rotten-egg odor. Approximately half (53%) of the patients had been unconscious which suggests that the concentration to which they were exposed was at least several hundred ppm. Other prominent symptoms were severe headache in 61% of the cases, dyspnea in 38%, nausea in 32%, cough in 30%, conjunctival irritation in 28%, vomiting in 23%, and pulmonary edema in 19% of the cases. The author did not use inferential statistics with his data. However, there is a statistically significant negative relationship between unconsciousness and dyspnea in that dyspnea was more likely if one had not been unconscious (χ^2, 1 df, $p < 0.03$).

Although most cases of non-lethal occupational exposure to hydrogen sulfide do not have long-term effects[41,42,41,43], long-term pulmonary effects have been published in a single-case report[44].

Lethality

Rat

Exposure of Sprague-Dawley rats for 5 minutes[45] to approximately 1655 ± 391 ppm resulted in severe dyspnea with exaggerated respiratory movements and audible respiratory sounds with copious amounts of frothy fluid emanating from the mouth and nose. Gross necropsy revealed evidence of pulmonary edema consisting of foamy fluid in the trachea and severe congestion of the lungs to the extent that they did not collapse when exposed. The pathology observed was dependent upon the inhalation route of exposure because rats dosed intraperitoneally with 30 mg/kg of NaHS in distilled water which was also lethal during the 5 minute observation period had no evidence of pulmonary pathology or histopathology. The dose of NaHS used is approximately twice the EC_{50} at 5 minutes in Sprague-Dawley rats[46].

In Fischer-344 rats exposed for 4 hours, exposure to levels greater than 500 ppm resulted in death with a 90% decrease in cytochrome *c* oxidase activity, and a level of 50 ppm produced a statistically significant ($p < 0.05$) decrease of 15 % in cytochrome *c* oxidase activity relative to air-exposed controls[47].

Adult Sprague-Dawley rats, weighing approximately 100 gm, exposed for 4 hours[48] had an LC50 of 444 ppm with a 95 percent confidence interval from 416-473 ppm. The dose response curve was quite steep. At 400 ppm (the lowest dose used) 3 of the 10 subjects died; at 475 ppm 7 of the 10 subjects died, and at 600 ppm 10 of the 10 subjects died.

Measurement of rat electroencephalogram and electrocardiogram during sulfide poisoning showed EEG disturbances and correlated changes in respiratory pattern which are compatible with the decreased central respiratory drive theory of hydrogen sulfide toxicity. In this study, respiratory arrest typically occurred before cardiac arrest[49].

Dog

Concentrations corresponding to various concentration time values and their effects on dogs are in the toxicity summary table. This set of observations[50] is the most comprehensive set of determinations within a species. Although the number of dogs used at each dose is not given in the article, it is from a time, circa 1925, when such details were not considered necessary. The systematic effects described in the toxicity summary table are mild depression at low concentrations, stimulation, including respiration, at higher concentration, and suppression of central respiratory drive.

Primate

Rhesus monkeys were observed past the time of unconsciousness in an exposure concentration of 500 ppm[51]. The monkeys typically became unconscious within 15 minutes of the onset of the exposure. The predictor of impending unconsciousness was repeated deep breaths with the mouth wide open. They fell with rigid extremities as if suddenly struck down. Respiratory and/or cardiac arrest followed unconsciousness

between approximately 2 and 20 minutes later. Histopathology of one animal who died following respiratory and cardiac arrest after 35 minutes of exposure did not show changes in the heart, brain, kidneys, or adrenals. A second monkey had respiratory arrest after 25 minutes of exposure, was resuscitated by chest wall compressions, and it was three days later when it lost consciousness after 17 minutes. Following sacrifice 5 days later, microscopic examination showed necrosis in the occipital cortex, necrosis, gliosis, and hyperemia of the basal ganglia, and a decreased number of cerebellar Purkinje cells. Moderate liver hyperemia was noted, but the heart, kidneys, and adrenals were normal. The third monkey was exposed for 22 minutes in an exposure which was stopped before respiratory arrest. The animal was unconscious for over 2 hours, somnolent for several days, had reduced food consumption and had abnormal and uncoordinated movement. Only slight improvement was noted by sacrifice 10 days after exposure. Microscopic examination showed parietal and occipital cortex necroses, decreases in the number of cerebellar Purkinje cells. Heart, liver, kidneys, and adrenals were normal. The pattern of brain damage in the animals who survived a few days is similar to that from other causes of hypoxia, so it is possible that the brain changes are secondary to the respiratory arrest and mitocondrial enzyme cytochrome oxidase inhibition.

Human

Human fatalities from hydrogen sulfide poisoning are not uncommon[35,52,23,53], but the reports which are most useful for safety standard development are those with known concentrations and durations of exposure.

Reconstruction of an accident[33] found measured hydrogen sulfide concentrations from 2000 to 4000 ppm in the area where a maintenance worker's body was found. Because the body was draped over the leaking pipe, this is consistent with knockdown in one to two breaths.

A multiple fatality accident[37] in a cistern with a measured concentration of hydrogen sulfide of about 1000 ppm involved immediate knockdown of 4 men as they entered the cistern. A fifth man wearing self-contained breathing apparatus was knocked down instantly when he removed the mask to shout instructions. Review articles have included assertions that hydrogen sulfide at 500 ppm leads to unconsciousness and cessation of breathing within a few minutes[9,28].

Ocular Irritation

Inflammation of the conjunctiva and cornea following hydrogen sulfide exposure is called "gas eye" [6] which includes[54] in various degrees: intense photophobia, excessive tearing, spasm of the eyelids, intense congestion, pain, blurred vision, and contracted pupils with sluggish reaction to light. Gas eye is an occupational disease in the petroleum refining and gas well drilling industries which is called "spinner's eye" in the rayon industry. The cornea may be hazy and sometimes a large number of small blisters could be seen. The corneal blisters heal rapidly with a local anesthetic and antibacterial ointment without residual vision problems[42].

Corneal lesions can also be produced in animal models. Albino rabbits did not have corneal lesions when exposed to 36-71 ppm of hydrogen sulfide at 90% relativity humidity for 5 days but when pure hydrogen sulfide vapor was streamed at the eyes for two hours, punctate corneal lesions were observed[55].

Changes in Dark Adaptation

Hydrogen sulfide has been reported[56] to change the time course of dark adaptation. The study presents data for three subjects, each of whom was tested once under control (air only) and hydrogen sulfide in air administered between minutes 15 and 20 of dark adaptation. It is not stated if the subjects were blind to the type of exposure. The data are plotted on a linear scale instead of a logarithmic scale typically used which makes small changes more conspicuous. The data points at the 15 minute time point show small increases in sensitivity for 2 of the subjects and a larger and more persistent increase in sensitivity for one of the two subjects at hydrogen sulfide concentrations of 0.007 and 0.009 ppm. All these changes are less than 0.5 log unit in magnitude and although the difference was detected by an unspecified statistical method, this result must be viewed extremely skeptically for three reasons: 1) the relative thresholds are shifted at the time of the start of the hydrogen sulfide exposure, 2) there is no within subjects replication, and 3) the magnitude of the changes are sufficiently small that they could potentially result from uncontrolled variation from unspecified factors. For example, dark adaptation curves are influenced by about the same extent reported or more by oxygen administration, a high-carbohydrate meal, 20 ml of ethanol, 10 mg of benzedrine, hypoglycemia, and metabolic rate changes[57].

