



## Nitroguanidine; CASRN 556-88-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

### STATUS OF DATA FOR Nitroguanidine

**File First On-Line 09/01/1989**

Category (section)	Assessment Available?	Last Revised
<b>Oral RfD (I.A.)</b>	yes	09/01/1989
<b>Inhalation RfC (I.B.)</b>	not evaluated	
<b>Carcinogenicity Assessment (II.)</b>	yes	09/01/1990

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Nitroguanidine

CASRN — 556-88-7

Last Revised — 09/01/1989

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.

### I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
<b>Reduced weight gain in female rats, maternal/fetal toxicity in rats, and equivocal evidence of developmental toxicity in rabbits</b>	NOAEL: 316 mg/kg/day LOAEL: 1000 mg/kg/day	3000	1	1E-1 mg/kg/day
<b>90-Day Rat Study</b>				
<b>Oral Exposure (diet)</b>				
<b>Morgan et al., 1988</b>				
<b>Coppes et al., 1988a,b</b>				

\*Conversion Factors: None

### I.A.2. Principal and Supporting Studies (Oral RfD)

Morgan E.W., M.J. Pearce, G.M. Zaucha, C.M. Lewis, G.T. Makovec and D.W. Korte, Jr. 1988. Ninety-day Subchronic Oral Toxicity Study of Nitroguanidine in Rats. Letterman Army Institute of Research, Presidio of San Francisco, CA. Institute Report No. 306, Toxicology Series 170. 173 p.

Coppes, V.G., G.A. Orner and D.W. Korte, Jr. 1988a. Developmental Toxicity Potential of Nitroguanidine in Rats. Letterman Army Institute of Research, Presidio of San Francisco, CA. Institute Report No. 257, Toxicology Series 174. 99 p.

Coppes, V.G., C.L. Gomez, D.K. Magnuson and D.W. Korte, Jr. 1988b. Developmental Toxicity Potential of Nitroguanidine In Rabbits. Letterman Army Institute of Research Praesidia of San Francisco, CA. Institute Report No. 298, Toxicology Series 184. 156 p.

The 90-day subchronic oral toxicity of nitroguanidine was evaluated in male and female Sprague-Dawley rats (Morgan et al., 1988). Nitroguanidine was administered in the diet at dose levels of 0, 100, 316, and 1000 mg/kg/day for 90 days. There were 15 animals/sex/dose. The addition of nitroguanidine to the diet consistently reduced food consumption and caused significant ( $p \leq 0.05$ ) increases in water consumption. Significantly ( $p \leq 0.05$ ) reduced weight gains were observed in the female high-dose group for 5 of the 13 weeks of the study period. No other clinical signs attributable to the test compound were observed during the study. Blood samples taken at necropsy for hematological and serum chemistry analyses exhibited no significant abnormalities that could be attributed to nitroguanidine dosing. Microscopic examination of tissues from the control and 1000 mg/kg/day dose group animals revealed no lesions attributable to the administration of nitroguanidine. The female 1000 mg/kg/day group had a significantly ( $p \leq 0.05$ ) increased brain-to-body weight ratio compared with that of the controls at terminal sacrifice. Based on a significant decrease in the rate of growth of female rats at 1000 mg/kg/day on weeks 5, 6, 8, 9 and 12, the NOAEL is 316 mg/kg/day.

The potential of nitroguanidine to produce developmental toxicity was evaluated in pregnant Sprague-Dawley rats (Coppes et al., 1988a). Nitroguanidine, suspended in 1% carboxymethylcellulose, was administered at doses of 0, 100, 316, and 1000 mg/kg/day by oral gavage on days 6 through 15 of gestation. Fetuses were delivered by cesarean section on day 20, weighed, examined externally, and processed in either Bouin's solution for visceral examination or alizarin red stain for skeletal examination. Following a generalized failure to thrive, two animals in the 1000 mg/kg/day group were significantly smaller than controls with an increased incidence of retarded ossification of the sternbrae, caudal vertebrae, and pubis. There was no evidence of developmental toxicity of nitroguanidine in rats under conditions of this study. Nitroguanidine produced maternal and fetal toxicity at the 1000 mg/kg/day dose level. The NOEL was 316 mg/kg/day.

