Silica, Crystalline Forms

CAS Registry Numbers:

14808-60-7 (quartz)
14464-46-1 (cristobalite)
1317-95-9 (tripoli)
15468-32-3 (tridymite)

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24-h ReV Development Support Document

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DSD History

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ACRONYMS AND ABBREVIATIONS

Acronyms and Abbreviations	Definitions
A	animal
AMCV	Air Monitoring Comparison Value
ARA	Applied Research Associates
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	bronchoalveolar lavage
C	concentration
°C	degrees Celsius
d	day
DF	deposition fraction
DSD	development support document
ESL	effects screening level
ET	extrathoracic
g/cm^3	grams per cubic centimeter
GSD	geometric standard deviation
h	hour(s)
H	humans
HEC	human equivalent concentration
LDH	lactate dehydrogenase
ln	natural log
LOAEL	lowest-observed-adverse-effect-level
mmHg	millimeters of mercury
µg	microgram
$µg/m^3$	micrograms per cubic meter
µm	micrometer or micron
mg	milligrams
mg/m^3	milligrams per cubic meter

Acronyms and Abbreviations	Definitions
MMAD	mass median aerodynamic diameter
MOA	mode of action
MPPD	multiple path particle dosimetry
MW	molecular weight
NAG	N-acetyl-glucosaminidase
NF	normalizing factor
NOAEL	no-observed-adverse-effect-level
P	pulmonary
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
RDDR	regional deposited dose ratio
ReV	reference value
RPF	relative potency factor
SD	Sprague-Dawley
T	time
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_D	incomplete database uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
URF	unit risk factor
USEPA	United States Environmental Protection Agency
V_E	minute volume

Chapter 1 Summary Tables

Table 1 provides the health-based 24-hour Reference Value (24-h ReV) from an acute evaluation of crystalline silica, which will be used as the 24-h Air Monitoring Comparison Value (AMCV) for evaluation of 24-h ambient air monitoring data. The 24-h ReV was developed based on TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2015). Please refer to the Silica, Crystalline Forms Development Support Document (DSD) (TCEQ 2009) for details on how other acute and chronic values were derived. Table 2 provides chemical/physical properties for crystalline silica.

Table 1. Acute Health-Based Screening Values for Silica, Crystalline Forms

Screening Level Type	Duration	Value 1 (µg/m³)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Acute ReV	24 h	24	--	M	A	--	Respiratory inflammation– increased neutrophils and lactate dehydrogenase in bronchoalveolar lavage fluid in Crl:CD BR rats (male)	Value applies to respirable silica ≤ 4 µm in diameter

Bold values used for air permit reviews; values have been rounded to two significant digits.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 2. Chemical and Physical Properties

Parameter	Value	Reference
Molecular Formula	SiO_2	ChemFinder 2004
Molecular Weight	60.0848 g/mol	ChemFinder 2004
Physical State	Solid	ATSDR 2019
Color	Off-white	Mallinckrodt Chemicals 2006
Odor	Odorless	Mallinckrodt Chemicals 2006
CAS Registry Numbers	14808-60-7 (quartz) 14464-46-1 (cristobalite) 1317-95-9 (tripoli) 15468-32-3 (tridymite)	ChemFinder 2004 CalEPA 2005; ACGIH 2006
Synonyms/Trade Names	Agate; Onyx; Quartz; Silica; Crystallized Silicon dioxide; Sand; Flint; Silica Flour, Cristobalite; Tripoli; Tridymite.	Mallinckrodt Chemicals 2006 ChemFinder 2004; ACGIH 2006
Solubility in water	Insoluble	ChemFinder 2004, ATSDR 2019
Log K_{ow}	Not available	---
Vapor Pressure	10 mmHg at 1732°C	Mallinckrodt Chemicals 2006
Vapor Density (air = 1)	Not available	---
Density (water = 1)	2.648 g/cm^3 (α quartz) 2.334 g/cm^3 (cristobalite) 2.265 g/cm^3 (tridymite)	ATSDR 2019
Melting Point	573°C (α quartz converts to ß quartz) 870°C (ß quartz converts to tridymite) 1470°C (tridymite converts to cristobalite) 1713°C (cristobalite)	ATSDR 2019
Boiling Point	2230°C	ChemFinder 2004/ Fisher Scientific Material Safety Data Sheet

