DODECANEDIOIC ACID

CAS # 693-23-2

ORAL RISK ASSESSMENT DOCUMENT

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AUTHORS, PEER REVIEWERS, AND ACKNOWLEDGEMENTS

Author:
NSF Toxicology Services
1.800.NSF.MARK
NSF International
789 Dixboro Road
Ann Arbor, MI 48105

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Internal NSF Peer Reviewers:
Clif McLellan, M.S.

External Peer Reviewers:
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Edward Ohanian, Ph.D. (Chairman, NSF Health Advisory Board)
Director, Health and Ecological Criteria Division
Office of Science and Technology/Office of Water
U.S. Environmental Protection Agency

Michael Dourson, Ph.D., DABT (Vice Chairman, NSF Health Advisory Board)
Director
TERA (Toxicology Excellence for Risk Assessment)

David Blakey, D.Phil.
Director, Environmental Health Science
Safe Environments Programme
Health Canada

Steven Bursian, Ph.D.
Professor
Michigan State University
.
Robert Hinderer, Ph.D.
Director of Health, Toxicology, and Product Safety
Noveon, Inc.

Ernest E. McConnell, D.V.M., M.S. (Path)
ToxPath, Inc.
Raleigh, NC

Jennifer Orme-Zavaleta, Ph.D.
Director, Research Planning and Coordination Staff
National Health and Environmental Effects Laboratory
U.S. Environmental Protection Agency

Calvin Willhite, Ph.D.
Department of Toxic Substances Control
State of California

EXECUTIVE SUMMARY

Dodecanedioic Acid – Oral Risk Assessment CAS # 693-23-2			
PARAMETER	**LEVEL[1]**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	74	mg/kg-day	From a human oral bolus dose study supported by studies using intravenous infusion.
Oral RfD (oral reference dose)	70	mg/kg-day	From the NOAEL with a 1x total uncertainty factor.
TAC (total allowable concentration)	30	mg/L	A TAC of 500 mg/L was calculated from the oral RfD, the default 70 kg body weight and 2 L/day water consumption of an adult, and a 20% relative source contribution for drinking water. The TAC was limited by the 30 mg/L water solubility of dodecanedioic acid.
SPAC (single product allowable concentration)	30	mg/L	A SPAC of 50 mg/L was calculated from the TAC based on the default 10 sources of dodecanedioic acid in drinking water. The SPAC was limited by the 30 mg/L water solubility of dodecanedioic acid.
STEL (short term exposure level)	30	mg/L	A STEL of 700 mg/L was calculated from the NOAEL using the default 10 kg body weight and 1 L/day water consumption of a child. The STEL was limited by the 30 mg/L water solubility of dodecanedioic acid.

[1] The specified levels are based on the only available controlled human study by the oral route, supported by studies at higher levels using intravenous infusion. The existence of large food sources of dodecanedioic acid or its precursor dodecanoic acid and human tolerance of higher levels by infusion suggest these levels are likely conservative. Further, the TAC, SPAC, and STEL are limited by the water solubility of the chemical and are not based on any observed health effect.

KEY STUDY	Passi, S., M. Nazzaro-Porro, M. Picardo, G. Mingrone, and P. Fasella. 1983. Metabolism of straight saturated medium chain length (C9 to C12) dicarboxylic acids. J Lipid Res 24:1140-1147.
CRITICAL EFFECT	No critical effect was identified in humans or laboratory animals over the tested dose ranges.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 1x for interspecies extrapolation • 1x for intraspecies extrapolation • 1x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL extrapolation • 1x for database deficiencies The total uncertainty factor is therefore 1x.
TOXICITY SUMMARY	Oral and parenteral studies in humans provided more direct representation of human response to dodecanedioic acid than animal studies. No signs of toxicity were seen in any of the volunteer subjects tested. Mild reductions in leukocyte (lymphocyte) counts were not considered adverse in the only repeated dose oral rat study. The single and repeated dose human and animal studies are in agreement regarding the lack of any health hazard from oral or parenteral exposure to this chemical. The mode of action of dodecanedioic acid is well understood. The chemical can be metabolized in the liver by the fatty acid β-oxidation pathway, and it can also be produced in the liver from dodecanoic acid, a common food oil component, by ω-oxidation. A *Salmonella typhimurium* reverse mutation assay produced negative results, as did a mouse bone marrow micronucleus assay. The only repeated dose oral study in laboratory animals was not adequate to address the carcinogenic potential of this compound. However, there is considerable human exposure to dodecanoic acid from food sources, and the human body is capable of producing dodecanedioic acid in the liver from dodecanoic acid by ω-oxidation. Based on negative findings for mutagenicity and clastogenicity, and on the extent of human exposure over time, dodecanedioic acid is *not likely to be carcinogenic to humans* based on U.S. EPA guidelines.
CONCLUSIONS	The existence of naturally occurring dodecanedioic acid or its precursor (dodecanoic acid) in edible plant and animal products as well as the existence of normal metabolic pathways for handling dietary dicarboxylic acids, which dodecanedioic acid has been shown to follow, suggest the potential for human toxicity is low. Based on the results of controlled human studies of the use of this chemical for parenteral nutrition, the drinking water action levels established in this document are protective of human health.

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **dodecanedioic acid** in drinking water, as an extractant from one or more drinking water system components evaluated under NSF/ANSI 61 (2005), or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI 60 (2005). Both non-cancer and cancer endpoints have been considered, and risk assessment methodology developed by the U.S. Environmental Protection Agency (U.S. EPA) has been used.

Non-cancer endpoints are evaluated using the reference dose (RfD) approach (Barnes and Dourson, 1988; Dourson, 1994; U.S. EPA, 1993; U.S. EPA, 2002), which assumes that there is a threshold for these endpoints that will not be exceeded if appropriate uncertainty factors (Dourson et al., 1996; U.S. EPA, 2002; WHO/IPCS, 2005) are applied to the highest dose showing no significant effects. This highest dose is derived from human exposure data when available, but more often is derived from studies in laboratory animals. Either the no-observed-adverse-effect level (NOAEL) taken directly from the dose-response data, or the calculated lower 95% confidence limit on the dose resulting in an estimated 10% increase in response (the LED_{10} or $BMDL_{10}$ from benchmark dose programs) can be used (U.S. EPA, 2003a). The lowest-observed-adverse-effect level (LOAEL) can also be used, with an additional uncertainty factor, although the benchmark dose approach is preferred in this case. The RfD is expressed in mg/kg-day. It is defined by the U.S. EPA as "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" (Barnes and Dourson, 1988; U.S. EPA, 1993; U.S. EPA, 2003b).

NSF uses the RfD to derive three product evaluation criteria for non-cancer endpoints. The total allowable concentration (TAC), generally used to evaluate the results of extraction testing normalized to static at-the-tap conditions, is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink two liters of water per day. A relative source contribution (RSC), to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered, is also applied in calculating the TAC. The relative source contribution should be data derived, if possible. Alternately, a 20% default contribution for water can be used (U.S. EPA, 1991a). The TAC calculation is then as follows:

$$\text{TAC (mg/L)} = \frac{[\text{RfD (mg/kg-day)} \times 70\text{ kg}] - [\text{total contribution of other sources (mg/day)}]}{2\text{ L/day}}$$

or

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-day)} \times 70\text{ kg}}{2\text{ L/day}} \times 0.2\text{ (RSC)}$$

The single product allowable concentration (SPAC), used for water treatment chemicals and for water contact materials normalized to flowing at-the-tap conditions, is the TAC divided by the estimated total number of sources of the substance in the drinking water treatment and distribution system. In the absence of source data, a default multiple source factor of 10 is used.