The same commentary as above applies to a study which involved combined effects of hydrogen sulfide and carbon disulfide on dark adaptation[58]. The small effect reported is not consistent between the two subjects.

There is simply insufficient information about the experimental conditions in these studies to rule out the many possible confounding variables for an effect as small as the one reported. Although intriguing, they are not, by themselves, adequate to use as a basis for the recommendation of exposure guidelines.

Mucosal Irritation

Fischer-344 rats exposed for 4 hours to hydrogen sulfide[59] had an increase in the overall cellularity of nasal lavage fluid of 139, 483, and 817% corresponding to exposure concentrations of 10, 200, and 400 ppm, respectively. Marked exfoliation of degenerated epithelial cells and exudation of netrophils were the basis for the increased cellularity. At a concentration of 400 ppm, there was a transient increase in protein levels in the nasal lavage fluid which indicates a corresponding transient change in vascular permeability. A transient increase in lactate dehydrogenase was also observed.

Exposure of Fischer-344 rats to 400 ppm for 4 hours[60] was associated with lesions of the anterior nasal cavity which were multifocal and located in regions of the dorsal meatus,

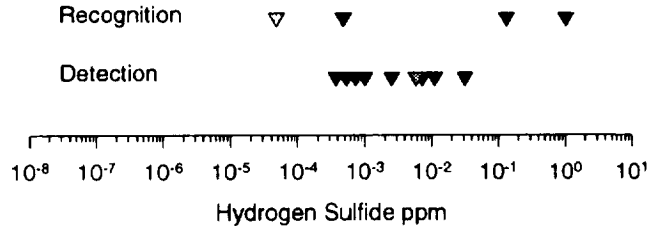
ethmoid conchae, and dorsolateral walls, but not the nasal septum. Lesions were not observed in squamous epithelium, and lesions of the respiratory epithelium showed evidence of repair within 44 hours after exposure, but lesions in the olfactory epithelium were still degenerating at 44 hours after exposure. The location of the lesions was considered typical of those from irritant gasses and the nature of the lesions was considered to be typical for injury of nasal epithelium[60].

Hydrogen sulfide olfactory thresholds

Sensory thresholds for hydrogen sulfide have been measured using many different procedures. Some investigators appear to be measuring detection of hydrogen sulfide which would be any detectable difference from pure air. Other investigators measure a recognition threshold where perception of the characteristic odor of hydrogen sulfide is relevant. In the only study located with both detection and recognition frequencies for different concentrations of hydrogen sulfide[61], the distribution of the frequency of detection reports had a lower median than the distribution of the frequency of recognition reports.

The variability within methods, when reported[62,56], generally has coefficients of variation (standard deviation as a percentage of the mean) of about 50% which is small relative to the differences in thresholds between methods of up to several log units.

Olfactory Thresholds



Hydrogen Sulfide Detection and Recognition Thresholds

Threshold Type	Method	ppm	Reference
100% Recognition	Not stated	1	(63)
Recognition	Not stated	0.13	(6)
Recognition (cylinder)	Room entry	0.00047	(64)
Recognition (from Na_2S)	Room entry	0.000047	(64)
Detection	Nasal tube	0.029	(61)
Detection	Not stated	0.011	(65)
Detection	Face port	0.0071	(66)
Detection	Face port	0.0058	(56)
Detection	Face port	0.0025	(62)
Detection	Not stated	0.001	(67)
Detection	Not stated	0.00072	(68)
Detection (subject 1)	Face port	0.00052	(69)
Detection (subject 2)	Face port	0.00037	(69)

Olfactory nerve desensitization

At concentrations above about 100 ppm, there is a loss of the apparent intensity of the odor of hydrogen sulfide after a few minutes of exposure. The reported loss of olfactory sensitivity is consistent with psychophysical magnitude estimation studies on the olfactory adaptation of n-propanol and n-pentanol[70]. In this study, the higher the adapting concentration, the higher the level at which magnitude estimates were non-zero.

In other words, the higher the concentration of the adapting stimulus, the higher was the concentration required to obtain a given level of pre-adaptation magnitude estimate. With hydrogen sulfide, the loss of olfactory sensitivity[42][6] makes reliance on smell for avoiding dangerous levels unsafe[9].

There are a variety of opinions about the effects of adaptation to hydrogen sulfide at concentrations near the detection threshold. Early investigators[68] asserted that the perceptible level of hydrogen sulfide was about 0.7 ppm and that "...the nose rapidly loses its power to distinguish such an odor." In warning that one could not, in general, depend on adaptation to reduce the awareness of odors, one review of the hydrogen sulfide perception [1] pointed out that the odor of hydrogen sulfide does not generally disappear completely, rather, it diminishes in apparent intensity.

Several approaches have been taken to the study of olfactory adaptation. Hydrogen sulfide was studied in a signal-detection oriented psychophysical procedure with continuous adapting stimuli[69]. The hydrogen sulfide target stimulus to be detected was 0.00053 ppm and only slightly above the detection thresholds for the two subjects. The hydrogen sulfide adaptation concentrations were 0.00029 and 0.00096 ppm. The test system used two face ports, one for the adaptation stimulus and one for the test stimulus which was either the target stimulus or pure air to assess the false alarm (guessing) rate. Subjects had numerous sessions in the adaptation port and every 20 seconds they were signaled to move to the detection port, take one breath of the sample stream and report either the presence or the absence of hydrogen sulfide. In this experiment, where the subjects were very near their detection threshold under optimal conditions, there was little evidence of adaptation to the hydrogen sulfide as measured by the detection performance to the target stimuli. In this experimental design, the variability in adaptation is confounded with the detectability of the target which could lead to a reduction in sensitivity to adaptation effects.

This research group also conducted a detection oriented adaptation using a group design with 24 female subjects[71]. In this situation there was clear adaptation to effluent which contained formaldehyde, phenol, and ammonia. The adapting and target stimuli were near the detection threshold. The adapting stimulus and pure air were alternated in the adaptation face port every 30 seconds. The detectability of the near threshold target stimulus increased for approximately 6 seconds and then decreased to an asymptotic level by 12 seconds after the start of the 30 second adaptation period. The authors reported d', a measure of detectability, not the proportions of hits (correct detections) and false alarms, however, by making the assumption that the false alarm rate was a given value, it is possible to convert the differences in d' to corresponding differences in the proportion of hits. If we assume that the false alarm rate was 20 percent, the corresponding maxima and minima of the detectability curve across the adaptation interval correspond to a change from about 95% hits to about 80% hits.

In summary, olfactory adaptation is most dramatic at relatively high levels of adapting stimulus, but it appears that adaptation can be measured to near-threshold adapting stimuli when the appropriate experimental design is used.

As an irritant, it is probably the case that perception of hydrogen sulfide involved the trigeminal nerve. The magnitude of the trigeminal nerve component was assessed in patients with unilateral olfactory nerve neurectomy, but intact trigeminal nerves[72]. This means that one nostril has normal perception and the other nostril has trigeminal-nerve-only perception, which was approximately 2/3 as sensitive. When butyl acetate was used as the odorant in a constant-sensation-level study where the subjects adjusted the simulus intensity to maintain a given perceived intensity, the subjects detected the stimulus at a lower intensity with the intact nostril and nervous system. In addition, both the intact and neurectomized sides showed adaptation over a period of slightly over 5 minutes. With normal subjects, and one of the two neurectomized subjects, adaptation was greater in both rate and magnitude with higher intensity stimuli as reflected in approximately doubling the level required to maintain a constant sensation over the adaptation interval.