Chapter 2 Background

The purpose of this document is to summarize the main steps involved in the development of the 24-h AMCV for crystalline silica. For chemicals detected in the ambient air monitoring network, short-term AMCVs have generally been used by the TCEQ to evaluate 1-h reported concentrations and long-term AMCVs are used to evaluate annual averages. Because TCEQ may be evaluating concentrations of crystalline silica collected over a 24-h duration in ambient air, a 24-h AMCV is the best comparator to evaluate ambient 24-h data. TCEQ thinks that using a short-term, 1-h AMCV to evaluate a 24-h ambient air sample is less appropriate than using a 24-h AMCV because toxic effects induced by 24-h of exposure may be governed by modes of action somewhat different than those influencing toxicity due to 1-h of exposure. A 24-h ReV is derived for human health hazards associated with threshold dose-response relationships and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups).

Please refer to the crystalline silica Development Support Document (TCEQ 2009) for detailed information on human and animal studies used in the derivation of other health- and welfare-based values for crystalline silica.

Chapter 3 Acute Evaluation

3.1 Health-Based 24-H Acute ReV

3.1.1 Key and Supporting Studies

There are no adequate studies evaluating the effects of acute exposure to crystalline silica in humans. The cumulative dose of respirable silica in exposed workers (respirable concentration multiplied by duration of exposure, mg/m^3-year) is the most important factor in the development of silicosis (ATSDR 2019, Leung et al. 2012). ATSDR minimal risk levels for humans were not derived for inhaled crystalline silica for any exposure duration (ie, acute, intermediate or chronic), because epidemiological studies of occupational populations show that silicosis occurs at the lowest estimated cumulative exposure levels (i.e., mg/m^3- year) that have been reported (ATSDR 2019). Moreover, given the serious nature of silicosis and the uncertainties associated with identification of a no-effect level, no minimal risk levels were derived for inhaled crystalline silica for any exposure duration. Silicosis is a progressive, irreversible, serious pulmonary fibrotic disease that may result in death due to respiratory failure or lung cancer (ATSDR 2019, Leung et al. 2012).

One acute and several subacute inhalation toxicity studies of crystalline silica in rodents have been performed. These studies demonstrate that the critical effect of acute exposure to

crystalline silica is inflammation and cytotoxicity in the respiratory tract. The key study exposed animals to crystalline silica as cristobalite. However, supporting studies also demonstrate inflammation and cytotoxicity following exposure to other forms of silica, including crystalline silica quartz and amorphous silica. While the crystalline forms of silica dust produce irreversible pulmonary inflammation and cytotoxicity, ultimately resulting in pulmonary fibrosis; the amorphous and other non-crystalline forms of silica only produce a transient pulmonary inflammation and cytotoxicity (Warheit et al. 1991, Warheit et al. 1995). The health- and welfare-based values for amorphous and non-crystalline silica are presented in separate Development Support Documents (TCEQ 2011, TCEQ 2009).

The data generated in the inhalation toxicity studies conducted in animals is relevant to the lung disease observed in humans (Leung et al. 2012). Pulmonary inflammation and cytotoxicity are observed in humans chronically exposed to high concentrations of crystalline silica in the workplace, and after a period of latency a pulmonary fibrosis termed silicosis may occur (Leung et al. 2012). This has been demonstrated in various inhalation toxicity studies in rodents exposed to high concentrations of crystalline silica.

3.1.1.1 Key Study – Warheit et al. 1995

Animal studies indicate that acute or subacute exposure to crystalline silica can elicit pulmonary inflammation and cytotoxicity, and after a period of latency will result in pulmonary fibrosis (Warheit et al. 1991, Warheit et al. 1995). Warheit et al. (1995) exposed groups of 24 CD Sprague-Dawley rats for 6 h/day (h/d) for 3 d to two forms of crystalline silica: 10 or 100 mg/m^3 cristobalite (mass median aerodynamic diameter [MMAD] = 3.4 – 3.6 µm) or 100 mg/m^3 α quartz (Min-U-Sil, MMAD = 3.3 – 3.5 µm). After termination of exposures, rats were sacrificed, and the lungs were lavaged. Some rats were retained for evaluations during a post-exposure phase of up to 3 months in duration. The bronchoalveolar lavage (BAL) fluid was evaluated for cell differential, lactate dehydrogenase (LDH) activity, N-acetyl glucosaminidase (NAG) activity, and protein concentration.

