

ADIPIC ACID

CAS # 124-04-9

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.
Jackie Russell, M.P.H.

External Peer Reviewers:

NSF gratefully acknowledges the efforts of the following experts on the NSF Health Advisory Board in providing peer review. These peer reviewers serve on a voluntary basis, and their opinions do not necessarily represent the opinions of the organizations with which they are affiliated.

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.

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

Adipic Acid – Oral Risk Assessment CAS # 124-04-9			
PARAMETER	LEVEL	UNITS	DERIVED
NOAEL (no-observed-adverse-effect level)	400	mg/kg-day	From 33-week and chronic repeated dose studies in rats
Oral RfD (oral reference dose)	4	mg/kg-day	From 33-week and chronic repeated dose studies in rats with a 100x total uncertainty factor
TAC (total allowable concentration)	30	mg/L	For a 70 kg adult drinking 2 L/day using a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	3	mg/L	From the TAC, using the default 10 sources of adipic acid in drinking water
STEL (short term exposure level)	100	mg/L	From a 19-week repeated dose study, for a 10 kg child drinking 1 L/day
KEY STUDY	Lang, K., and Bartsch, A-R. 1953. Über den stoffwechsel und die verträglichkeit der adipinsäure. Biochem Zeitschrift 323:462-468; with support from Horn, H.L., E.G. Holland, and L.W. Hazelton. 1957. Safety of adipic acid as compared with citric and tartaric acid. Agric Food Chem 5(10):759-762.		
CRITICAL EFFECT	A weight of evidence NOAEL was established based on effects including reduced survival, diarrhea, decreased body weight during growth, and intestinal and liver pathology.		
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL • 1x for database deficiencies The total uncertainty factor is therefore 100x.		
TOXICITY SUMMARY	Adipic acid has been used as a direct food additive for several decades. The JECFA Acceptable Daily Intake (ADI) is 0-5 mg/kg. Bolus oral doses of up to 10 g (~140 mg/kg for a 70 kg adult) adipic acid were tolerated by humans. Several repeated dose oral studies in rats, from five weeks to lifetime duration, have been conducted on adipic acid resulting in NOAEL values in the range of 400-3,000 mg/kg-day. Decreased body weight was observed in most studies with survival, diarrhea, chronic intestinal inflammation, regeneration activity in the principal part of the kidney, and enlargement of liver cell nuclei and occasionally whole cell volume observed in some instances at high doses. Some of these effects may have been related to administration of adipic acid in a wheat/milk diet, or to acidity of the chemical. Although the feeding studies were old and did not include all the endpoints required under current guidelines, few adverse effects were noted in the examined hematology and clinical parameters, or in the macroscopic and microscopic examination of many organs and tissues after lifetime exposure. The limited correlation of toxicity with exposure duration likely resulted from the rapid (within a few hours) and extensive (~ 70%) metabolism of adipic acid to carbon dioxide. Adipic acid is normally metabolized by the mammalian fatty acid β-oxidation pathway. Developmental toxicity studies in rats, mice, hamsters, and rabbits have been performed with adipic acid. No adverse effects were noted in dams or fetuses at maternal doses approaching 300 mg/kg-day given during the period of organogenesis. Adipic acid was not mutagenic in <i>Salmonella typhimurium</i> reverse mutation assays. Chromosomal aberration assays, although uniformly negative, had sufficient protocol deficiencies based on current guidelines to preclude a conclusion regarding clastogenicity. A chronic study in rats did not detect any treatment-related tumors, but used an inadequate number of animals and assessed too few endpoints to meet current guidelines. Due to deficiencies in the only available chronic study as well as in the genetic toxicity studies, the data are inadequate for an assessment of human carcinogenic potential under current regulatory guidelines.		
CONCLUSIONS	Based on the studies reviewed, the metabolic pathway for adipic acid, and the uncertainty factors applied, the TAC, SPAC, and STEL drinking water action levels derived in this document are protective of public health.		

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **adipic 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 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), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), A Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002), and Health Effects Testing Guidelines (U.S. EPA, 2005b).

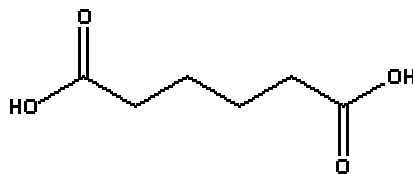
The literature search strategy employed for this compound was based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following data banks were searched:

- ChemID Plus
- 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/ETIC)
- TOXLINE
- Toxcenter (Toxicology Center)
- Chemical Carcinogenesis Research Information System (CCRIS)
- Medline (via PubMed)
- Integrated Risk Information System (IRIS)
- Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS)

The literature search for this chemical was conducted on September 1, 2004 and updated on June 29, 2005. This document includes all relevant information retrieved as a result of those searches.

