0061

Hydrogen sulfide; 7783-06-4; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Substance name

File First On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)		
Inhalation RfC Assessment (I.B.)		
Carcinogenicity Assessment (II.)		

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name – Hydrogen sulfide

CASRN -- 7783-06-4

Last Revised -- 00/00/0000

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

No appropriately executed oral subchronic study of H_2S was found. Therefor, no oral RfD was derived due to database deficiencies.

I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name – Hydrogen sulfide
CASRN -- 7783-06-4
Last Revised -- 00/00/0000

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and

Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
Nasal lesions of the olfactory mucosa	NOAEL: 13.9 mg/m^3 (10 ppm) NOAEL (ADJ): 3.48 mg/m^3 NOAEL (HEC): 0.64 mg/m^3	300	1	2E-3 mg/m^3
Rat Subchronic Inhalation Study	LOAEL: 41.7 mg/m^3 (30 ppm) LOAEL (ADJ): 10.4 mg/m^3 LOAEL (HEC): 1.91 mg/m^3			

Brenneman et al. (2000)

*Conversion Factors and Assumptions -- MW = 34.08. Assuming 25 C and 760 mmHg, NOAEL (mg/cu.m = 10 ppm x 34.08/24.45 = 13.9 mg/m^3. NOAEL(ADJ) = 13.9 mg/m^3 × 6 hours/24 hours = 3.48 mg/m^3. The NOAEL(HEC) was calculated for a gas:respiratory effect in the extrathoracic region. $V_{E(rat)}$ = 0.19 liters/minute, $V_{E(human)}$ = 13.8 liters/minute, SA_{rat} = 15 cm^2, SA_{human} 200 cm^2. $RGDR_{ET} = (V_E/SA_{ET})_{rat}/(V_E/SA_{ET})_{human}$ = (0.19/15)/(13.8/200) = 0.184 = NOAEL(ADJ) x RGDR = 0.64 mg/m^3

**The study by Brenneman et al. (2000) replaces the study by CIIT (1983a) as the principal study for RfC determination. The previous RfC determined from the study by CIIT (1983a) was 2.1E-3mg/m^3.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Brenneman, K.A., James, R.A., Gross, E.A., and Dorman, D.C. (2000) Olfactory loss in adult male CD rats following inhalation exposure to hydrogen sulfide. Toxicologic Pathology 28(2): 326-333.

Brenneman and coworkers (2000) exposed 10-week-old male CD rats (12/exposure group) to 0, 10, 30, and 80 ppm (0, 14, 42, and 111 mg/m^3) H_2S for 6 hr per day, 7 days per week, for 10 weeks. At the end of the 10 week exposure, animals were euthanized with CO_2 and the noses of the animals were dissected free. The nasal cavities were examined at 6 different cross-sectional levels for lesions. The lesions were graded in severity by a subjective scale: 0 = normal; 1 = mild; 2 = moderate; 3 = marked; and 4 = severe. No effects were observed in the control or 10 ppm exposure animals that were considered treatment-related. Nasal lesions of the olfactory mucosa were observed in the 30 and 80 ppm (42 and 111 mg/m^3) exposure animals and consisted of multifocal, bilaterally symmetrical olfactory neuron loss and basal cell hyperplasia affecting the lining of the dorsal medial meatus and dorsal and medial region of the ethmoid recess. The severity of the observed lesions varied between mild and severe. At level 3 of the nose, the most rostral margin of the olfactory epithelium is integrated with the rostral portion of the respiratory epithelium. Olfactory neuron loss was only observed in 80 ppm (111 mg/m^3) exposure animals at this level of the nose. At level 4 of the nasal cavity, mild to moderate olfactory neuron loss was observed in the 30 ppm (42 mg/m^3) exposure animals, which increased in severity to moderate or severe in the 80 ppm (111 mg/m^3) exposure animals. Basal cell hyperplasia was observed in both exposure groups at this level of the nasal cavity but was more pronounced in the 30 ppm exposure group. At level 5 the nasal cavity, mild to moderate olfactory neuron loss and mild basal cell hyperplasia mainly affecting the nasal septum, dorsal nasal cavity, and marginal ethmoturbinate was observed both exposure groups, except the nasal septum which was not affected in the 30 ppm exposure group. The same pattern and severity of lesions were observed at level 6 except only the 80 ppm (111 mg/m^3) exposure group was affected.