Pulmonary Irritation

Bronchoalveolar lavage fluid from Fischer-344 rats exposed for 4 hours to hydrogen sulfide[59]at 400 ppm had increased levels of lactate dehydrogenase and alkaline phosphatase. This indicates cytotoxic changes in the pulmonary epithelium which correspond to the edmatogenic properties of hydrogen sulfide. In humans[9], rhinitis, pharyngitis, laryngitis, bronchitis, and pneumonia are consequences of inflammation of the respiratory tract. In addition[9], potentially life-threatening pulmonary edema can occur following exposures at concentrations over 250 ppm of sufficient duration.

A single 4-hour exposure of Fischer-344 rats to approximately 439 ppm of hydrogen sulfide produced marked but transient pulmonary edema and fibrinocellular alveolitis only in the proximal alveolar region of the lung and caused necrosis of ciliated bronchiolar cells[73].

After 4 hours of exposure of Fischer-344 rats to hydrogen sulfide at 0, 50, 200, or 400 ppm, the lungs were lavaged and pulmonary alveolar macrophages (PAM) collected and oxygen uptake measured[74]. The number of PAM collected was approximately the same in the different dose groups but the viability was lower in the 400 ppm group. Oxygen uptake was increased almost two-fold by zymosan stimulation in polymorphonuclear leukocytes (PMN) from the 0 and 50 ppm groups but not increased in PMN from the 200 and 400 ppm groups. Zymosan is used to stimulate particle-induced phagocytosis. *In-vitro* treatment of PAM with equimolar concentrations of sulfide, sulfite, and sulfate showed that only the sulfide group did not have a zymosan-stimulated increase in respiratory rate[74] which is consistent with the hypothesis that sulfide inhibits cytochrome-c.

Fischer-344 rats exposed for 4 hours[75] to 194 ppm of hydrogen sulfide had minimal microscopic signs of pulmonary edema consisting of focal areas of perivascular edema and occasional accumulations of proteinaceous material in alveoli. Although the microscopic signs of edema were minimal, there was a 17-fold increase in protein concentration relative to control and a 50% increase in lactate dehydrogenase in bronchoalveolar lavage fluid. Focal areas of red atelectasis were observed at necropsy.

When Fischer-344 rats were exposed to 290 ppm of hydrogen sulfide for 4 hours, pulmonary edema was more pronounced. Microscopic examination revealed patches of alveolar edema with substantial perivascular and peribronchial interstitial edema. Bronchoalveolar lavage fluid protein concentration was elevated 130-fold and lactate dehydrogenase activity more than doubled. Surfactant surface properties of adsorption to the water interface and surface tension reduction. The authors interpret this data as indicating that the causation of pulmonary edema by hydrogen sulfide is a threshold phenomena.

It is possible that there is a neural component of the defense against hydrogen sulfide produced exfoliation of respirator epithelia and pulmonary edema. Pretreatment with capsaicin to deplete substance P levels was associated with greater exfoliation and edema following exposure to approximately 400 ppm of hydrogen sulfide for 4 hours[76]. There was also increased lethality in the capsaicin pretreated group. This finding is consistent with the hypothesis that a subpopulation of vagal afferent C nerve fibers may be involved in pulmonary defense.

Cardiovascular Effects

Perhaps the most important effect of hydrogen sulfide on the vascular system with respect to acute lethality is the ability of hydrogen sulfide to produce rapid profound vasodilation and consequently a precipitous drop in blood pressure which is followed up to several minutes later by respiratory arrest. Physiological studies on cats which measured the diameter of a pial artery viewed through a cranial port, blood pressure, and apnea clearly showed the temporal relationships involved[11]. By analogy to fainting when the peripheral blood vessels become extremely dilated[77], the dramatic drop in blood pressure by approximately half in a little over 2 minutes is probably responsible for the initial hydrogen sulfide induced loss of consciousness or knockdown effect. This hypothesis is consistent with the observation that rhesus monkeys[51] exposed to hydrogen sulfide were described as appearing to be struck down when they became unconscious, an event which proceeded respiratory arrest.

Rats with a catheter for blood pressure measurement implanted in the tail vein were dosed intraperitoneally with sodium sulfide as a model of hydrogen sulfide exposure. Blood pressure dropped precipitously upon sulfide administration but the authors did not measure the vascular system and suggest, probably incorrectly, cardiogenic hypotension as the mechanism[78] of the blood pressure drop.

In addition to effects on vasomotor tone, hydrogen sulfide appears to have direct effects on cardiac function. Exposure of approximately one-year old mixed breed rabbits[79] to hydrogen sulfide at 71.9 ppm for 1.5 hours rendered the animals unconscious. Electrocardiograms at the end of exposure showed repolarization disorders indicated by inverted and flattened T waves. Arrhythmia was not seen. Additional information about these studies and the other parameters studied is available in a publication[80] in German.

Exposure of rabbits to 71.9 ppm for 0.5 hours repeated on 5 days[79] led to arrhythmias, primarily ventricular extrasystoles and bigeminal rhythm or multiple pacemakers, in 15 of the 17 animals. Repolarization disorders of the ventricles were observed including flattened T waves and/or temporary changes in the electrical axis in 7 of the animals. Administration of sodium citrate, which binds calcium ions, was reported to immediately restore normal rhythm. In some cases one dose was apparently sufficient to permanently restore normal rhythm, and in other cases the arrhythmia reappeared after several hours and was again treated with sodium citrate.

Qualitative analysis by histochemistry on sections of the hearts of the exposed animals indicated a decrease in the intensity of the stain for ATP phosphonohydrolase and a slight decrease in $NADPH_2$ oxidoreductase in myocardial cells which suggests a direct toxic effect of hydrogen sulfide on these cells[79].

Effects on Blood and Blood Components

Blood samples from humans acutely exposed to hydrogen sulfide in a very small sample was found to have lower than control levels of δ-aminolevulinic acid synthase[81]. Because levels of δ-aminolevulinic acid synthase were found to be below control levels in 8 of 17 workers examined who have occupational hydrogen sulfide exposure in the pulp industry, it has been suggested that hydrogen sulfide has the possibility of cumulative biological effects on heme synthesis[82]. This is the only suggestion of cumulative toxicity encountered in the hydrogen sulfide literature examined.

In-vitro studies[83] of polymorphonuclear leukocytes (PMN) from human blood exposed to 1 mM sulfide showed they were not impaired in their myeloperoxidase activity or ability to initiate a respiratory burst. Their ability to phagocytose and kill bacteria was only slightly reduced. Interestingly, products of the respiratory burst were able to rapidly oxidize sulfide.

Central Nervous System

Exposure to hydrogen sulfide for a few minutes at high concentrations but not resulting in unconsciousness appears to be able to produce a neuropsychological syndrome indicative of brain damage[84]. Paradoxically, it is possible to be rendered unconscious and recover without apparent residual injury[85,41]. If there is prolonged respiratory arrest, there will be signs of anoxic brain damage as shown in monkeys[51]. Because of the difficulty in obtaining accurate exposure information, the effects of hydrogen sulfide on the nervous system appear to be quite variable[86].

Adequate artificial ventilation more than doubles the LD_{50} for intraperitoneal sodium sulfite lethality. Because no neuronal necrosis was observed in major brain regions of animals surviving 1.2 to 1.6 times the unventilated LD_{50}, it has been suggested[78] that sulfide does not produce histotoxic necrosis but that cerebral ischemia may be the cause of central nervous system sequela to hydrogen sulfide poisoning.