2.0 PHYSICAL AND CHEMICAL PROPERTIES

Adipic acid is a dicarboxylic acid with synonyms of 1,6-hexanedioic acid, hexanedioic acid, adipinic acid, acifloctin, acinetten, adilactetten, and 1,4-butanedicarboxylic acid. It has the following structure, and physical and chemical properties are listed in Table 1:



Food Chemicals Codex (FCC, 1996) specifications for use of adipic acid as a food ingredient include that it be 99.6-101.0% $C_6H_{10}O_4$, have a melting point in the range of 151.5-154 °C, < 0.0003% (3 ppm) arsenic as As, < 0.001% (10 ppm) heavy metals as Pb, < 0.002% residue on ignition, and < 0.2% water. Aqueous solutions of 0.1, 0.2, 0.4, 0.6, 1.2, and 2.5% adipic acid have pH values of 3.2, 3.1, 3.0, 2.9, 2.8, and 2.7, respectively (Informatics, Inc., 1974). Adipic acid is quite stable to air oxidation even when heated under pressure to approximately 60 °C (Informatics, Inc., 1974).

Table 1. The physical and chemical properties of adipic acid

Property	Data	Reference
Empirical Formula	C ₆ H ₁₀ O ₄	ChemFinder, 2005
CAS#	124-04-9	ChemFinder, 2005
Molecular Weight	146.1426	ChemFinder, 2005
Physical State and Color	Crystals or powder, white	HSDB, 2005
Melting Point	152 °C 153.2	Budavari, 1996 SRC, 2005
Boiling Point	337.5 °C at 760 mm Hg (with decomposition)	SRC, 2005 Informatics, Inc., 1974
Density	1.360	Budavari, 1996
Vapor Pressure	3.18E-007 mm Hg at 25 °C (extrapolated)	SRC, 2005
Water Solubility	14,000 mg/L at 10 °C 30,800 mg/L at 34 °C	HSDB, 2005 SRC, 2005
K _a	K _{a1} = 3.9 x 10 ⁻⁵ K _{a2} = 5.3 x 10 ⁻⁶	Ough, 1963
pK _a	4.44 (experimental) pK _{a1} = 4.4418 at 25 °C pK _{a2} = 5.412 at 25 °C	SRC, 2005 HSDB, 2005 HSDB, 2005
n-Octanol/Water Partition Coefficient (log K _{ow})	0.08 (experimental)	SRC, 2005
Henry's Law Constant (air/water partition coefficient)	4.71E-012 atm·m ³ /mole at 25 °C (estimated)	SRC, 2005

2.1 Organoleptic Properties

Adipic acid in crystal or powder form is odorless, with an acid taste (FAO, 1967; Informatics, Inc., 1974). When equimolar amounts of tartaric, citric, fumaric, and adipic acids were added to a standard white wine, panelists judged adipic acid to be the least sour (Ough, 1963). Panelists preferred citric or tartaric acids to adipic acid.

3.0 PRODUCTION AND USE

3.1 Production

Adipic acid is classified as a high production volume chemical in both the United States (U.S. EPA, 1990) and the European Union (OECD, 2000). This indicates that at least one million pounds per year are produced or imported at each location. Adipic acid is produced in two oxidation steps, the first being the air oxidation of cyclohexane to a mixture of cyclohexanone and cyclohexanol, and the second being nitric acid oxidation of the ketone-alcohol mixture (HSDB, 2005). An alternate production method eliminating the emission of nitrous oxide was proposed by Sato et al. (1998). Cyclohexene was converted directly to adipic acid in a six-step process involving epoxidation using a quaternary ammonium hydrogen sulfate phase-transfer catalyst followed by oxidation with 30% aqueous hydrogen peroxide. Another method for the production of adipic acid was proposed by Niu et al. (2002). It involved batch-fed fermentation to synthesize *cis*-,*cis*-muconic acid from D-glucose using a genetically engineered strain of *Escherichia coli* bacteria, followed by hydrogenation of the *cis*-,*cis*-muconic acid to adipic acid.

3.2 Use

The major use of adipic acid, consuming ~ 85% of production, is in the manufacture of nylon 6/6 fibers and resins. Adipic acid may also be a component of plasticizers, particularly di-2-ethylhexyl adipate, and of cross-linked polyester resins (HSDB, 2005).