The Chemical Industry Institute of Toxicology (CIIT, 1983 a,b,c) exposed male and female $B_6C_3F_1$/CrlBr mice, Sprague Dawley rats, and Fischer 344 rats to 0, 10.1, 30.5, or 80.0 ppm (14, 42, and 111 mg/m^3) H_2S for 6 hr/day, 5 days per week for 90 days (10 mice/sex/group, 15 Sprague Dawley rats/sex/group). In mice, body weight gain depression between week 0 and week 13 of exposure was 30% and 40% in high-dose males and females, respectively. Feed consumption was significantly reduced in the high-exposure animals. Gross pathology of surviving animals also revealed no gross lesion that were considered compound-related. Histological examination of surviving animals revealed only one lesion that was considered compound-related. Male (8/9) and female (7/9) mice exposed to 80 ppm (111 mg/m^3) H_2S exhibited minimal to mild inflammation of the anterior portion of the nasal mucosa. No other histological findings were considered compound-related. In Sprague Dawley rats, body weight gain depressions of 11.7% and 20% were evident in male and females exposed to 80 ppm H_2S, respectively. None of the histopathologic changes were considered treatment-related by the study authors. In Fischer 344 rats, weight gain depressions of 9.8% and 10.9% were evident in male and females exposed to 80 ppm (111 mg/m^3) H_2S, respectively. Sulfhemoglobin levels were significantly increased in males exposed to 80 ppm (111 mg/m^3) H_2S. None of the histopathologic changes were considered treatment-related by the study authors.

Dorman et al. (2000) exposed adult male Spague-Dawley rats to 0, 10, 30, or 80 ppm (14, 42, and 111 mg/m^3) H_2S 6 hr/day, 7 days/week for 70 consecutive days. No deaths or adverse clinical signs were observed in F_0 males for any exposure group. Male rats from all exposure groups displayed mild to marked sensory neuron loss and basal cell hyperplasia in the olfactory mucosa lining the dorsal medial meatus and the dorsal medial region of the ethmoid recess (only males were examined). However, the study authors do not state if there was a dose-response relationship for these observed effects. The study authors noted a higher incidence of seminiferous tubular degeneration (intratubular sperm stasis, tubular mineralization, sperm granulomas, and multinucleated giant cells) and epididymal changes (degenerate sperm forms in the lumen, aspermia, and oligospermia) in the 80 ppm (111 mg/m^3) exposure. Also, one incidence each of sperm granuloma and unilateral necrosis of the cauda was present in the 80 ppm (111 mg/m^3) exposure group.

___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF = The uncertainty factor of 300 represents 3 ($10^{1/2}$) for interspecies extrapolation, 10 for sensitive populations, and 10 for subchronic exposure. The interspecies uncertainty factor of 3 was used rather than 10 because a dosimetric adjustment from rat to human was used.

MF = None

___I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

The study by Brenneman et al. (2000) replaces the study by CIIT (1983a) as the principal study for RfC determination. The study by Brenneman was considered to be the best study for derivation of an inhalation RfC for several reasons. First, the critical effect (nasal lesions of the olfactory mucosa) has been reported by other study authors (Dorman et al. 2000; CIIT 1983), and the effect is consistent with the irritant properties of this gas. Secondly, the pulmonary system has been reported to be a target organ of H_2S toxicity by numerous researchers. Third, the LOAEL and NOAEL for nasal lesions of the olfactory mucosa occur at lower concentrations than those in the other subchronic studies and would provide a more conservative RfC value compared to the other subchronic studies.

Dorman et al. (2000) examined fertility and developmental effects in Sprague-Dawley rats. Virgin male and female Sprague-Dawley rats (12/sex/group) were exposed to 0, 10, 30, or 80 ppm (0, 14, 42, or 111 mg/m^3) H_2S 6 hr/day, 7 days/week for two weeks prior to breeding. Exposure was continued during a 2-week mating period and then throughout gestational days 0-19 (GD 0-19). Evidence of copulation (vaginal plug or sperm in vaginal lavage fluid) during the 2-week mating period was considered GD 0. On postnatal day (PND) 4, litters were randomly reduced to 4 animals per sex when possible. Remaining pups were euthanized and discarded without being examined. Dams and pups were then exposed PND 5-18. Non-pregnant adult females were exposed for an additional 23-24 days following the 2-week breeding period. Adult males were exposed to H_2S for 70 consecutive days. There were no statistically significant