Cases of workers whose exposure history included exposure to hydrogen sulfide have been reported with normal magnetic resonance imaging but abnormal neuropsychological and x-ray scintillation tomography[87].

It has been suggested[88] based on *in vitro* studies with neuroblastoma cells that reductions in sodium channel function in neurons may be the mechanism responsible for the reduction of central respiratory drive with hydrogen sulfide poisoning. Sulfide plus either taurine or cysteic acid reversibly abolished sodium channel currents in these studies[88].

Exposure of female mice for 2 hours to 100 ppm of hydrogen sulfide was caused by a decrease in labeled leucine incorporation in cerebral protein and myelin for 48 hours[89]. Incorporation of leucine was normal by 72 hours.

Measurement of performance on electric shock motivated avoidance tasks[90] with concurrent exposure and performance was used to estimate behavioral disruptions levels. Wistar rats were trained on either discriminated or non-discriminated avoidance task to press a lever to postpone a scheduled electric shock. The animals were tested during the two-hour hydrogen sulfide exposure. Relative to baseline levels, 300 to 400 ppm of hydrogen sulfide produced increase in response rates and increases in shocks taken on the non-discriminated avoidance task. At a level of 400-500 ppm the effect was more profound and there was a rebound type carryover effect to higher response rates when tested 24 hours after exposure which returned to baseline levels after 48 hours.

The discriminated avoidance task animals exposed to 400-500 showed decreases in average response rate, but did not show higher than baseline levels when tested 24 hours later.

On the discriminated avoidance task, there were dose related decreases in mean avoidance rates with increasing dose during exposure. The mean percent avoidances was decreased during the two-hour test session at concentrations above 200 ppm.

Rats on the non-discriminated avoidance task exposed to 400-500 ppm of hydrogen sulfide during an extinction test showed the most rapid decline in responding.

These measures of behavioral performance suggest that exposure levels relatively near those which are lethal to some strains of rats are required to produce significant behavioral disruptions. However it is important to note that the effects begin within the first 10 minute performance period which would not be expected to be near lethal levels. In addition, the relatively clear data suggests that the system being affected is quite consistent. It may be that hydrogen sulfide has effects on performance, perhaps generally depressant effects like those of other solvents, which have never been experimentally assessed.

The nervous system mediates the effects of hydrogen sulfide on respiration. Hydrogen sulfide in low concentrations stimulates respiration and high concentrations inhibits respiration[91]. At concentrations ranging from about 250 to 500 ppm hydrogen sulfide

appears to stimulate the carotid and aortic chemosensors[1,92] which leads to increased demand for increased central respiratory drive and increase the rate and depth of respiration[92]. At higher concentrations, hydrogen sulfide appears to directly reduce central respiratory drive which originates in the brainstem. There is evidence from animal studies that, even when regional differences in brain blood flow are taken into account, there is a selective uptake of sulfide by the brainstem[46], electrocardiographic changes associated with direct effects on heart muscle [79], and changes in amino acid neurotransmitter levels in the brainstem[93]. When whole rate brain homogenates were fractionated[46], approximately 27% of the endogenous sulfide was in the mitochondrial fraction. A dose of 50 mg/kg of NaHS administered by intraperitoneal injection more than doubled the sulfide levels in the myelin, mitochondrial, and synaptosomal fractions. The increase in the synaptosomal concentration implies that the sulfide is being accumulated in neurons.

When NaHS was administered to male Sprague-Dawley rats by intraperitoneal injection[46], there was a strong correlation between the logarithm of the dose administered, the percent mortality, and the brain sulfide level. There was an endogenous level of sulfide in the brain, and the brain sulfide level corresponding to the LD_{100} was only approximately 3-fold higher.

Administration of twice the LD50 (30 mg/kg) of NaHS by intraperitoneal injection[94] was associated with increased brainstem concentrations of catecholamines, dopamine, and 5-hydroxytryptamine which is consistent with the inhibition of monoamine oxidase activity observed at a dose of 100 mg/kg. This is a potential mechanism for interference with central respiratory drive.

Mechanisms of Action

Hydrogen sulfide appears to have more than one mechanism of action which is an interesting parallel to the historic observation that different types of hydrogen sulfide intoxication had completely different names when they were not known to be caused by the same agent.

In addition to the biochemical mechanisms of the toxicity of hydrogen sulfide, it is also reasonable to propose a physiological/behavioral component to the mechanism of the lethality of hydrogen sulfide at high concentrations where there appears to be a knockdown effect, especially in the relatively common multiple-attempted-rescuer fatalities. As discussed in the cardiovascular section of this document, the hypothesis is that before the events which ultimately cause death occur, such as diminution of central respiratory drive, there is a physiological response to hydrogen sulfide of profound vasodialation followed by a large drop in blood pressure which causes syncope which impairs the behavioral ability to escape from the exposure environment. This hypothesis of a cardiovascular/behavioral component at high dose exposure is a sequence of events different than that described in the classic hydrogen sulfide literature[91] which has been interpreted[52] as meaning that there is a loss of central respiratory drive followed by syncope.

The most important cellular mechanism of action of hydrogen sulfide appears to be similar to that of cyanide in that it is probably an intracellular toxin which disrupts electron transport and inhibits cytochrome oxidase *in vitro* and *in vivo*[47] with a potency *in vitro* similar to that of cyanide[95]. The concentration of hydrogen sulfide which inhibits mitocondrial respiration by 50% and the LD_{50} are within the 95% confidence interval bounds of a regression model describing the relationship between the two concentrations for a set of mitocondrial respiration inhibiting compounds[96]. This finding may be taken as weak evidence that inhibition of mitocondrial respiration accounts for most of the lethality from hydrogen sulfide.

Hydrogen sulfide in low concentrations stimulates respiration and high concentrations inhibits respiration[91]. At concentrations ranging from about 250 to 500 ppm hydrogen sulfide appears to stimulate the carotid and aortic chemosensors[1,92] which leads to increased demand for increased central respiratory drive and increase the rate and depth of respiration[92]. At higher concentrations, hydrogen sulfide appears to directly reduce central respiratory drive[1,91] which originates in the brainstem.

Medical Treatment

Cessation of exposure and artificial respiration and administration of oxygen are recommended [97]. Because hydrogen sulfide does not appear in the breath in high concentrations even after exposure up to 700 ppm[5], it would appear that the risk to rescuers in the administration of artificial respiration after the cessation of exposure would be minimal.

Methemoglobinemia Induction

While administration of nitrates to produce methemoglobin has a clear protective effect in animals when administered before exposure to hydrogen sulfide[98], the utility of the induction of methemoglobin following exposure is less clear because the lifetime of sulfide in oxygenated blood is only minutes in duration[99], if it has been used successfully[100,101].

In Germany, 4-dimethylaminophenol (DMAP) is used to induce metheglobinemia in the treatment of cyanide poisoning and has been suggested[102] for hydrogen sulfide poisoning to induce metheglobinemia very shortly after poisoning.

When performed very shortly after exposure and following adequate oxygenation, the standard procedure in the United States procedure is similar to that for cyanide poisoning. Amyl nitrite perles by inhalation (30 seconds per minute) until an intravenous line is obtained to deliver 10 ml of 3% sodium nitrite intravenously over 4 minutes[95,97].