Adipic acid is widely used in food as a buffering and neutralizing agent, especially in baking powder and soft drink powders because it is not hygroscopic (Ito et al., 1979). The U.S. Food and Drug Administration (U.S. FDA, 2005) lists numerous acceptable uses of adipic acid as a direct or indirect food additive. Adipic acid is affirmed as generally recognized as safe (GRAS) as a direct food additive with purity and use limitations under 21 CFR 184.1009. Specified good manufacturing practice maximum levels on an as served basis are 5.0% for condiments and relishes; 1.3% for snack foods; 0.55% for gelatin and puddings; 0.45% for dairy product analogs; 0.3% for fats and oil; 0.3% for meat products; 0.1% for gravies; 0.05% for baked goods; 0.005% for non-alcoholic beverages; 0.0004% for frozen dairy desserts; and 0.02% or less for all other food categories. The major indirect food additive use for adipic acid is as a monomer in food grade polyamide or polyester polymers. Adipic acid polymers are sanctioned under the U.S. Code of Federal Regulations, Title 21 (U.S. FDA, 2005) for use as components of paper and paperboard in contact with aqueous and fatty (176.170) or dry (176.180) foods; as components of resinous and polymeric coatings (175.300) or resinous and polymeric coatings for polyolefin films (175.320); or as a component of cellophane (177.1200), laminates for use at ≥ 250 °F (177.1390), nylon resins (177.1500), polyethylene phthalate polymers (177.1630), polyurethane resins (177.1680), cross-linked polyester resins (177.2420), and rubber articles intended for repeated use (177.2600).

Food grade adipic acid is used in pH adjustment prior to polymerization of some polymeric coagulation and flocculation chemicals evaluated under NSF/ANSI 60 (2005). This use results in negligible adipic acid in the finished treatment chemical. Food grade adipic acid is also used as a component of some tracer dyes certified under NSF/ANSI 60 (2005) for brief and infrequent use, generally at the part-per-billion level, or for off-line use with flushing prior to use of the system for drinking water. NSF interest in a risk assessment for adipic acid is as a surrogate for a proprietary alicyclic polyester dimer, and for adipic acid ester lubricant components.

4.0 ANALYTICAL METHODS

Since adipic acid is not volatile, many analytical methods depend on the use of derivatives. Older methods used the melting point of one or more derivatives including amide, anilide, p-toluidide, p-nitrobenzyl ester, p-bromophenacyl ester, or p-phenylphenacyl ester for identification (Informatics, Inc., 1974). Other early methods included isotope dilution, partition chromatography, and infrared absorption of the sodium salt (Informatics, Inc., 1974). Current methods are generally based on gas chromatography after derivatization to increase volatility.

4.1 General Methods of Analysis

Early investigators used thin layer chromatography to analyze adipic acid. Passera et al. (1964) separated complex mixtures of carboxylic acids using silica gel thin-layer chromatography plates

washed free of iron and other ions with an ethylene diamine tetraacetic acid solution. Two solvent systems, 70:30 propanol:ammonia and 70:40:20:2 ethanol:chloroform:ammonia:water, were used to separate acids and keto acids, including adipic acid. Color was developed using 2,6-dichlorophenolindophenol in 95% alcohol. Carboxylic acids retained the color longer under ultraviolet light than keto acids, thus allowing them to be distinguished. Miyazaki et al. (1969) separated aliphatic dibasic acids by thin layer chromatography using silica gel-kieselguhr plates impregnated with aqueous acetic acid vapors and developed using a 100:17.5 v/v solution of benzene and 80% aqueous acetic acid. Dibasic acids were detected using 0.2% alcoholic bromocresol green at pH 6. Monobasic acids migrated with the front and did not interfere.

Complex mixtures of mono- and dicarboxylic acids were analyzed by derivatization to their methyl esters with a boron trifluoride-methanol solution, separation by packed column gas chromatography, and detection using thermal conductivity or flame ionization (de Lindemann, 1970). Overlapping peaks were occasionally observed. Some branched acids interfered with the analysis of n-acids, and interference also occurred when the monocarboxylic acid content of the sample was much greater than the dicarboxylic acid content.

Ito et al. (1979) analyzed aqueous solutions of soft drink powders and crackling candy for adipic acid, by first adjusting the pH to >10 and extracting with diethyl ether, discarding the ether containing fatty substances. The aqueous layer was then adjusted to $\text{pH} < 2$, saturated with sodium chloride, and extracted with diethyl ether. The ether extract was dried, filtered, concentrated under vacuum, and methylated with diazomethane. After adjusting to volume, an aliquot of the derivatized sample was analyzed by packed column gas chromatography with flame ionization detection. The detection limit was 1 ppm, and recoveries of 20 or 200 ppm adipic acid from crackling candy or of 200 ppm adipic acid from reconstituted grape or orange soft drink mix ranged from 91.3-98.2%, with the lowest recovery from the sample spiked with 20 ppm adipic acid.