The potential of nitroguanidine to produce developmental toxicity was evaluated in pregnant New Zealand White rabbits (Coppes et al., 1988b). Nitroguanidine, suspended in 1% carboxymethylcellulose, was administered at doses of 0, 100, 316, and 1000 mg/kg/day by oral gavage on days 6 through 18 of gestation. Fetuses were delivered by Cesarean section on day 29, weighed and examined externally. The soft tissues were examined while the body was being eviscerated for subsequent processing in alizarin red stain for skeletal examination. Ten dams in the 1000-mg/kg/day group died or were terminated in a moribund condition following a generalized failure to thrive. The dams administered nitroguanidine at 1000 mg/kg/day exhibited weight loss and decreased food consumption. There was an increased incidence of resorptions in all dose groups. Fetuses in the 1000 mg/kg/day group were lighter in weight and had an increased incidence of retarded ossification of the sternbrae, olecranon, patellae, and phalanges. There were no dose-related malformations. On the basis of these findings, we concluded that

nitroguanidine had no teratogenic potential. There is weak to equivocal evidence for potential developmental toxicity based on percent resorptions in all dose groups.

### **I.A.3. Uncertainty and Modifying Factors (Oral RfD)**

UF — Used in accordance with Agency guidelines, 10 for interspecies diversity, 10 for intraspecies diversity, 10 for less-than-lifetime NOAEL and 3 to account for equivocal evidence of developmental effects and data gaps.

MF — None

### **I.A.4. Additional Studies/Comments (Oral RfD)**

The 90-day subchronic oral toxicity of nitroguanidine was evaluated in male and female ICR mice (Frost et al., 1988). There were 15 animals/sex/ dose. Nitroguanidine was administered in the diet at dose levels of 0, 100, 316, and 1000 mg/kg/day for 90 days. The addition of nitroguanidine to the diet had no effect on food consumption or weight gains, but there was a significant dose- response increase in water consumption. Several serum chemistry parameters did exhibit statistically significant ( $p \leq 0.05$ ) alterations from the control values, but these changes were isolated occurrences with no consistent dose- related trends being noted. With the exception of the brain-to-body weight ratio in the high-dose males at interim sacrifice, organ weights and their respective ratios were not significantly affected by dosing. Microscopic examination of tissues from the control and 1000 mg/kg/day dose group animals revealed no lesions attributable to the administration of nitroguanidine. The findings of increased water consumption suggest that nitroguanidine, which is excreted unchanged in the mouse's urine, may be acting as an osmotic diuretic. The finding of increased brain-to-body weight ratios in male mice at 1000 mg/kg/day at interim sacrifice is supportive of a 316 mg/kg/day NOAEL.

### **I.A.5. Confidence in the Oral RfD**

Study — Medium

Database — Medium

RfD — Medium

The critical studies were well conducted and given a medium confidence rating. The supporting subchronic study in mice, with nitroguanidine administered in the diet, was also well conducted. However, since no lifetime studies exist, a medium confidence in the database is selected. Medium confidence in the RfD follows.

### **I.A.6. EPA Documentation and Review of the Oral RfD**

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

Other EPA Documentation — U.S. EPA, 1990

Agency Work Group Review — 05/17/1989

Verification Date — 05/17/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Nitroguanidine conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or (202)566-1676.

### **I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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### **I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name — Nitroguanidine

CASRN — 556-88-7

Not available at this time.

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## **II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Nitroguanidine

CASRN — 556-88-7

Last Revised — 09/01/1990

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day.

The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

## **II.A. Evidence for Human Carcinogenicity**

### **II.A.1. Weight-of-Evidence Characterization**

Classification — D; not classifiable as a human carcinogen.

Basis — Pertinent data regarding carcinogenicity have not been located in the available literature.

### **II.A.2. Human Carcinogenicity Data**

None.

### **II.A.3. Animal Carcinogenicity Data**

None.

