

DODECANEDIOIC ACID

CAS # 693-23-2

ORAL RISK ASSESSMENT DOCUMENT



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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. <i>J Lipid Res</i> 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 <i>Salmonella typhimurium</i> 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 <i>not likely to be carcinogenic to humans</i> 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 LED₁₀ or BMDL₁₀ 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.

This accounts for the possibility that more than one product in the water and/or its distribution system could contribute the contaminant in question to drinking water.

Finally, a short-term-exposure level (STEL), at a higher level than the TAC, may be calculated for contaminants such as solvents expected to extract at higher levels from new product, but also expected to decay rapidly over time. The STEL is calculated from the NOAEL or the LED₁₀ of an animal study of 14- to 90-days duration, with uncertainty factors appropriate to the duration of the study. The contaminant level must decay to a level at or below the TAC under static conditions, or to a level at or below the SPAC under flowing conditions within 90 days, based on the contaminant decay curve generated from over-time laboratory extraction data.

Endpoints related to cancer are evaluated using modeling to fit a curve to the appropriate dose-response data (U.S. EPA, 1996a, U.S. EPA, 1999; U.S. EPA, 2003c; U.S. EPA, 2005a). If there is sufficient evidence to use a non-linear model, the LED₁₀ or BMDL₁₀, divided by the anticipated exposure, is calculated to give a margin of exposure. If there is insufficient evidence to document non-linearity, a linear model drawing a straight line from the LED₁₀ or BMDL₁₀ to zero, is used as a default. If a linear model (generally reflecting a genotoxic carcinogen) is used, a target risk range of 10⁻⁶ to 10⁻⁴ is considered by the U.S. EPA to be safe and protective of public health. (U.S. EPA, 1991a). For the purposes of NSF/ANSI 60 (2005) and 61 (2005), the TAC is set at the 10⁻⁵ risk level, and the SPAC is set at the 10⁻⁶ risk level. Use of a higher risk level is not ruled out, but would generally require documentation of a benefit to counteract the additional risk.

The RfD, TAC, SPAC, and STEL values derived in this document are based on available health effects data and are intended for use in determining compliance of products with the requirements of NSF/ANSI 60 (2005) and 61 (2005). Application of these values to other exposure scenarios should be done with care, and with a full understanding of the derivation of the values and of the comparative magnitude and duration of the exposures. These values do not have the rigor of regulatory values, as data gaps are generally filled by industry or government studies prior to regulation. Data gaps introduce uncertainty into an evaluation, and require the use of additional uncertainty factors to protect public health.

The general guidelines for this risk assessment include those from the National Research Council (NRC, 1983) and from The Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a; 1997b). Other guidelines used in the development of this assessment may include the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), draft revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), draft final Guidelines For Carcinogen Risk Assessment (U.S. EPA, 2003c), final Guidelines For Carcinogen Risk Assessment (U.S. EPA, 2005a), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998), A Review of the Reference Dose and Reference Concentration Process (U.S. EPA, 2002), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), and Health Effects Testing Guidelines (U.S. EPA, 2005b).

The literature search strategy employed for this compound was based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following data banks were searched:

- ChemIDplus
- Registry of Toxic Effects of Chemical Substances (RTECS)
- Hazardous Substances Data Bank (HSDB)
- GENE-TOX
- Environmental Mutagen Information Center (EMIC)
- Developmental and Reproductive Toxicology (DART)
- TOXLINE – Core and Special
- TRI (Toxics Release Inventory)
- Chemical Carcinogenesis Research Information System (CCRIS)
- Medline (via PubMed)
- Integrated Risk Information System (IRIS)
- Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS)
- Current Contents (as requested)

Literature searches for this chemical were conducted on March 1, 2001 and March 10, 2005. This document includes all relevant information retrieved as a result of those searches.