Lindström et al. (2004) tested C_8 , C_{18} and end-capped C_{18} silica and hydroxylated polystyrene-divinylbenzene resin solid sorbent extraction tubes for the separation of adipic acid as a hydrolysis product of poly(butylene adipate). Acidic methanol was the preferred extraction solvent, as it converted the acid to its methyl ester. Analysis was by capillary column gas chromatography with electron impact mass spectrometric detection. The extraction efficiency was 79% for adipic acid, and the linear calibration range was 1-500 ng/ μL .

An analytical method for adipic acid as a hydrolysis product of acetylated di-starch adipate, using glutaric acid as an internal standard, was developed by Mitchell et al. (1982). After acidification of the sample, free adipic acid was formed and extracted with ethyl acetate. Solvent was removed by vacuum distillation, and the trimethylsilyl derivative of adipic acid was prepared using N,N-bis-trimethylsilyl-trifluoroacetamide. The derivative was analyzed by packed column gas chromatography with flame ionization detection. The detection limit was reported to be 0.10 $\mu\text{g/g}$.

4.2 Analysis in Biological Matrices

Several groups have used variations of the same method to analyze adipic acid and other dicarboxylic acids in urine. A measured amount of urine was acidified to pH 1.0 and extracted. The dried, concentrated extract was methylated (Borg et al., 1972; Liebich et al., 1980) or silylated (Gregerson et al., 1980a; Naylor et al., 1980) to form methyl or silyl derivatives of the dicarboxylic acids. These derivatives were separated by gas chromatography, and detected and quantitated using either flame ionization or mass spectrometric detection.

Naylor et al. (1980) modified this method to detect lesser quantities of dicarboxylic acids in normal urine and serum. The extraction solvent was 2:1 v/v chloroform:methanol, and the derivatizing agent was sulfuric acid in n-butanol. The resulting di-n-butyl esters were analyzed by gas chromatography with flame ionization and/or mass spectrometric detection. An additional clean-up step was used for serum samples, separating the carboxylic acid n-butyl esters from the fatty acid n-butyl esters using a short silica gel column prior to gas chromatography.

Urinary adipic acid has also been analyzed using diethyl ether extraction, derivatization with 9-anthryldiazomethane to form a fluorescent compound, separation by reverse phase high performance liquid chromatography, and fluorescence detection (Yoshioka et al., 1994). Recovery from urine spiked with 34.2-137.0 $\mu\text{mol/L}$ (5-20 mg/L) adipic acid ranged from 92-106%. Although there was good correlation ($r = 0.993$) between this method and analysis by gas chromatography/mass spectrometry, results from the high performance liquid chromatography method were consistently lower.

Hagan et al. (1999) developed a urine screening method to detect 14 organic acidemias. A specified volume of urine incorporating 2-ketocaproic acid as an internal standard was prepared and applied to a modified diatomaceous earth solid phase extraction column. The eluate was dried, reacted to form silyl derivatives, brought to the desired volume with n-hexane, and analyzed by capillary column gas chromatography with detection by ion trap mass spectrometry. The upper limit of linearity for adipic acid was 1 ng/ μL (1 $\mu\text{g/mL}$).

A direct alkylation method for the determination of adipic acid in urine was developed by Adinolfi and Bicking (1985). Urine was extracted with methyl iodide in dichloromethane, using 1-phenylhexane as an internal standard, and analyzed by gas chromatography. Extraction was done at high dilution and with added mercuric sulfate to overcome inhibition of the extraction by urinary chloride. The only significant chromatographic peaks were adipic acid and the internal standard, making the method selective for adipic acid. In the event of chromatographic interference, ethyl iodide could be used to prepare the ethyl rather than the methyl derivative.

5.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Food is the major source of human exposure to adipic acid, where it is used as a direct food additive. Drinking water and consumer products, as well as air, surface water, wastewater, and groundwater pollution represent relatively minor sources of human exposure. Industrial

effluents, combustion products, and photochemical reactions in the atmosphere represent potential environmental adipic acid sources.