Hyperbaric Oxygen

A study in rats showed that administration of hyperbaric oxygen at 3 atmospheres pressure is significantly more effective at preventing death than oxygen at 1 atmosphere

or sodium nitrite alone, and that a combination of sodium nitrite administration and oxygen at 3 atmospheres was best among the combinations tested[49].

Hyperbaric oxygen has been used successfully in a case of severe human hydrogen sulfide poisoning[103].

SUBCHRONIC AND CHRONIC EXPOSURE

Subchronic Data

General

Rats, Fischer-344[104] and Sprague-Dawley[105], and mice, B6C3F1[106], were exposed to hydrogen sulfide for 6 hours a day, 5 days a week, for at least 90 days at concentrations of 0, 10.1, 30.5, and 80 ppm. A statistically significant reduced body weight gain was noted in both sexes and both types of rats at 80 ppm. In the Fischer-344 rats and the male Sprague-Dawley rats, the mean body weights were more that 90% of control and the difference was not considered biologically significant. In female Sprague-Dawley rats, the body weights were < 90% of control and considered biologically significant. Brain weight was significantly reduced in male Sprague-Dawley rats which was declared the LOAEL. Clinical signs, ratings of neurologic function, opthalmoscopic examinations, hematology, serum chemistry, and urinalysis were all normal. In the rats, histopathology (including 4 sections of the nasal turbinates) did not detect abnormalities relative to controls. In the mice at 80 ppm, inflammation which was rated minimal to mild was observed in 8 of 9 males and 7 of 9 females. The lesion was in the anterior portion of the nose and included both squamous and respiratory epithelium. Thus, 80 ppm is considered a LOAEL in the mice with a NOAEL at 30.1 ppm.

Mice exposed to 71.9 ppm of hydrogen sulfide for 85 days had a two-thirds decrease in mean pulse rate[107].

Groups of 10 young male white rats were assigned to control or hydrogen sulfide exposures at 0.014 ppm, and 7.2 ppm[65] with exposures of 12 hours per day over a period of three months. Reduced weight gain was observed at 7.2 ppm but not in 0.014 ppm or controls. Slight irritation was reported in the thracheal and bronchial mucosa of the 7.2 ppm group and there were less pronounced changes in the 0.014 ppm group.

A summary of rat studies[28] involving exposure to hydrogen sulfide at 1, 10, or 100 ppm for 8 hours per day for 5 weeks reported no effect on airways resistance, dynamic compliance, tidal volume, minute volume or heart rate. Methacholine challenge revealed that some of the rats were hyperresponsive to the challenge. The hyperactive response to challenge was observed in some rats after exposure to 1 ppm of hydrogen sulfide. The authors comment that prolonged exposure may add more individuals to the sensitive group.

Rabbits were exposed to 20-25 ppm of hydrogen sulfide for 4 hours per day for 150 days in a study[108] where one of the animals was removed from the study after 30 days and a

second did not gain weight during the exposure and lost weight in the 60-day follow-up period. In a study in rabbits, "long term" exposures were performed at 100 ppm and only slight histological changes were found in the liver, kidney, and testis[109].

Rhesus monkeys were exposed to 20 ppm of hydrogen sulfide continuously for 90 days without lethality. Lung pathology was detected in 50% of the animals upon histopathologic examination, but it is not much higher than the 40% incidence in the control group[110]. If is extremely unfortunate that this study did not include detailed clinical or ophthalmic examinations.

Nervous System

Groups of 10 young male white rats were assigned to control or hydrogen sulfide exposures at 0.014 ppm, and 7.2 ppm. Exposures were 12 hours per day over a period of three months and flexor and extensor chronaxie were measured. In the control group, the flexor chronaxie was less than the extensor chronaxie throughout the experiment, but in the 0.014 ppm group the values were similar for weeks 3 through 9, and the curves were reversed for many of the weeks in the 7.2 ppm group. The authors interpret their results as reflecting changes in the cerebral cortex[65].

Golgi stained brain sections from rats in the 7.2 ppm group had dendritic changes, thickening and swelling, which were not observed in the other groups.

Developmental Toxicity

In a pilot study with female Sprague-Dawley rats exposed to 0, 50, 100, or 150 ppm of hydrogen sulfide 6 hours per day[111] during gestational days 6 to 20, 100 ppm was identified as a NOAEL for maternal effects and developmental effects because there was significant maternal weight loss at 150 ppm.

In a study[112] which included postpartum exposure, Sprague Dawley rats were exposed 7 hours per day from gestational day 5 through day 21 postpartum. Statistically significant early pinna detachment and hair development was observed. Earlier hair development was also seen at 50 ppm and neither was affected at 75 ppm. In addition, there was a dose-related trend toward longer parturition times at the higher doses with an elevation of 142 percent relative to the controls at 75 ppm.

Pregnant Sprague Dawley exposed 7 hours per day from day 5 after mating until postnatal day 21 to hydrogen sulfide at concentrations of either 20 or 50 ppm had alterations of the cerebellar Purkinje cell dendritic fields and their growth characteristics[113] when analyzed in Golgi stained preparations.

Gravid Sprague-Dawley rats were exposed for 7 hours per day to 20, 50, or 75 ppm throughout gestation, and for 21 days post partum [114]. Clinical chemistry measures were made on postpartum days 7, 14, and 21. Serum glucose levels were elevated at all doses but glucose levels in the pups and triglyceride and cholesterol levels were not significantly from control except an elevated cholesterol value for cholesterol in the 50

ppm group after 21 days of exposure of the pups. Levels of alkaline phosphatase, lactate dehydrogenase, serum glutamic oxaloacetic transaminase, and serum protein were unchanged.

Chronic Exposure Data

Human

Early industrial hygiene investigations in a viscose rayon plant indicated that if the overall plant average level was below 20 ppm, there were no cases of conjunctivitus reported, but, at levels above 20 ppm, conjunctivitus reports were frequent[54]. Viscose rayon plants also involved exposure to carbon disulfide. The author suggests that carbon disulfide and atomized spinning bath liquid cause hypersensitivity to hydrogen sulfide[54]. Other than the conjunctivitus, there do not appear to be sensory system toxicities reported in the hydrogen sulfide literature[115].

Chronic Hydrogen Sulfide Syndrome

The existence of a chronic intoxication syndrome with hydrogen sulphide has been questioned[42,116], and discussed[9].

The concensus of the literature appears to be that the potential for cumulative action is small and that low concentrations, e.g. 20 ppm, are without harm over long exposure periods[9]. In the environmental context, a much lower standard has been recommended by a state environmental resource center as described in a review[9]. The level recommended by the state environmental group is 0.01 ppm of hydrogen sulfide and is apparently based on subjective complaints such as fatigue and nausea and an objective of protecting hypersusceptible individuals with an uncertainty factor which appears to be approximately 9 relative to the lowest concentration mentioned as producing subjective complaints.

Epidemiological Data

An epidemiology study involving factor analysis of associated factors in 6500 cases of occupational eye irritation "spinner's eyes" led the author[117] to conclude that eye irritation occurred after 6 to 7 hours at 10 ppm of hydrogen sulfide and after 4 to 5 hours at 14 ppm. Concurrent exposure to carbon disulfide increased the sensitivity to hydrogen sulfide. Although few details are presented in the paper, it claims to represent 6500 cases of eye irritation. It is useful to note that Haber's rule approximately holds for these data points.

Carcinogenesis Studies

Useful information about the relationship between hydrogen sulfide and carcinogenesis was not located. A study of a related compound sulfide compound which did not find evidence of cancer was considered unreliable in assessing the probability of carcinogenesis of hydrogen sulfide[9].