In comparison to sham-exposed control rats, exposure to crystalline silica in the form of cristobalite or α quartz resulted in pulmonary inflammation characterized by increases in percentages of granulocytes (primarily neutrophils, $p < 0.05$) and elevated indices of cytotoxicity (LDH and NAG activity, and protein concentration, $p < 0.05$) in BAL fluid, which persisted through 90 days after termination of the 3-d exposure. In addition, rats exposed to crystalline silica developed progressive pulmonary histopathologic findings within one month after the 3-d exposures.

A no-observed-adverse-effect-level (NOAEL) was not identified for the crystalline forms of silica. The lowest-adverse-effect-level (LOAEL) for cristobalite was 10 mg/m^3, and for α quartz was

100 mg/m^3; these are free-standing LOAEL concentrations. The LOAEL of 10 mg/m^3 cristobalite was chosen as the point of departure (POD) for derivation of the 24-h ReV for crystalline silica.

3.1.1.2 Supporting Studies

One acute study in rats (Warheit et al. 1991) and several subacute studies in rats and mice (including Porter et al. 2001; 2002a; 2002b, and Castranova et al. 2002) were available for review and many are discussed in the DSD for crystalline silica (TCEQ 2009). As described in that document, Warheit et al. (1991) also identified a free-standing LOAEL of 10 mg/m^3 for pulmonary inflammation and cytotoxicity, as well as pulmonary histopathologic findings, in rats exposed for 6 h to 10, 50, or 100 mg/m^3 α quartz. Since the finalization of the DSD for crystalline silica, an additional subacute study (Sellamuthu et al. 2017) was published. Sellamuthu et al. (2017) exposed 8 male Fischer rats/group to filtered air or 15 mg/m^3 Min-U-Sil 5 crystalline silica (α quartz, MMAD = 1.6 µm, geometric standard deviation [GSD] = 1.6) for 6 h/d for 5 d. All rats were then retained for a 44-week post-exposure period. At the end of the 44-week post-exposure period, BAL fluid was collected for evaluation, peripheral blood was collected for white blood cell differential counts, lung tissue and BAL cells were evaluated for gene expression, and histopathologic examination was performed on the lungs. Similar to the findings in the previously-discussed studies, 5 d of exposure to 15 mg/m^3 Min-U-Sil 5 crystalline silica resulted in increases in indices of inflammation (alveolar macrophages, polymorphonuclear leukocytes, monocyte chemoattractant protein-1 concentration) and cytotoxicity (albumin concentration, LDH activity) in BAL fluid in comparison to rats exposed to filtered air. Pulmonary fibrosis was seen in crystalline silica-exposed rats. Increases in peripheral blood polymorphonuclear leukocytes; and alterations in expression of various genes related to pulmonary toxicity (predominantly inflammation) were seen in crystalline silica-exposed rats relative to filtered air-exposed rats. The exposure concentration in this study, 15 mg/m^3, was a free-standing LOAEL.

3.1.2 Mode of Action

Crystalline silica forms include quartz, cristobalite, tripoli, and tridymite and may be associated with development of silicosis in workers. Crystalline silica particles of respirable size deposit in the distal airways and are phagocytosed by resident alveolar macrophages. Reactive oxygen species are generated, and inflammatory cytokines are released with recruitment of additional phagocytic cells. Crystalline silica particles cannot be degraded and may be retained in the lungs for years following cessation of exposure. This biopersistence leads to death of macrophages. The crystalline silica particles are released and engulfed by other marcrophages, perpetuating the process of phagocytosis and cell death. This results in release of mediators, deposition of collagen by fibroblasts, and a pulmonary fibrosis termed silicosis (ATSDR 2019, Leung 2012).