5.1 Sources of Human Exposure

Adipic acid is a commonly occurring trace constituent in human serum and urine, as measured in newborns and children. Borg et al. (1972) reported mean adipic acid levels in the urine of four normal newborns and two normal 0.5-1 year old children as 0.01 and ~ 0.002 mmol/L (1.46 and ~ 0.29 mg/L), respectively. Gregersen et al. (1980b) reported adipic acid concentrations on the order of 2-62 µg/mg creatinine in 10 normal newborns. The mean urinary adipic acid concentration in a group of 10 children 3-9 years old was 2-15 µg/mg creatinine, and the mean serum adipic acid level in a group of 10 children 5-13 years old was 2-5 µg/100 mL (Gregersen et al. (1980a).

The largest and most likely source of human exposure to adipic acid occurs as a result of its use as a direct food additive (U.S. FDA, 2005). Indirect food additive use may also result in exposure. Adipic acid is the major metabolite of the plasticizer di-(2-ethylhexyl) adipate, used in medical devices and food and water contact materials (Takahashi et al., 1981). Nylon, polyester, and other polymers incorporating adipic acid used in food and drinking water contact may result in exposure, although the adipic acid is incorporated into the polymer chain in these applications and is therefore much less available. Exposures may result from adipic acid in drinking water, air or soil, but these sources would be negligible in comparison with dietary exposure.

5.2 Sources of Environmental Exposure

5.2.1 Air

Numerous atmospheric studies have identified adipic acid as a primary or secondary air pollutant. Exhaust samples from gasoline and diesel engines collected under idling conditions had concentrations of adipic acid 28 and 144 times, respectively, the ambient air concentrations in Los Angeles, California (Kawamura and Kaplan, 1987). This led the authors to conclude that engine exhaust was a primary source of atmospheric adipic acid. Rogge et al. (1991) reported that fine carbon particles from frying or charbroiling meat resulted in fine aerosol adipic acid emission levels of 1.6-17.2 mg/kg meat. The aerosol concentration was dependent on the method of cooking (charbroiling > frying) and the type of meat (regular hamburger > extra lean hamburger).

Schuetzle et al. (1975) identified adipic acid in samples of Pasadena, California air particulates collected during the fall of 1972. Adipic acid was detected in particulate samples having diameters of 1-2 µm or less, but not in samples having greater diameters. Concentrations over a 24-hour period ranged from 0.04 to 0.78 µg/m³. Significant diurnal variation, with a peak in mid-afternoon, suggested that adipic acid was a secondary pollutant derived from photochemical oxidation. Adipic acid was also reported in the range of 1.5-8.9 µg/m³ in nine samples of atmospheric particles having diameters ≤ 3.5 µm taken in a 24-hour period during a photochemical smog episode in Southern California during the summer of 1973 (Cronn et al., 1977). The maximum concentration again occurred in mid-afternoon, coinciding with the ozone

maximum and leading the authors to suggest oxidation of cycloalkenes and diolefins as a likely source. Concentrations of atmospheric adipic acid at sites in downtown and west Los Angeles, California ranged from 0.08-3.31 nmol/m³ or 0.012-0.48 µg/m³ (Kawamura and Kaplan, 1987). Atmospheric adipic acid showed a seasonal trend, with a maximum in Southern California air during June, 1982 (Rogge et al., 1993).

Yokouchi and Ambe (1986) identified adipic acid in aerosol samples collected in April, 1985 in a suburban area 60 km northeast of Tokyo, Japan surrounded by agriculture and forests with occasional motor vehicle traffic. Average concentrations of 2.3 and 5.2 ng/m³ adipic acid were also detected in two inland mountainous locations in Japan, suggesting long-range transport and photochemical transformation from coastal areas with large pollution sources (Satsumabayashi et al., 1990). Adipic acid concentrations in aerosol samples taken in Tokyo, Japan during 1992 were in the range of 31-79 ng/m³ (Semépré and Kawamura, 1994). Atmospheric adipic acid also showed a seasonal trend in Tokyo, Japan, with a maximum in August during 1988-1989 (Kawamura and Ikushima, 1993). Adipic acid has been detected at a much lower concentration of 0.039 ng/m³ in a remote marine location in the North Pacific Ocean, suggesting natural oceanic precursors (Kawamura and Gagosian, 1987). Adipic acid has been detected in ≤ 10 µm 24-hour aerosol samples from Christchurch, New Zealand (Wang and Shooter, 2004). Mean concentrations of glutaric plus adipic acids, which could not be separated by the analytical method used, were 7.2 ng/m³ in the summer of 2001, and 38 ng/m³ in the winter of 2002. Higher concentrations in winter were attributed to extensive burning of wood and coal.