### **II.A.4. Supporting Data for Carcinogenicity**

Nitroguanidine was not mutagenic for *Salmonella typhimurium* strains nor was it mutagenic for mouse lymphoma cells in the presence or absence of rat hepatic homogenates (Ishidate and Odashima, 1977; Kaplan, 1982; McGregor et al., 1980; U.S. Department of Defense, 1978). Nitroguanidine-associated recombinant activity was not observed in *Saccharomyces cerevisiae* (McGregor et al., 1980) and it was negative in dominant lethal assays with rats and mice (U.S. Department of Defense, 1978).

There was no evidence of DNA damage in nitroguanidine-treated WI-38 cells (U.S. Department of Defense, 1978); however, nitroguanidine did show evidence of clastogenicity in a screening test in Chinese hamster lung cells (Ishidate and Odashima, 1977).

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## **II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure**

None.

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## **II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure**

None.

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## **II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)**

### **II.D.1. EPA Documentation**

Source Document — U.S. EPA, 1990

The Health Advisory for Nitroguanidine has received Agency Review.

### **II.D.2. EPA Review (Carcinogenicity Assessment)**

Agency Work Group Review — 01/11/1990

Verification Date — 01/11/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Nitroguanidine conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or (202)566-1676.

### **II.D.3. EPA Contacts (Carcinogenicity Assessment)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

## **VI. Bibliography**

Substance Name — Nitroguanidine  
CASRN — 556-88-7

### **VI.A. Oral RfD References**

Coppes, V.G., G.A. Orner and D.W. Korte, Jr. 1988a. Developmental Toxicity Potential of Nitroguanidine in Rats. Letterman Army Institute of Research, Presidio of San Francisco, CA. Institute Report No. 257, Toxicology Series 174. 99 p.

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Frost, D.F., E.W. Morgan, Y. Letellier, et al. 1988. Ninety-day Subcrhonic Oral Toxicity Study of Nitroguanidine in Mice. Letterman Army Institute of Research (Institute Report No. 319), Praesidia of San Francisco, CA. 33 p.

Morgan E.W., M.J. Pearce, G.M. Zaucha, C.M. Lewis, G.T. Makovec and D.W. Korte, Jr. 1988. Nintey-day Subschronic Oral Toxicity Study of Nitroguanidine in Rats. Letterman Army Institute of Research, Presidio of San Francisco, CA. Institute Report No. 306, Toxicology Series 170. 173 p.

U.S. EPA. 1990. Drinking Water Health Advisory for Nitroguanidine (NQ). Office of Drinking Water, Washington, DC.

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### **VI.B. Inhalation RfC References**

None

### **VI.C. Carcinogenicity Assessment References**



Ishidate, M. and S. Odashima. 1977. Chromosome Tests with 134 Compounds on Chinese Hamster Cells in Vitro-A Screening for Chemical Carcinogens. *Mutat. Res.* 48: 337-354.

Kaplan, D.L., J.H. Cornell and A.M. Kaplan. 1982. Decomposition of Nitroguanidine. *Environ. Sci. Technol.* 16(8): 488-492.

McGregor, D.B., C.G. Riach, R.M. Hastwell and J.C. Dacre. 1980. Genotoxic Activity on Microorganisms of Tetryl, 1,3-Dinitrobenzene and 1,3,5- Trinitrobenzene. *Environ. Mutat.* 2: 531-541.

U.S. Department of Defense. 1978. AD-A064949. Available from Defense Technical Information Center. Write to Documents, Cameron Station, Alexandria, VA 22314, or call (703)274-7633.

U.S. EPA. 1990. Health Advisory for Nitroguanidine. Office of Drinking Water, Washington, DC.

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## VII. Revision History

Substance Name — Nitroguanidine  
CASRN — 556-88-7

Date	Section	Description
09/01/1989	I.A.	Oral RfD summary on-line
09/01/1990	II.	Carcinogen assessment on-line
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

## VIII. Synonyms

Substance Name — Nitroguanidine

CASRN — 556-88-7

Last Revised — 09/01/1989

- 556-88-7
- GUANIDINE, NITRO-
- NITROGUANIDINE
- alpha-NITROGUANIDINE
- 1-NITROGUANIDINE
- 2-NITROGUANIDINE
- NITROGUANIDINE, DRY (DOT)
- PICRITE (the explosive)
- UN 0282 (DOT)