3.1.3 Health-Based Acute 24-H ReV

3.1.3.1 Selection of the Point of Departure (POD) and Critical Effect

The critical effect for derivation of the 24-h ReV is pulmonary inflammation and cytotoxicity, which was seen following acute and subacute exposures to crystalline silica. Considering the acute and subacute studies performed, Warheit et al. (1995) provides a conservative LOAEL-based POD of 10 mg/m^3 for derivation of a 24-h, health-protective ReV.

3.1.3.2 MOA and Dose Metric for the Critical Effect

In some of the supporting studies, data on lung concentrations of the parent chemical are available. Measurement of the lung concentrations of silica was provided by Warheit et al. (1991) at the highest exposure concentration of 100 mg/m^3 following 3 d of exposure at 6 h/day. Because data on lung concentrations are not available for exposure concentrations in the key study, exposure concentration of the parent chemical will be used as the default dose metric.

3.1.3.3 Adjustments to the POD

3.1.3.3.1 Default Exposure Duration Adjustment

In the key study (Warheit et al. 1995), rats were exposed to crystalline silica for 6 h/d for 3 d. Crystalline silica persists and is not expected to clear considerably in between each day of exposure. The 6-h exposure duration concentration (C_1) in the key study by Warheit et al. (1995) was adjusted to a POD_{ADJ} of 24-h exposure duration (C_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 1, where both concentration and duration play a role in toxicity:

$$C_2 = [(C_1) \times (T_1 / T_2)] = [(10 \text{ mg/m}^3) \times (6 \text{ h}/24 \text{ h})] = 2.5 \text{ mg/m}^3 = POD_{ADJ}$$

3.1.3.3.2 Dosimetry Adjustments from Animal to Human Exposure

Crystalline silica is a solid particle, and the lung deposition of solid particles can be different between rodents and humans. Therefore, the Applied Research Associates (ARA) multiple path particle dosimetry model (MPPD) v 3.04 program was used to calculate the deposition fraction of silica in the target respiratory regions to allow for appropriate dosimetry adjustments from rats to humans. Parameters necessary for this program include particle diameter, particle density, chemical concentration, and respiratory tract regions considered for deposition. According to Warheit et al. (1995), the MMAD of the silica used was 3.4 to 3.6 μm; the more conservative MMAD of 3.4 μm was used for calculation of deposition fraction. No geometric standard deviation (GSD) was reported; a default of 1.0 was used for GSD. The particle density of cristobalite silica is 2.334 g/cm^3 (Table 2). The chemical concentration is the POD_{ADJ} of 2.5

mg/m^3. Because the MMAD of the silica particles is of a respirable size (≤ 4.0 μm) and the critical effects were identified from BAL fluid, the target region for crystalline silica was the total particle distribution for the tracheobronchial and pulmonary regions. Both Warheit et al. 1991 and Warheit et al. 1995 used Charles River Sprague Dawley CD rats, with initiation of exposures at 8 weeks of age. Therefore, based on body weight curves available on the Charles River Laboratories website, a mean body weight of 228 grams in male rats was input into the MPPD software. Based on equation 4-4 in USEPA guidance 1994 (ln [V_E in L/min] = b_0 + b_1 ln [body weight in kg], where ln refers to natural log), a body weight of 228 g in rats corresponds to a minute volume (V_E) of 166.6 mL. Based on the symmetric SD rat model, a tidal volume of 1.63 mL and breathing frequency of 102/min was input into the MPPD software program. For human, using the Yeh Schum symmetric model, a minute volume of 842.74 mL and breathing frequency of 16.38/min, which results in a minute volume of 13,800 mL/min, was input into the MPPD software program. All remaining values used were default values in the MPPD program. Once the total particle distribution was determined (Appendix 1 - Figures 1 and 2), the Regional Deposited Dose Ratio (RDDR) was calculated as follows:

$$RDDR = [(V_E)_A / (V_E)_H] \times [DF_A / DF_H] \times [NF_H / NF_A]$$

where: V_E = minute volume

DF = deposition fraction in the target region of the respiratory tract

NF = normalizing factor

A = animal

H = human

RDDR = [166.6 mL/min / 13,800 mL/min] x [0.2502 / 0.1855] x [543,200 cm^2 / 3422.5 cm^2]