Atmospheric adipic acid has been shown to be washed out by various forms of precipitation. Kawamura et al. (1996) analyzed adipic acid in samples from three snow and nine rain events in Southern California from late 1982 to mid-1984. The snow samples had concentrations in the range of 0.006-0.054 µM (~ 0.9-7.9 µg/L). The rain samples had concentrations in the range of 0.031-0.47 µM (~ 4.5-69 µg/L). Initial samples taken by Sempéré and Kawamura (1994) in Tokyo, Japan during two rain events and one snow/sleet precipitation event had adipic acid concentrations of 3.07-5.17 µg/L. When sequential samples were taken during a precipitation event, both studies showed a trend in the dicarboxylic acid concentration to decrease over time, although adipic acid had some deviations from this trend. Travis et al. (1987) reported that adipic acid was one of the 10 most abundant constituents of materials in hazardous waste streams incinerated, with 36,100 metric tons of adipic acid incinerated per year.

5.2.2 Water

Dowden and Bennett (1965) reported that the median tolerance limit of the fish *Lepomis macrochirus* to adipic acid in a reference dilution water was < 330 mg/L. Leenheer et al. (1982) reported 4.7 mg/L adipic acid in process retort water from oil shale processing. Adipic acid was one of numerous petrochemicals shown to be amenable to methane fermentation treatment (Chou et al., 1978). Under laboratory conditions after a 10-day lag time, enriched acetate cultures were able to remove adipic acid at the rate of 50 mg/L-day. After 90 days of acclimation, the utilization rate of adipic acid was 67%. Adipic acid was also well degraded in each of six tests of biodegradability used by Gerike and Fischer (1979): the coupled unit test and the Japanese MITI test as models for communal sewage treatment; the Zahn-Wellens test and the Swiss EMPA test as models for industrial sewage treatment; and the Sturm, modified OECD screening

and closed bottle tests as models for surface water treatment. Zahn and Wellens (1980) reported > 90% degradation of adipic acid within five days, with a one-day adaptation time, in their standardized test using activated sludge. Biodegradation of adipic acid was also good in an aqueous non-acclimated activated sludge solution when measured by electrolytic respirometry (Urano and Kato, 1986).

5.2.3 Dust and Soil

Kawamura and Kaplan (1987) reported 78.0 and 40.4 nmol/g (11.4 and 5.9 µg/g) adipic acid in dust near the University of California at Los Angeles geology building and in downtown Los Angeles, respectively. They also reported 1.47 nmol/g (0.21 µg/g) in soil around the geology building and 3.89 nmol/g (0.57 µg/g) in soil on the north campus. The fulvic acid fraction of a bog sediment sample had 14 nmol/g (2.0 µg/g) adipic acid.

Soil samples collected from beneath a landscape lawn were capable of degrading adipic acid to carbon dioxide (Sharabi and Bartha, 1993). At 1 mg/g soil, 84% of the added adipic acid was converted to carbon dioxide within 30 days, with approximately 63% conversion during the first week. When added to 25 g of soil at 0.25, 0.5, 1.0, or 2.0 mg/g, 78.8, 79.1, 91.5, or 94.1% of the adipic acid, respectively, could be accounted for as carbon dioxide within 22 days.

5.2.4 Natural Sources

Certain microorganisms are capable of producing adipic acid. A *Pseudomonas* species microorganism capable of using cyclohexane as its sole carbon source was isolated by Anderson et al. (1980). Cell-free extracts of this organism were capable of oxidizing cyclohexanone to 6-hydroxyhexanoate that, under aerobic conditions, was further metabolized to adipate. Trower et al. (1985) isolated a *Xanthobacter* species microorganism also capable of using cyclohexane as the sole carbon source through the same sequential reaction to cyclohexanol, cyclohexanone, ε-caprolactone, 6-hydroxyhexanoate, and finally adipic acid.

6.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

Human studies have shown that a single oral dose of up to 50 g adipic acid was tolerated, although causing diarrhea in some subjects. Human doses in the range of 1-10 g were well tolerated and showed dose-dependent urinary excretion of 30-80% of the administered dose within 48 hours. Saturation of the metabolic pathway(s) was inferred, since higher doses resulted in greater excretion of the parent compound.

Nearly complete gastrointestinal absorption of orally administered adipic acid was inferred from metabolism studies in laboratory animals and elimination/excretion studies in humans and animals. Adipic acid was not retained to an appreciable extent in peripheral tissues. The key metabolism study in rats demonstrated 70% conversion to carbon dioxide and seven urinary metabolites, with five of those identified and one tentative identification.