SYNERGISTIC EFFECTS

Concurrent Chemical Exposure

It is possible that concurrent carbon disulfide exposure combined with an aerosol of aqueous trithiocarbonate aviscose rayon spinning bath solution stimulant increases the sensitivity of the conjunctiva and cornea to hydrogen sulfide exposure[54]. Investigators of hydrogen sulfide effects in industrial settings frequently comment that concurrent carbon disulfide exposure increases the sensitivity of the eye to hydrogen sulfide[55,54,117].

Rabbits exposed to hydrogen sulfide at 36-71 ppm at a relative humidity of 90% for 5 days did not have corneal lesions and neither did rabbits exposed to carbon disulfide at a level of 23 ppm for 5 days and 50 ppm for two additional days. Exposure[55] to 36-71 ppm of hydrogen sulfide concurrently with 13-17 ppm of carbon disulfide in one animal and 23 ppm in another gave rise to corneal lesions after 3 and 2 days, respectively. Exposure to 14 - 28 ppm of hydrogen sulfide and 23 ppm of carbon disulfide for 5 days produced no lesions, but when the hydrogen sulfide concentration was increased to 36 - 71 ppm corneal edema and mucus hypersecretion quickly developed.

Decreases in pulse rate and forced swimming time have been described in mice exposed to 0.1 mg/l (71.9 ppm) in combination with 20 mg/l butylene with approximately 85 days of exposure with the conclusion that lower hydrocarbons enhance the toxicity of hydrogen sulfide[107].

In Sprague-Dawley rats exposed to 400 or 800 ppm of carbon disulfide 6 hours per day during days 6 through 20 of gestation, the carbon disulfide effects of reduced maternal weight gain, reduced fetal body weight, and a low incidence of club foot observed were enhanced[111] by concurrent exposure to 100 ppm of hydrogen sulfide.

The synergism of carbon disulfide and hydrogen sulfide was studied[118] with groups of animals with five groups. In addition to the control group there were two groups exposed to carbon disulfide alone at 0.1 and 1 mg/m^3 and two additional groups with the same concentrations of carbon sulfide plus hydrogen sulfide corresponding to 0.07 or 0.7 ppm, respectively. Synergism relative to carbon disulfide alone at the same concentration was observed with both hydrogen sulfide concentrations on alanine aminotransferase, urinary coproporphyrin, serum acetylcholinesterase, but not with body weight gain.

A 70-day exposure of 24 hours per day[58] did not reveal synergistic effects in an animal study with carbon disulfide at 0.008 mg/m^3 and hydrogen sulfide at 0.01 mg/m^3.

Teratologic effects have been reported in the offspring of rats following prolonged exposure to low concentrations to a mixture of hydrogen sulfide and carbon disulfide[119].

Rhesus monkeys exposed to mixtures including hydrogen sulfide at 20 ppm with methyl mercaptan at 50 ppm, indole at 10.5 ppm, and scatole at 3.5 ppm[120,110] had 80 percent mortality which was not explained by the lethality of the component gases tested. It is possible that the mixture of sulfer compounds either has interactive toxicity, i.e. exposure

to compound A sensitizes to the lethality of exposure to compound B, or, perhaps, the mechanisms to handle the load of sulfur containing compounds were overwhelmed. Unfortunately, detailed information is not presented in the report about the timing of the primate deaths.

Exercise

Healthy young men were studied while inhaling 0, 0.5, 2 and 5 ppm of hydrogen sulfide during graded exercise on a cycle ergometer[121] during submaximal and maximal exercise. Heart rate and expired ventilation were unaffected. There was an increase in blood lactate levels at 5 ppm but the maximal power output was not significantly altered. The authors concluded that healthy young males can exercise at their maximum metabolic rate while breathing 5 ppm hydrogen sulfide during short-term graded exercise.

Age

It has been reported that the effects of hydrogen sulfide on dogs may be influenced by age. Blood from puppies was much slower at oxidizing hydrogen sulfide than was blood from adult dogs[21].

TOXICITY SUMMARY TABLE

Conc.	Exposure Duration	Species	Effects	Reference
0.13 ppm	Instant	Human	Odor Recognition Threshold.	(6)
0.014 ppm	12 h day for 3 months	Male white rat	"Slight to negligible" change in flexor and extensor chronaxie and barely perceptible mucosal irritation.	(65)
4.6 ppm	Instant	Human	Odor "Really noticeable"; moderate intensity.	(6)
7.2 ppm	12 h day for 3 months	Male white rat	Decreased weight gain, clear changes in flexor and extensor chronaxie, mucosal irritation, and abnormal dendrites in Golgi stained cerebral cortex sections.	(65)
10 ppm	4 h	Fischer-344 rat	Increased cellularity in the nasal cavity, primarily degenerated epithelial cells and exuded neutrophils.	(59)
20 ppm	Work day/ work week	Human	Average viscose rayon plant level below which conjunctivitis was not observed.	(54)
20 ppm	90 days, continuous	Mice	26 of 100 mice died. Half of the mice had liver pathology and 33 percent had lung pathology.	(110)
20 ppm	90 days, continuous	Sprague-Dawley rat	12 of 50 rats died. One third of the rats had lung pathology.	(110)
20 ppm	90 days, continuous	Rhesus monkey	None of 10 monkeys died, but 50 percent had lung pathology compared to 40% of the controls.	(110)
20 ppm	7 hr/day	Sprague-	Statistically significant earlier pinna detachment	(112)

Conc.	Exposure Duration	Species	Effects	Reference
	gestational day 6 through day 21 postpartum	Dawley rat, 80-90 days old	and hair development. Earlier hair development was seen at 50 ppm and neither was affected at 75 ppm.	
20 ppm	7 hr/day gestational day 6 through day 21 postpartum	Sprague-Dawley rat, 80-90 days old	Alterations (severe) in organization and growth characteristics of Purkinje cell dendritic fields.	(113)
20 to 25 ppm	4 hours per day for 150 consecutive days	Rabbit	One rabbit removed from study after 30 days and a second did not gain weight during the exposure period.	(108)
27 ppm	Instant	Human	Odor "Strong, cogent, forceful, not intolerable".	(6)
30.5 ppm	6 hr/day, 5 days/week, 90 days	B6C3F1 mouse	NOAEL	(106)
36 - 71 ppm	5 days	Albino rabbit	No corneal lesions when exposed with 90% relative humidity. Number of subjects and hours per day of exposure were not specified.	(55)
36 - 71 ppm	3 days	Albino rabbit	When exposed with 90% relativity and carbon disulfide at 23 ppm in one subject or after 2 days with 17-23 ppm in another. Hours per day of exposure was not specified. Carbon disulfide alone for 5 days at 23 ppm and 2 additional days at 50 ppm did not produce lesions in 2 rabbits studied.	(55)
50 ppm	4 h	Fischer-344 rat	Lung mitocondrial cytochrome c oxidase decreased ($p < 0.05$) 15 % relative to control.	(47)
50 to 100 ppm	1 h	Human	Mild conjunctivitis and respiratory tract irritation.	(6)
71.9 ppm	1.5 h	Adult rabbit	Animals lost consciousness. ECG showed repolarization disorders but not arrhythmia.	(79)
71.9 ppm	0.5 h x 5 d	Adult rabbit	Ventricular extrasystoles and bigeminal rhythm or multiple pacemakers observed in 15 of 17 animals.	(79)
80 ppm	6 hr/day, 5 days/week, 90 days	Sprague-Dawley rat	LOAEL: females had decreased body weight less than 90% of controls and statistically significant decreased brain weight in males.	(105)
80 ppm	6 hr/day, 5 days/week, 90 days	Fischer-344 rat	NOAEL: body weight decreased but > 90% of controls.	(104)
80 ppm	6 hr/day, 5 days/week, 90 days	B6C3F1 mouse	LOAEL: inflammation of nasal mucosa in anterior segment of the nose in 8 of 9 males and 7 of 9 females; decreased weight gain in last weeks of study.	(106)
100 ppm	2 h	CB-20 mouse	Decreased leucine incorporation in brain protein and myelin 24 and 48 hours after exposure.	(89)