RDDR = 2.58

The RDDR was then used to dosimetrically adjust from an animal POD to a human equivalent concentration POD (POD_{HEC}).

$$POD_{HEC} = POD_{ADJ} \times RDDR = 2.5 \text{ mg/m}^3 \times 2.58 = 6.45 \text{ mg/m}^3 = 6{,}450 \text{ μg/m}^3$$

3.1.3.4 Adjustments to the POD_{HEC}

The POD_{HEC} based on a LOAEL from the Warheit et al. (1995) study was used and UFs were applied to derive the acute 24-h ReV (i.e., assuming a threshold MOA for a noncarcinogenic endpoint). The following UFs were applied to the POD_{HEC} of 6,450 μg/m^3: 10 for intraspecies variability (UF_H), 3 for interspecies variability (UF_A), 3 for LOAEL to NOAEL extrapolation (UF_L), and 3 for database uncertainty (UF_D).

- A full UF_H of 10 was used to account for intraspecies variability. Because human data were insufficient to develop a toxicity factor and the variability of an acute response in humans is unknown, animal data were used to derive the 24-h ReV.

- A UF_A of 3 was used for extrapolation from animals to humans because dosimetric adjustments from animal-to-human exposure were conducted, which account for toxicokinetic differences but not toxicodynamic differences.

- A UF_L of 3 was necessary, as a NOAEL was not available for acute or relevant subacute exposures. Although rats were exposed for 6 h/d for 3 d, for a total exposure duration of 18 h, the duration adjustment applied was conservative (6 h/24 h), based on a 6 h/d exposure, rather than summing the total exposure (18 h/24 h). Therefore, a UF_L of 3 was used for the extrapolation from a LOAEL to a NOAEL, instead of a UF_L of 10.

- A UF_D of 3 was used due to the lack of acute studies in other species. An adequate number of acute and subacute studies in rats was available, but prenatal developmental toxicity studies in animals have not been performed with crystalline silica. Epidemiological studies have not identified developmental effects in association with crystalline silica (ATSDR 2019). In the key study, the numbers of animals estimated that were evaluated at each interval (6 male rats/interval) were considered sufficient for toxicologic evaluation.

  Thus, the 24-h ReV = POD_{HEC} / (UF_H x UF_A x UF_L x UF_D)

  = 6,450 µg/m^3 / (10 x 3 x 3 x 3)

  = 23.89 µg/m^3

  = 24 µg/m^3 (rounded to two significant figures)

3.1.3.5 Health-Based 24-h Acute ReV

The resulting 24-h acute ReV was rounded to two significant figures at the end of all calculations. (Table 3).

Table 3. Derivation of the Acute 24-H ReV

Parameter	**Summary**
Study	Warheit et al. 1995
Study population	CD Sprague Dawley rats, 24 males/group sacrificed at end of exposure (6 h/day for 3 d) and various intervals up to 3 months post-exposure
Study quality	High
Exposure Methods	Inhalation
LOAEL	10 mg/m^3
NOAEL	Not identified
Critical Effects	Pulmonary inflammation and cytotoxicity
POD	10 mg/m^3 (LOAEL)
Duration	6 h/d for 3 d
Extrapolation to 24-h	10 mg/m^3 x (6 h/24 h) = 2.5 mg/m^3 = 2,500 $\mu g/m^3$
POD_{HEC}	6,450 $\mu g/m^3$
Total UFs	270
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	3
Database UF *Database Quality*	3 Medium
Acute 24-h ReV	**24 $\mu g/m^3$**

3.2 Acute 24-H ReV for Air Monitoring Evaluation

The acute 24-hour evaluation resulted in the derivation of the following value:

- acute 24-hour ReV = 24 μg/m^3

The health-based 24-h ReV of 24 μg/m^3 may be used as the health-based 24-h AMCV for evaluation of ambient air data. This value is sufficiently conservative for the adequate protection of public health for the exposure duration and adverse effects considered.