6.1 Absorption

Rusoff et al. (1960) dosed unspecified numbers of male Carworth Farms albino rats with 50 mg of 1-¹⁴C or 2-¹⁴C adipic acid by gavage in water. Based on total radioactivity recovered from breath and urine samples collected during overnight fasting following dosing, the authors concluded that adipic acid was almost completely absorbed at the dosed concentration.

6.2 Distribution

Adipic acid has been found at autopsy in the aqueous humor of a patient with a disorder of fatty acid metabolism (Coude et al., 1991). The level in aqueous humor was about one third of that found in the plasma.

Enders (1941, as summarized in Informatics, Inc., 1974) dosed young rats at 0.243 g/day and adult rats at 0.73 g/day by gavage for four weeks. Rats sacrificed 72 hours after the last dose had no detectable accumulation of adipic acid in tissues.

Rusoff et al. (1960) dosed unspecified numbers of male Carworth Farms albino rats with 50 mg of 1-¹⁴C or 2-¹⁴C adipic acid by gavage in water. Animals were sacrificed after overnight fasting. Radioactivity in organs and tissues was minimal with the liver and kidney having the highest residual radioactivity levels. Quantitative data were not reported.

6.3 Metabolism

6.3.1 Studies in Humans

Weitzel (1942) studied the fate of ingested adipic acid in three human subjects. Subjects were maintained on a calorically sufficient control diet free of meat and milk, consisting primarily of potatoes, bread, and 50 g olive oil per day. The protocol for the first two subjects consisted of up to four days on the control diet, with 1.46, 2.92, 4.38, and 7.30 g ((21, 42, 63, and 104 mg/kg) adipic acid added to the diet as single doses in water solution on the subsequent four days. The subjects were given the control diet for one day until urinary excretion of the highest dose was complete, and then another 7.30 g (104 mg/kg) adipic acid dose was administered, but this dose was divided and given throughout the day. The protocol for the third subject omitted the two lower doses and, following the control diet, consisted of 4.38 g (63 mg/kg) as a single dose on Day 1, 7.30 g as a divided dose (35 mg/kg x 3) on Day 3, and 7.30 g (104 mg/kg) as a single dose on Day 5. Daily 24-hour urine samples were collected throughout the study, and 10% of each sample was used for analysis of urinary adipic acid. Adipic acid dosed but not accounted for by urinary excretion was said by the authors to have been “processed” (metabolized) by the body.

The first subject excreted 37, 41, and 56% of the three lowest doses as urinary adipic acid within 24 hours of dosing, and 73 and 75% of the high and divided high doses within 48 hours. The second subject excreted 58, 66, and 66% of the three lowest doses within 24 hours of dosing, plus 74% of the high dose and 58% of the divided high dose within 48 hours. The third subject excreted 15% of the 4.38 g (63 mg/kg) dose within 24 hours, as well as 22% of the divided high

dose and 30% of the single high dose within 48 hours. The author concluded that smaller quantities of adipic acid were better utilized than greater quantities, that there was considerable individual variation in the utilization of adipic acid, and that a divided dose was more efficiently utilized than the same dose administered as a bolus.

Early interest in the human metabolism of adipic acid focused on its potential conversion to oxalic acid (Kabelitz, 1943). Two healthy subjects consumed a standard low-oxalate diet for four days prior to initiation of the experiment, and for the three experimental days. Adipic acid was given directly in one experiment, and as its glyceride in a second experiment, by duodenal probe at a dose of 50 g. Urine was collected for oxalic acid analysis two days before, the day of, and two days following administration of the compound. Only results from administration as the glyceride were reported. The author stated there was no significant difference following acid or glyceride administration. A few subjects experienced vomiting or diarrhea following compound administration and were replaced in the study. Mean urinary oxalate concentrations pre-and post-dosing were, respectively, 16.2 and 17.9 mg for Subject 1 and 12.3 and 13.1 mg for Subject 2. The author concluded that the urinary excretion of oxalic acid by humans was not significantly affected by either adipic acid or any of the other dicarboxylic acids studied.

6.3.2 Studies in Laboratory Animals

Mori (1918) studied the metabolism of adipic acid, synthesized by the author, in rabbits of unspecified strain. Five rabbits were used with varying protocols, and all dosing was by subcutaneous injection. The first rabbit was administered 2.0 g doses of adipic acid on Days 1, 11, and 19, followed by a 0.8 g dose, divided into four portions given at 3-hour intervals, on Day 26 and another 0.8 g dose given at once on Day 30. The second rabbit was administered a 2.0 g dose on Day 1, and a 0.8 g dose, divided into four portions given at 3-hour intervals, on Day 9. The remaining three rabbits were administered single 0.8-g doses. Adipic acid in the urine was determined by crystallization and confirmed by combustion analysis. Urinary oxalic acid was also determined. Average recovery of adipic acid in all experiments was 61.63 %, with the range in multiple dose experiments from 48.73-63.80%, and the range in the three single-dose experiments from 70.30-73.63%. Oxalic acid was detected up to 0.019 g following the 2.0-g doses, and at up to 0.0084 g following the 0.8 g doses. Thus, approximately 1% of the adipic acid dose was recovered as urinary oxalic acid.