Conc.	Exposure Duration	Species	Effects	Reference
100 ppm	6 hr/day gestational days 6 to 20	Sprague-Dawley rat	NOAEL for maternal effects and developmental effects.	(111)
100 to 150 ppm	Many hours	Dog	Local irritation.	(50)
194 ppm	4 hours	Fischer-344 rat	17-fold increase in protein concentration relative to control and 50% increase in lactate dehydrogenase activate in bronchoalveolar lavage fluid. Microscopic examination showed focal areas of perivascular edema and occasional accumulations of proteinaceous material in alveoli.	(75)
200 to 300 ppm	1 hour	Dog	Local irritation and slight general symptoms if inhaled longer.	(50)
200 to 300 ppm	2 hours	Wistar rat	Decreased discriminated avoidance performance to avoid electric shock.	(90)
290 ppm	4 hours	Fischer-344	Focal areas of red atelectasis were observed at necropsy. Microscopic examination revealed patches of alveolar edema with substantial perivascular and peribronchial interstitial edema. Bronchoalveolar lavage fluid protein concentration was elevated 130-fold and lactate dehydrogenase activity more than doubled. Surfactant surface properties of adsorption to the water interface and surface tension reduction.	(75)
300 to 400 ppm	2 hours	Wistar rat	Decreased response rate and increased number of shocks taken on non-discriminated (Sidman) avoidance.	(90)
400 ppm	4 h	Sprague-Dawley rat	3 of 10 died at this concentration which was the lowest tested.	(48)
400 ppm	4 h	Fischer-344 rat	Decreased bronchoalveolar cell counts and increased protein concentrations increased 30-fold in lung lavage fluid.	(59)
444 ppm 95% C.I. 416-473	4 h	Sprague-Dawley rat	LC_{50} value.	(48)
200 to 300 ppm	1 h	Human	Marked conjunctivitis and respiratory tract irritation.	(6)
500 ppm	Few minutes to an hour	Human	Respiratory arrest, unconsciousness.	(9,28).
500 ppm	Typically, less *than 15 minutes*	Rhesus monkey	Unconsciousness, described as if struck down.	(51)
500 ppm	22 minutes	Rhesus monkey	Animal was unconscious for over 2 hours and was somnolent, had decreased food consumption	(51)

Conc.	Exposure Duration	Species	Effects	Reference
			and uncoordinated movements. Only slight improvement was noted by sacrifice 10 days after exposure. Microscopic examination showed parietal and occipital cortex necroses, decreases in the number of cerebellar Purkinje cells. Heart, liver, kidneys, and adrenals were normal.	
500 ppm	35 minutes	Rhesus monkey	Respiratory and cardiac arrest, death. Histopathologic changes were not seen in the heart, brain, kidneys, or adrenals.	(51)
500 ppm	25 minutes then 17 minutes 3 days later	Rhesus monkey	Initial exposure ended at respiratory arrest. Resuscitation by thoracic wall compressions. Second exposure ended when the monkey lost consciousness. Following sacrifice 5 days later, microscopic examination showed necrosis in the occipital cortex, necrosis, gliosis, and hyperemia of the basal ganglia, and a decreased number of cerebellar Purkinje cells. Moderate liver hyperemia was noted, but the heart, kidneys, and adrenals were normal.	(51)
>500 ppm	4 h	Fischer-344 rat	Death with 90% decrease in cytochrome c oxidase activity.	(47)
500 to 700 ppm	< 1 hour	Dog	Local irritation and slight systematic symptoms within 1 hour. May cause death after several hours of exposure.	(50)
500 to 700 ppm	0.5 to 1 h	Human	Dangerous subacute poisoning.	(6)
700 to 1000 ppm	Brief	Human	Possible acute poisoning: rapid unconsciousness, cessation of respiration, and death.	(6)
900 ppm	< 30 minutes	Dog	Systemic symptoms.	(50)
900 ppm	< 1 hour	Dog	Possible death.	(50)
1000 ppm	Immediate (1 to 2 breaths)	Human	Collapse and death of 5 adult males.	(37)
1000 to 2000 ppm	Brief	Human	Rapid unconsciousness, cessation of respiration and death in a few minutes.	(6)
1500 ppm	15-30 minutes	Dog	Death.	(50)
1655 ± 391 ppm	5 m	Sprague-Dawley rat	Death within the 5 minutes with severe pulmonary edema.	(45)
> 1800 ppm	Almost immediate	Dog	Death.	(50)
2000-4000	Immediate (1 to 2 breaths)	Human	Collapse and death of an adult male.	(33)

EXPOSURE LIMITS SET BY OTHER ORGANIZATIONS

Organization	Limit	Type	Concentration	Duration	Reference
OSHA (Final)	PEL	TWA	10 ppm	8 hours	(2)
OSHA (Final)	STEL	STEL	15 ppm		(2)
OSHA (Transitional)	PEL	Ceiling Level	20 ppm		(122)
OSHA (Transitional)	PEL	Peak	50 ppm	10 minutes	(122)
MSHA		TWA	10 ppm		(2)
France	OEL	TWA	5 ppm		(2)
France	OEL	STEL	10 ppm		(2)
ACGIH	TLV	TWA	10 ppm	8 hours per day and 40 hours per week	(123)
ACGIH	TLV	STEL (TWA)	15 ppm	up to 15 minutes up to 4 times per day	(123)
NIOSH	REC	Ceiling	10 ppm	10 minutes	(122)
NIOSH	IHLH		300 ppm		(122)
IERC		TWA	0.01 ppm	8 hour average	(9)
EPA	RfC		0.0013 ppm		(3)

*Table of Abbreviations

OSHA	Occupational Safety and Health Administration
ACGIH	American Conference of Governmental Industrial Hygienists
NIOSH	National Institute of Occupation Safety and Health
TWA	Time-weighed average
TLV	Threshold limit value
PEL	Permissible exposure level
STEL	Short-term exposure limit
OEL	Occupational exposure limit
REC	Recommended Exposure Ceiling
IHLH	Immediately Hazardous to Life and Health
IERC	Illinois Environmental Resource Center
EPA	Environmental Protection Agency
RfC	Reference Concentration

The transitional OSHA limits were in effect during a transition period between September 1989 and December 1992 when the final rule limits became effective. The IERC level is a recommendation.

SPACECRAFT MAXIMUM ALLOWABLE CONCENTRATIONS

TABLE

Duration	1 Hour	24 Hour	7 Day	30 Day	180 Day
ppm Hydrogen sulfide	25	2	0.003	0.003	0.0003

RATIONALE

The seriousness of the effects of exposure to hydrogen sulfide decreases with decreasing exposure from sudden lethality at concentrations above about 1000 ppm, through pulmonary irritation at moderate concentrations of 50 to 100 ppm or more over a few hours; eye irritation at lower concentrations on the order of 20 ppm, and to offensive odor at concentrations of a few ppm. There appears to be sufficient separation in the levels giving rise to the effects that a safety guideline which protects against an effect at a given level will protect against those at higher levels in the rank ordering. In other words, a safety guideline based on eye irritation will, in virtually all cases, protect against pulmonary irritation and lethality.