2.0 PHYSICAL AND CHEMICAL PROPERTIES

Dodecanedioic acid is an aliphatic dicarboxylic acid with synonyms of 1,12-dodecanedioic acid, 1,10-decanedicarboxylic acid, and decamethylenedicarboxylic acid (HSDB, 2005). It has the following structure, and physical and chemical properties listed in Table 1:

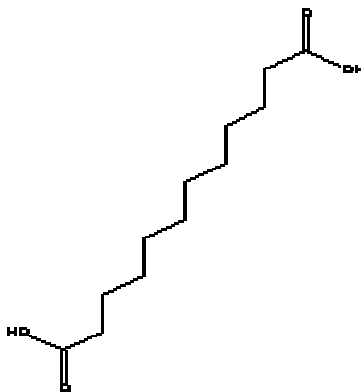


Table 1. The physical and chemical properties of dodecanedioic acid

Property	Data	Reference
Empirical Formula	C ₁₂ H ₂₂ O ₄	ChemFinder, 2005
CAS#	693-23-2	ChemFinder, 2005
Molecular Weight	230.3034	ChemFinder, 2005
Physical State and Color	Solid	OECD/SIDS, 1996
Melting Point	128-130 °C 130-132 °C	ChemFinder, 2005 HSDB, 2005
Boiling Point	245 °C at 10 mm Hg	ChemFinder, 2005
Density	0.953 g/cm ³ at 140 °C	IUCLID, 2000
Vapor Pressure (Log (VP-mmHg))	-4.968 at 25 °C	OECD/SIDS, 1996
Water Solubility	Slightly soluble in hot water 30 mg/L at 23 °C	HSDB, 2005 OECD/SIDS, 1996
pK _a	Not Located	-
n-Octanol/Water Partition Coefficient (log K _{ow})	3.07 (calculated)	OECD/SIDS, 1996
Henry's Law Constant (air/water partition)	Not Located	-

2.1 Organoleptic Properties

No studies determining the organoleptic properties of dodecanedioic acid were located.

3.0 PRODUCTION AND USE

3.1 Production

Production quantity was reported to be 5,000-25,000 tons per year (OECD/SIDS, 1996). Dodecanedioic acid is a high production volume chemical in both the European Union (OECD, 2000) and the United States (U.S. EPA, 2005c). Dodecanedioic acid is produced from petroleum feedstocks, generally by oxidation of cyclododecene or cyclododecanol (Kirk-Othmer, 1985). Liu and Kuo (1989) isolated the yeast *Candida tropicalis* NTU-512 from Taiwan soil and produced a genetically modified mutant that assimilated n-dodecane and produced dodecanedioic acid. Dodecanedioic acid was produced in 15% yield from sunflower oil by the fungus *Rhizopus stolonifer* (El-Sharkawy, 1996).

3.2 Use

The major use for dodecanedioic acid is in the manufacture of Nylon 612 resins, produced by condensation of hexamethylenediamine and dodecanedioic acid. These resins are acceptable under 21 CFR 177.1500 for repeated use contact with food at temperatures not to exceed 212 °F (U.S. FDA, 2005). Other sanctioned uses of dodecanedioic acid or its derivatives are listed under the following 21 CFR sections (U.S. FDA, 2005):

- 176.170, Components of paper and paperboard in contact with aqueous and fatty foods;
- 175.300, Resinous and polymeric coatings; and
- 177.1200, Cellophane.

Dodecanedioic acid is also used as a chemical intermediate for dyestuffs, adhesives, detergents, other plastics, and building materials (OECD/SIDS, 1996).

Dodecanedioic acid is a minor component of incidental food contact lubricants (U.S. FDA/CFSAN, 2005). Esters of dodecanedioic acid are also used as lubricants. Palm, coconut, and soy oil fatty acid microemulsions containing dodecanedioic acid have been tested as diesel fuels (ECD, 2005)

4.0 ANALYTICAL METHODS

Dodecanedioic acid, along with its metabolites and other organic acids, can be analyzed by a number of methods including thin layer chromatography, gas chromatography with flame ionization or mass spectrometric detection, or high performance liquid chromatography with ultraviolet or radioactivity detection.