reproductive performance (mating index, fertility index, postimplantation loss per litter, and number of late resorptions or stillbirths) effects in F_0 animals. Also, the number of live pups, litter size, average length of gestation, and average number of implants per female were not affected. In F_0 males, there was no effect on sperm production or morphology. The study authors however noted a higher incidence of seminiferous tubular degeneration (intratubular sperm stasis, tubular mineralization, sperm granulomas, and multinucleated giant cells) and epididymal changes (degenerate sperm forms in the lumen, aspermia, and oligospermia) in the 80 ppm (111 mg/m^3) exposure. Also, one incidence each of sperm granuloma and unilateral necrosis of the cauda was present in the 80 ppm (111 mg/m^3) exposure group. There were no histological findings in the females which were considered treatment related. In pups, there were no statistically significant increases in structural malformations. There were also no significant differences in pup weight gain or development (pinnae detachment, surface righting, incisor eruption and negative geotaxis, vaginal patency, preputial separation, and eyelid separation). Pups also did not exhibit any treatment-related effects on motor activity, acoustic startle response, passive avoidance observed, FOB, or surface righting ability. Pup terminal body and organ weights in all exposure group were comparable to controls, and no gross observations were considered treatment related by the study authors. Microscopic examination of nervous tissues failed to demonstrate any treatment-related effects in pups.

While the inhalation RfC was based on the critical effect of nasal lesions, neurotoxicity of H_2S may also be important. In at least one study (Hannah and Roth, 1991), effects on neurological measures in rats were seen at doses almost as low (20 ppm) as those used in the determining study for the RfC by Brenneman et al (2000). In support of the importance of neurological effects, several authors (Tvedt et al., 1991; Kilburn, 1993; Wasch et al., 1989) have reported long-term adverse neurological sequelae of H_2S-induced unconsciousness including psychological dysfunction, brain damage, and dementia. For these reasons,an additional uncertainty factor of 3 ($10^{1/2}$) was considered for incorporation in the RfC for H_2S.

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Medium

Data Base -- Medium

RfC -- Low

The overall confidence in the RfC assessment is low; confidence in the principal study is medium because it was well-designed and conducted, and examined sensitive endpoints. However, it was subchronic in duration, and only male rats were examined. The overall confidence in the database is medium because the endpoints are supported by other subchronic studies. A chronic inhalation study in rats and mice, with additional dose groups, would increase the confidence in the database.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- This assessment is not presented in any existing U.S. EPA document.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to _____.

Other EPA Documentation -- _____

Agency Consensus Date -- __/__/__

___I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Hydrogen sulfide CASRN
CASRN-- 7783-06-4
Last Revised -- 00/00/0000

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

_VI. BIBLIOGRAPHY

Substance Name -- Hydrogen sulfide CASRN
CASRN-- 7783-06-4
Last Revised -- 00/00/0000

__VI.A. ORAL RfD REFERENCES

None

__VI.B. INHALATION RfC REFERENCES

Brenneman, K.A., James, R.A., Gross, E.A., and Dorman, D.C. (2000) Olfactory loss in adult male CD rats following inhalation exposure to hydrogen sulfide. Toxicologic Pathology 28(2): 326-333.

CIIT (Chemical Industry Institute of Toxicology). 1983a. 90-Day vapor inhalation toxicity study of hydrogen sulfide in B6C3F1 mice. EPA/OTS 0883-0255.

CIIT (Chemical Industry Institute of Toxicology). 1983b. 90-Day vapor inhalation toxicity study of hydrogen sulfide in Fischer-344 rats. EPA/OTS 0883-0255.

CIIT (Chemical Industry Institute of Toxicology). 1983c. 90-Day vapor inhalation toxicity study of hydrogen sulfide in Sprague-Dawley rats. EPA/OTS 0883-0255.

Dorman, D. C., Brenneman, K. A., Struve, M. F., Miller, K. L., James, R. A., Marshall, M. W., and Foster., P. M. (2000) Fertility and developmental neurotoxicity effects of inhaled hydrogen sulfide in Sprague-Dawley rats. Neurotoxicol Teratol 22(1):71-84.

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

_VII. REVISION HISTORY

Substance Name -- Hydrogen sulfide CASRN
CASRN-- 7783-06-4

Date	Section	Description
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_VIII. SYNONYMS

Substance Name - Hydrogen sulfide
CASRN -- 7783-06-4
Last Revised -- 0/00/00

Acide sulfhydrique [French]

Acide sulphhydrique

Dihydrogen monosulfide

Dihydrogen sulfide

EINECS 231-977-3

FEMA No. 3779

HSDB 576

Hydrogen sulfide

Hydrogen sulfide (ACGIH:OSHA)

Hydrogen sulfide (H2S)

Hydrogen sulfure [French]

Hydrogen sulfuric acid

Hydrogen sulphide

Hydrogene sulfure [French]

Hydrogene sulphure

Hydrosulfuric acid

Idrogeno solforato [Italian]

RCRA waste number U135

Schwefelwasserstoff [German]

Sewer gas

Siarkowodor [Polish]

Stink DAMP

Sulfur hydride

Sulfureted hydrogen

Zwavelwaterstof [Dutch]