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Provisional Peer-Reviewed Toxicity Values for

Titanium
(CASRN 7440-32-6)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER:

Jon Reid, National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY:

National Center for Environmental Assessment, Cincinnati, OH

This document was externally peer reviewed under contract to:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300)

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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR TITANIUM (CASRN 7440-32-6)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

No reference dose (RfD), reference concentration (RfC), or cancer assessment for titanium is included on the United States Environmental Protection Agency (U.S. EPA) IRIS database (U.S. EPA, 2010) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). The HEAST did not report any RfD or RfC values for titanium (U.S. EPA, 2003), and the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994) does not contain any assessments for titanium. The toxicity of titanium has not been reviewed by ATSDR (2008). CalEPA (2008) has not derived toxicity values for exposure to titanium. No occupational exposure limits for titanium have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2005), or the Occupational Safety and Health Administration (OSHA, 2010).

Titanium has not been evaluated under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). The HEAST (U.S. EPA, 2003) does not report any carcinogenicity values for titanium. The International Agency for Research on Cancer (IARC, 1999) has reviewed the carcinogenic potential of titanium as a surgical implant and has determined that there is inadequate evidence to classify the carcinogenicity of such implants. Therefore, IARC has designated titanium as a Group 3 agent, which is defined as an agent "*Not Classifiable as to Their Carcinogenicity to Humans*." Titanium has been reviewed by the World Health Organization (WHO, 1982), and intramuscular injection of titanium metal was found to induce fibrosarcomas and lymphosarcomas in rats. However, the WHO has concluded that the available data on the carcinogenicity of titanium do not indicate that this effect occurs in humans. Titanium is not included in the *11th Report on Carcinogens* (NTP, 2005). CalEPA (2002) has not prepared a quantitative estimate of the carcinogenic potential of titanium.

Literature searches were conducted on sources published from 1900 through May 2010 for studies relevant to the derivation of provisional toxicity values for titanium, CAS No. 7440-32-6. Searches were conducted using EPA's Health and Environmental Research Online

(HERO) evergreen database of scientific literature. HERO searched the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for toxicity assessment values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 1 provides information for all of the potentially relevant studies.

Though three sources containing information on titanium exposure were identified in Table 1, the literature search revealed no human or animal studies, acute, short term, or chronic, that are useful for developing toxicity values for titanium. Intramuscular information cannot be translated to meaningful data for development of toxicity values.

DERIVATION OF PROVISIONAL VALUES

Limitations in the available data preclude development of both cancer and noncancer toxicity values.

CANCER WEIGHT OF EVIDENCE DESCRIPTOR

Limitations in the data preclude development of a weight-of-evidence descriptor.

MODE-OF-ACTION DISCUSSION

Limitations in the data preclude determination of a mode-of-action discussion.

Table 1. Summary of Potentially Relevant Data for Titanium (CASRN 7440-32-6)

Category	Number of Male/Female, Species, Study Type, Study Duration	Dosimetry	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL	Reference	Comments
Human								
1. Oral (mg/kg-day)								
None								
2. Inhalation (mg/m^3)								
Subchronic	None							
Chronic	1 Male (type of study and duration not reported)	Not provided	Fibrosis	None	Not run	None	Husten, 1959	A worker in the hard metal industry reported fibrosis; however, this worker was also exposed to other elements more likely responsible for fibrosis.
Developmental	None							
Reproductive	None							
Carcinogenic	None							
Animal								
1. Oral (mg/kg-day)								
None								
2. Inhalation (mg/m^3)								
None								

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