4.1 Analysis in Water

Dodecanedioic acid has been detected in water using Method 625 (U.S. EPA, 2005d), involving solvent extraction, concentration, gas chromatographic separation, and mass spectrometric detection. The detection limit is approximately 0.004 mg/L.

4.2 Analysis in Biological Matrices

Bergseth et al. (1988) used thin layer chromatography, following sample extraction and hydrolysis, to analyze free fatty acids in liver homogenates. Passi et al. (1983), Greco et al. (1997; 1998), Bertuzzi et al. (1997), and Bergseth et al. (1988; 1990) used high performance liquid chromatography with ultraviolet or radioactivity detection to analyze dodecanedioic acid and its metabolites in plasma, urine, feces, and tissue homogenates. Samples were pretreated by ultrafiltration, cation exchange, or trichloroacetic acid precipitation, as appropriate, before ethyl acetate extraction. Azelaic acid or erucic acid was used as an internal standard. Extracts were derivatized with p-bromophenylacetyl bromide using an *N,N*-diisopropylethylamine catalyst prior to high performance liquid chromatography. Passi et al. (1983) purified the derivatives of serum, urine, or feces samples using thin layer chromatography before the liquid chromatography step, and verified the identity of the chromatographed derivatives by mass spectrometry. Capristo et al. (1999) and de Gaetano et al. (1999) applied a similar method to the analysis of the triglyceride of dodecanedioic acid, or the free acid, in plasma and urine samples. The detection limit for the triglyceride was 5 ng. Tserng and Jin (1991) used extraction followed by gas chromatography with flame ionization or electron impact mass spectrometric detection of trimethylsilyl derivatives to analyze for dodecanedioic acid in liver homogenates. Pentadecanoic acid was used as an internal standard. Recovery of dodecanedioic acid was $106 \pm 6\%$. Vamecq et al. (1989) and Draye et al. (1988) used a similar method of extraction and capillary column gas chromatography of trimethylsilyl derivatives, with pentadecanoic acid as an internal standard and flame ionization detection, to analyze dodecanedioic and other organic acids in urine.

5.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

5.1 Sources of Human Exposure

Food is the major source of human exposure to dodecanedioic acid, either directly or indirectly. Dodecanoic acid is an approximately 50% component of coconut and palm kernel oils, and these oils contain a small percentage of the dicarboxylic acid (ChemicalLAND21, 2005; CoconutOil-Online, 2005). Further, dodecanoic acid can be converted *in vivo* to dodecanedioic acid by ω -oxidation in the liver. Animal products also contain dodecanoic acid, although to a lesser extent than the major edible plant products. A serving of lean beef, for example, has approximately 24 mg dodecanoic acid (Nutritiondata, 2005). A continuous infusion of sodium dodecanoate has been tested in humans as an alternate dietary energy source, particularly in diabetic patients, as it is completely metabolized, promotes gluconeogenesis, and does not induce ketogenesis (Greco et al., 1998; Cyberlipid, 2005).

Occupational exposure to dodecanedioic acid is reportedly minimal (OECD/SIDS, 1996), as it is produced in a closed system. The only duties involving potential contact with the substance are bagging and hopper car loading. Other human exposure sources include use of Nylon 612 for consumer products, especially those that contact food or drinking water.

5.2 Sources of Environmental Exposure

Dodecanedioic acid occurs naturally in the fatty acid components of plants and seeds such as coconuts and palms (ChemicalLAND21, 2005). It is also produced by the action of yeasts (Liu and Kuo, 1989) and fungi (El-Sharkawy, 1996). Dodecanedioic acid was a minor component of a marine aerosol sample collected in the North Pacific Ocean (Kawamura and Gagosian, 1988). Environmental contamination could occur during packaging, transport, or use of the chemical as an intermediate, and from waste Nylon 612 and other products deposited in landfills.