Chapter 4 References

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Appendix 1 MPPD Program Outputs for Key Study (Warheit et al. 1995)

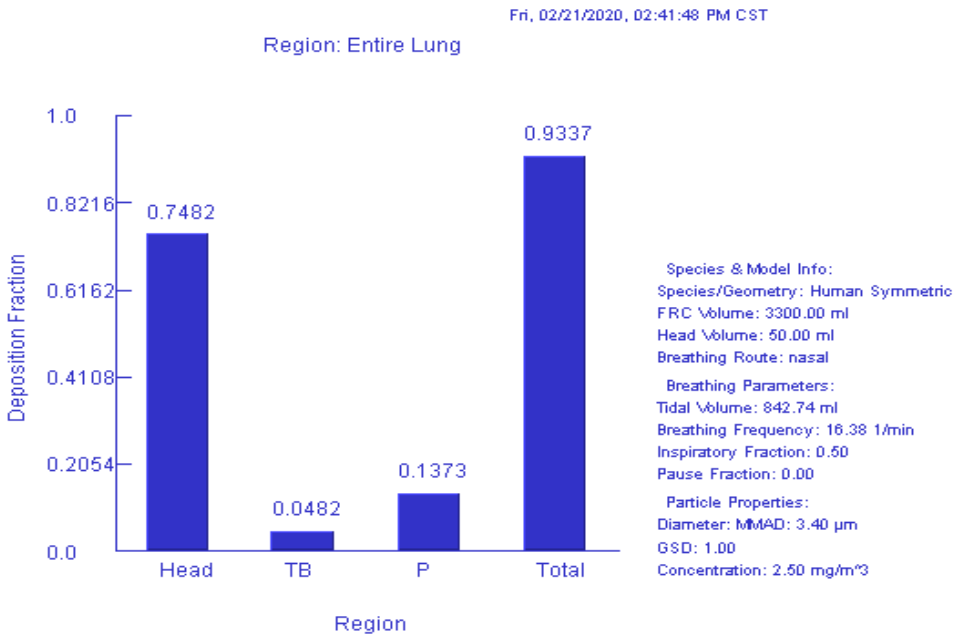

Figure 1. Human output from the MPPD model

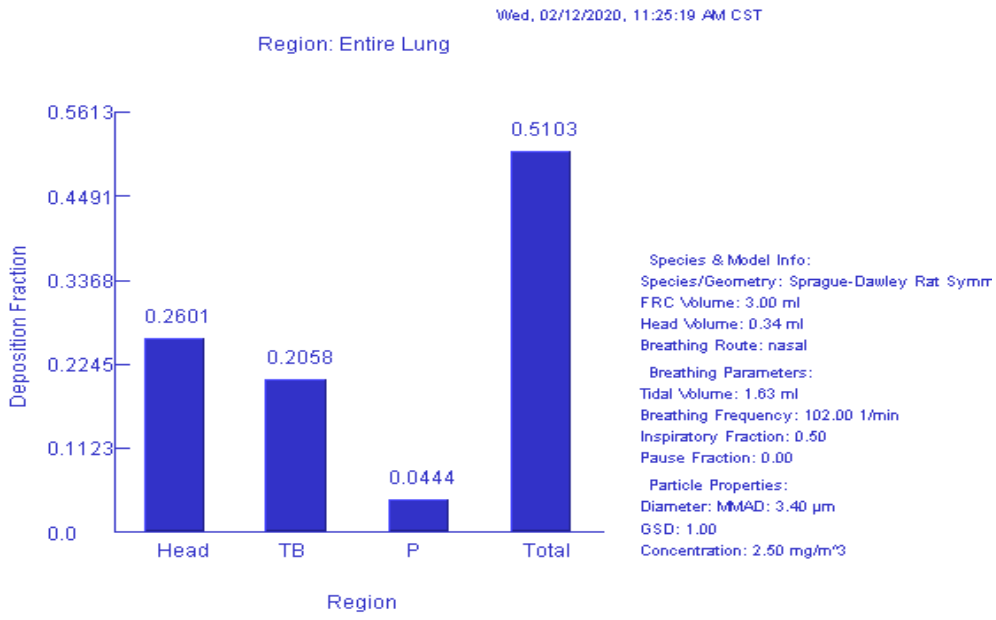

Figure 2. Rat output from the MPPD model