In parallel to the NRC distinction of acute, subacute, and chronic hydrogen sulfide intoxication, the rationale for the recommended SMAC value is different for 1 hour, 24 hours, and longer durations because they are based on protection against different effects.

Because the toxic effects of hydrogen sulfide are noncarcinogenic, it is appropriate to apply an uncertainty factor approach to obtain the SMAC values. There is very little good data but an adequate amount of fair data on human exposures to make weight of evidence judgments about appropriate exposure levels. The general approach used with hydrogen sulfide was to use relatively small uncertainty factors applied to human data and compare the level obtained with alternative calculations or relevant animal data.

The general formula for calculating a reference dose is:

$$RfD = \frac{NOAEL}{UF_1 \bullet UF_2 \bullet UF_3 \bullet UF_4 \bullet UF_5 \bullet MF}$$

The uncertainty factors used in the formula are defined in the table below. Unless otherwise mentioned in the rationale, the value used for the factor is 1.

Factor	Purpose	Range	Default value

			used in this document
UF1	Accommodate human variability	1 - 10	1
UF2	Extrapolation from animals to humans	1 - 10	1
UF3	Extrapolation from subchronic to chronic exposure	1 - 10	1
UF4	Extrapolation from LOAEL to NOAEL	1 - 10	1
UF5	Database inadequacy factor	1 - 10	1
Modifying	Expert opinion factor	1 - 10	1

1-Hour SMAC

The 25 ppm 1-hour value is based on prevention of conjunctivitis by taking the low end of the range of human exposure to hydrogen sulfide, which is reported to cause mild conjunctivitus and pulmonary effects [6] at a value of 50 ppm and applying a modifying factor of 2 in the reference dose equation. The modifying factor is intended to make the level correspond to an average concentration instead of a ceiling value.

A modifying factor of 2 is appropriate when starting with the 1-hour human exposure report because there is summarized human data to the effect that hydrogen sulfide exposure concentrations from 200-300 ppm are associated with "marked" conjunctivitis and respiratory tract irritation while 50-100 ppm produces "slight" conjunctivitis and respiratory tract irritation after one-hour of exposure[6]. Because 50 ppm of hydrogen sulfide is on the low end of range for "slight" conjunctivitis and irritation, a modifying factor of 2 should eliminate most irritation and let the level correspond to an average instead of a peak value.

The suggested value of 25 ppm is close to the 20 ppm level described as being without problems [54] in an occupational setting even with carbon disulfide present in concentrations up to 30 ppm. Thus the occupational value back extrapolated to 1 hour gives approximately the same value as direct 1-hour data with a modifying factor.

Although based on human data, the proposed 1-Hour SMAC level is also below the 36-71 ppm of hydrogen sulfide in a mixture with about 20 ppm of carbon disulfide which caused corneal lesions in rabbits after 3 to 5 days[55]. Because carbon disulfide appears to increase the sensitivity of the eye to the effects of hydrogen sulfide, the rabbit and human data can be considered in good agreement.

At the concentration level of 25 ppm proposed for the 1-Hour SMAC however, the odor can be expected to be very intense[6].

24-Hour SMAC

The 24-Hour SMAC is proposed as 2 ppm based upon application of Haber's rule to the value of 10 ppm associated with human eye irritation after 6 hours[117] by dividing the value by 4 and rounding down.

This is slightly more liberal than the 1 ppm which would be obtained by applying Haber's rule to the 1-Hour proposed SMAC value and dividing by 24.

Applying Haber's rule to the ACGIH work day exposure standard for hydrogen sulfide[123] of 10 ppm for an 8-hour day and dividing by 3 gives a rounded value of 3 ppm so the lower value of 2 ppm derived above is slightly more conservative.

A continuous exposure study with rhesus monkeys for 90 days provides a check on the safety of the 24-Hour SMAC level by bridging from the 8-hour per day work day to a continuous exposure scenario. Clinical observations were not reported in the monkey study, so the important finding is that there was no lethality[110]. In other words, the study provides no evidence to suggest that continuous exposures are different in kind from partial day exposures.

7-Day SMAC

The 7-Day SMAC is proposed as 0.003 ppm based upon the approximate midpoint of the range of thresholds reported for hydrogen sulfide detection/recognition with the default uncertainty and modifying factor values of 1. There is variability between methods for measuring the hydrogen sulfide detection threshold which is larger than the inherent differences in sensitivity between individuals. The value used as representative of the odor detection threshold is intended to represent the lower end of casual perception, not the detection thresholds which may be obtained in signal detection oriented or other specialized psychophysical procedures. For the 7-day SMAC value, this should provide a level which is near the threshold of detection reported across studies when observations are made under optimal conditions. The subjective intensity of the odor of hydrogen sulfide will be reduced in apparent intensity by some extent due to both adaptation to the odor of hydrogen sulfide [1,68] and other background odors which also will make hydrogen sulfide more difficult to detect in an ambient background than in pure air. The objective is to set the level such that there is minimal perception of the odor of hydrogen sulfide, an approach which has been recommended in setting allowable terrestrial ambient levels[61].

Use of odor detection threshold as the reference effect in setting the SMAC values for 7-day and longer exposures should protect against all the other effects of hydrogen sulfide because of the rank order of the effects and because the concensus of the literature is that hydrogen sulfide does not manifest cumulative toxicity. There is approximately a thousand-fold difference, effectively, an uncertainty factor, between the SMAC value and

the level which was reported as producing dendritic alterations in continuously exposed rats. The lack of cumulative toxicity is consistent with the data which indicates that the body endogenously generates and has mechanisms to metabolize hydrogen sulfide. The existence of the metabolic paths and the ubiquitous nature of endogenous hydrogen sulfide generation makes it reasonable to consider hydrogen sulfide a threshold type of toxicant which does not cause problems unless the detoxification capacity is exceeded. Continuous exposure of rhesus monkeys for 90 days to hydrogen sulfide at 20 ppm did not result in lethality and did not detect unique toxicity[110] which is additional evidence that hydrogen sulfide is a threshold toxicant.

30-Day SMAC

By the same reasoning as for the 7-Day SMAC, the 30-Day SMAC is proposed as 0.003 ppm.

180-Day SMAC

By the same general reasoning as for the 7-Day SMAC, the 180-Day SMAC is proposed as 0.0003 ppm by changing the UF3 value to 10 because of the lack of continuous exposure data over 90 days. This level is approximately one third of the EPA inhalation reference dose[3] calculated based on rodent mucosal irritation with an uncertainty factor product of 1000 and a modifying factor value of 1.

Synergistic factors

The most salient synergistic factor is concurrent carbon disulfide exposure which is considered to increase the sensitivity of the eye to hydrogen sulfide[55,117]. Because the carbon disulfide levels involved in animal studies were about 20 ppm and higher in the factory exposures[6] and because the ACGIH level for carbon disulfide is 10 ppm[123] it is very likely that the eventual carbon disulfide SMAC value will not be significantly more than 20 ppm, and, therefore, the group-limit concept for combining SMAC values for mixtures[124] should be adequately protective.

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