6.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

Human and animal studies show that ingested dodecanedioic acid is rapidly distributed to the plasma and tissues. Metabolism occurs in the liver via β -oxidation, to sebacic, suberic, and adipic acids, respective 10-, 8-, and 6-carbon dicarboxylic acids, and then to succinate and acetyl-CoA. Carbon dioxide (20-80%) and urinary excretion (< 10%) account for most of a dodecanedioic acid dose to humans and rats within 24 hours following administration.

6.1 Absorption

Nutritionists have studied dodecanedioic acid for utilization in parenteral nutrition, and have measured the caloric delivery obtained from that use of the chemical in humans (Bertuzzi et al., 2000), suggesting it is well utilized. Detection of carbon dioxide in expired air, and shorter chain fatty acids such as sebacic, suberic, and adipic in rat urine following administration (Bergseth et al., 1988) suggest that dodecanedioic acid is well absorbed in that species.

6.2 Distribution

6.2.1 Studies in Humans

Bertuzzi et al. (1995) used equilibrium dialysis to determine that there were 3.1 binding sites per albumin molecule in human plasma with a $6.4 \times 10^3 \text{ M}^{-1}$ affinity constant. Mingrone et al. (1996), using equilibrium dialysis, determined that there were 2.93 binding sites per albumin molecule in human plasma. They determined an affinity constant of $8.76 \times 10^3 \text{ M}^{-1}$. According to Bertuzzi et al. (1995), dodecanedioic acid had lower affinity for binding with serum proteins than similar chain-length monocarboxylic acids, indicating it could be largely free in serum and more readily available for tissue uptake.

Five healthy human volunteers (three male, two female) were administered powdered dodecanedioic acid, orally in gelatin capsules, once per week for five weeks at increasing doses of 0.5, 1.0, 2.0, 3.5, and 5.0 g (Passi et al., 1983). Using the 68 kg average of the weight range of the subjects, these doses correspond to approximately 7.4, 15, 30, 52, and 74 mg/kg or 1.1, 2.1, 4.2, 7.4, or 11 mg/kg-day averaged over the week. Blood samples were collected hourly for 10 hours after administration for measurement of dicarboxylic acids in serum. Samples collected prior to compound administration served as controls. After the 0.5 g dose, dodecanedioic acid was detected in serum at 0.1 µg/mL two hours after dosing, with only traces (defined as 5-20 ng/mL) detected after three and four hours. After the 5.0 g dose, serum levels of dodecanedioic acid were 0.6, 1.0, and 0.9 µg/mL at the 2-, 3-, and 4-hour sampling times, respectively, with traces detected at the 1- and 7-hour sampling times. Thus, the peak serum level was achieved approximately three hours after ingestion.

Two liquid formula test meals were administered one week apart to five healthy male volunteers of 69.7 kg average weight (Mingrone et al., 1999). Both test meals had 53.3% of calories from glucose and 16.7% from amino acids. The remaining 30% of calories were supplied by either soybean oil emulsion in soybean lecithin or by the disodium salt of dodecanedioic acid with a small amount of [1-12- ^{14}C]radiolabeled dodecanedioic acid. Blood samples were drawn from a venous catheter in an antecubital vein at 0, 10, 20, 30, 40, 60, 80, 90, 120, 150, 160, 180, 200, 240, 260, 270, 280, 300, 330, and 360 minutes for dodecanedioic acid determination. Blood samples every half hour were also analyzed for plasma glucose and insulin. The plasma dodecanedioic acid concentration peaked at 825 mmol/L 120 minutes after the test meal, then declined to 370 mmol/L and < 100 mmol/L at 240 and 360 minutes, respectively. No difference in plasma insulin was observed between the two diets, although there was a borderline significant difference in glycemia.

Greco et al. (1998) infused 0.24 mmol/min sodium dodecanedioate (99.8% purity) in five healthy volunteers and five patients with non-insulin-dependent diabetes mellitus for 195 minutes (~ 55 mg/min; total 10,800 mg or 154 mg/kg). Blood was taken every 15 minutes after the start of infusion, for a period of 360 minutes, for the analysis of plasma dicarboxylic acids. Plasma dodecanedioic acid reached a peak concentration of 1.2 µM approximately 135 minutes after the start of infusion in both healthy and diabetic subjects. Area under the dodecanedioic acid plasma curve was 27% higher in diabetics, but the result was not statistically significant.

6.2.2 Studies in Rats

Mingrone et al. (1994) used equilibrium dialysis to determine the binding of dodecanedioic acid to male Wistar rat serum albumin. Only one binding site was clearly identified, having a dissociation constant of 0.147 mM. They predicted a maximum binding of 1.57 mol/mol albumin. The authors noted that albumin binding of monocarboxylic acids modulated their transport to tissues and cellular uptake, while tissue uptake in this dodecanedioic acid experiment was very fast (5% per minute).

Groups of 10 male Wistar rats were given single 20, 50, or 100 mg doses of powdered dodecanedioic acid in gelatin capsules followed by water (Passi et al., 1983). These doses represented approximately 77, 190, or 390 mg/kg based on the reported weight range of the rats. Blood samples were collected for the analysis of serum dodecanedioic acid before and for six days following dosing. Serum dodecanedioic acid concentrations were 0.5, 0.8, and 0.3 µg/mL at the low dose and 3.4, 4.8, and 2.1 µg/mL at the high dose 24, 48, and 72 hours following compound administration, respectively. Traces of dodecanedioic acid (defined as 5-20 ng/mL) were detected at 96 hours at the two highest doses. In studying a series of dicarboxylic acids, the authors noted that diacid solubility and serum level were inversely proportional to chain length.

Passi et al. (1983) also studied the distribution to serum and tissues in 25 Wistar rats (sex not specified) following administration of 100 µCi of [10,11-³H]dodecanedioic acid. Rats were sacrificed 1, 2, 6, 12, 72, or 96 hours following administration. Lipid extracts of kidneys, liver, heart, pancreas, adipose tissue, brain, adrenals, and lungs were separated into non-carboxylic acid, dicarboxylic acid, phospholipid, and triglyceride fractions. All fractions were analyzed by scintillation counting, the dicarboxylic acid fraction following derivatization of free fatty acids and separation of the derivatives by high performance liquid chromatography. Serum radioactivity rose steadily for 2-3 hours, then declined slowly and was detectable, primarily in the form of diacid metabolites, for at least 72 hours. Total tissue radioactivity was highest in liver, lungs, and kidneys but the label was found in all tissues. Peripheral tissue ³H peaked 24 hours following compound administration and declined slowly thereafter, except in adipose tissue where radioactivity was still increasing at the 96-hour sampling point. Lipid radioactivity included very small amounts of dodecanedioic, sebacic, suberic, and adipic acids for the first 24 hours, but was also detected in all fatty acids whether saturated or unsaturated. The level of radioactivity in residual matter from tissues was higher than the 20-40% found in the lipid extracts. Radioactivity was distributed in the whole phospholipid or triglyceride molecule rather than in just the fatty acid portion. The authors concluded that dodecanedioic acid underwent β-oxidation and that the production of labeled succinyl-coenzyme A or acetyl-coenzyme A, capable of entering the Krebs cycle and other metabolic pathways explained the wide distribution of radiolabel observed.

Bergseth et al. (1988) investigated the fate of dodecanedioic acid *in vivo*. Two male Wistar rats were injected intraperitoneally with 3 µCi (1-¹⁴C) dodecanedioic acid plus a 0.5 µmol tracer dose (~ 0.3 mg/kg) of non-radioactive acid (> 97% purity). Since less than half of the injected radioactivity was recovered in urine and expired CO₂ over a 24-hour period, liver lipids and lipids of the testicular fat pads were analyzed and were found to incorporate 2.7 and 0.6% of the administered radioactivity, respectively.

Bergseth et al. (1988) also perfused male Wistar rat hindquarters with whole blood containing 30 μM dodecanedioic acid for two hours. Only trace amounts of radioactivity could be detected in muscle homogenate, and the perfusate contained almost all the radioactivity when sampled at 30 and 60 minutes and at the end of the 2-hour experiment.

Bertuzzi et al. (1997) investigated the kinetics of dodecanedioic acid in rats. Thirty five male Wistar rats were given intraperitoneal injections, following an 8-hour fast, of 0.8 mmol/kg (~184 mg/kg) disodium dodecanedioate of unspecified purity. Blood samples were taken at unspecified time points 5-90 minutes after the injection. A one-compartment model, which included consideration of binding of dodecanedioic acid to albumin, was used to describe the kinetics of dodecanedioic acid in plasma. Absorption of the acid from the peritoneum into the bloodstream was described by a decreasing exponential with an unknown rate constant. Estimates of 0.275/minute for the absorption rate, 244.5 mL/kg for the distribution volume, 17.82 μmol per minute per kilogram for the maximal rate of tissue uptake, and 138.5 μM for the uptake constant were obtained. Dodecanedioic acid was cleared from rat plasma in about 90 minutes.

In a parallel experiment, Bertuzzi et al. (1997) investigated the effect of dodecanedioic acid on glucose kinetics. Thirty-five male Wistar rats were given intraperitoneal injections, following an 8-hour fast, of 0.8 mmol/kg (~184 mg/kg) disodium dodecanedioate of unspecified purity. Thirty control rats were similarly injected with an equal volume of physiological saline. Immediately after dosing, each of these rats received an intravenous bolus injection of 139 kBq D-[U- ^{14}C]glucose via the tail vein. Blood samples were taken at unspecified time points 5-120 minutes after glucose injection.

Dodecanedioic acid represented approximately 20% of the lipid-derived energy supplied by standard total parenteral nutrition formulations. From the parameter estimates, the glucose pool size was estimated to be 2.30 mmol/kg, and basal disappearance rates of 82.13 $\mu\text{mol}/\text{min}\cdot\text{kg}$ for control rats and 36.71 $\mu\text{mol}/\text{min}\cdot\text{kg}$ for rats treated with dodecanedioic acid were calculated. The rate of disappearance of plasma glucose was lower in rats treated with dodecanedioic acid, but the authors considered this effect transient since dodecanedioic acid was cleared from the plasma in 90 minutes. Recycling between the glucose and precursor pools was reduced in dodecanedioic acid treated rats, attributed to possible reduction of glucose routed to the precursor pool due to glucose precursors (succinate) supplied by dodecanedioic acid. The authors concluded that dodecanedioic acid represented an interesting energy substrate.

Capristo et al. (1999) injected 18 male Wistar rats intravenously via the tail vein with 53 mg of a sodium salt of a triglyceride of dodecanedioic acid. Rats were fasted for 24 hours prior to dosing, and water was used as the vehicle. The molecular weight of the tridodecanedioylglycerol was 728 as an acid and 794 as a sodium salt. No other purity information was provided. Rats were anesthetized and blood samples were collected by cardiac puncture from two rats 5, 10, 20, 30, 40, 50, 60, 80, and 120 minutes after the injection. Plasma was analyzed for the triglyceride and for free dodecanedioic acid and its metabolites. Data were fit to a bi-exponential decay equation. The equation was based on a kinetics model assuming enzymatic hydrolysis of the triglyceride at a rate linearly dependent on precursor concentration, and tissue uptake of the free dodecanedioic acid as a linear function of available free acid. The plasma dodecanedioic acid