Rose et al. (1925) studied the nephrotoxicity of a series of dicarboxylic acid in rabbits. 1,5-Pentanedioic acid (glutaric acid) was highly nephrotoxic but there were no significant differences in nephrotoxicity between other even- and odd- carbon dicarboxylic acids. The authors concluded that β -oxidation of dicarboxylic acids was unlikely because odd-carbon acids would yield glutaric acid and produce more nephrotoxicity than was detected in their experiment.

The metabolism of dicarboxylic acids was studied in liver slices of an unspecified strain of rat (Edson, 1936). The general conclusion was that metabolism increased oxygen consumption and that adipic acid was not ketogenic in well-nourished liver and was not antiketogenic in the liver of starved animals.

Lang and Bässler (1953) showed that adipic and other dicarboxylic acids were metabolized through the tricarboxylic acid cycle of the rabbit kidney, but not the rabbit liver. The authors concluded that metabolism of dicarboxylic acids did not remain at an intermediate stage but always proceeded to carbon dioxide and water. Lang and Bartsch (1953) concluded, on the basis of an elimination study in rats, that adipic acid did not induce its own metabolism.

Rusoff et al. (1960) dosed unspecified numbers of male Carworth Farms albino rats with 50 mg of 1-¹⁴C or 2-¹⁴C adipic acid by gavage in water. Animals were fasted while expired air and urine samples were collected overnight (24 hours) following dosing. Approximately 70% of the administered radioactivity was recovered as exhaled carbon dioxide. Expired carbon dioxide peaked at approximately 60 minutes in rats dosed with 1-¹⁴C adipic acid and declined rapidly thereafter. The peak carbon dioxide concentration occurred approximately 90 minutes after rats were dosed with 2-¹⁴C adipic acid and the exhaled carbon dioxide concentration declined slowly thereafter. The authors concluded that the carboxyl group carbon was metabolized faster than the second carbon of adipic acid.

Fractionation of the urine samples on an ion-exchange column resulted in seven radioactive peaks, with no significant qualitative or quantitative differences in samples from rats dosed with 1-¹⁴C or 2-¹⁴C adipic acid. One peak could not be identified, and one peak represented unchanged adipic acid. Remaining peaks represented urea, glutamic acid, lactic and β -ketoadipic acids (co-eluted), malic acid (tentative identification), and citric acid. The authors noted that lactic acid could have been an end product of succinic acid.

Identification of β -ketoadipic acid suggested that β -oxidation was involved in the metabolism of adipic acid. Two additional experiments were performed in order to investigate this possibility. In the first, fasted male Carworth Farms albino rats (unspecified number) were dosed by stomach tube with 50 mg 1-¹⁴C adipic acid in 3 mL water, and were also injected intraperitoneally with 2 mL of 0.5M sodium malonate to inhibit the oxidation of succinate, but not acetate. Radioactive succinic and adipic acids were identified in 24-hour urine samples from these rats. In the second experiment, male Carworth Farms albino rats (unspecified number) were dosed in feed with 250 mg/kg 1-¹⁴C adipic acid and 100 mg γ -phenyl- α -aminobutyric acid in order to accumulate urinary acetate. The presence of radioactive acetyl- γ -phenyl- α -aminobutyric acid in 48-hour urine samples led the authors to conclude that substantial use of part of the adipic acid molecule to form acetyl groups occurred. When sacrificed two hours after dosing, fasted male Carworth Farms albino rats dosed by stomach tube with 100 mg 1-¹⁴C adipic acid and 400 mg glucose in water solution were reported as having radioactive glycogen in their livers.

Rusoff et al. (1960) also dosed male Carworth Farms albino rats with ¹⁴C sodium bicarbonate and nonradioactive adipic acid to determine whether radioactive carbon dioxide had a role in metabolite formation. Radioactive citric acid was formed, suggesting to the authors that radioactive carbon dioxide interacted with a non-radioactive adipic acid intermediate.

The metabolism of adipic acid based on the experiments of Rusoff et al. (1960) is summarized in Figure 1.

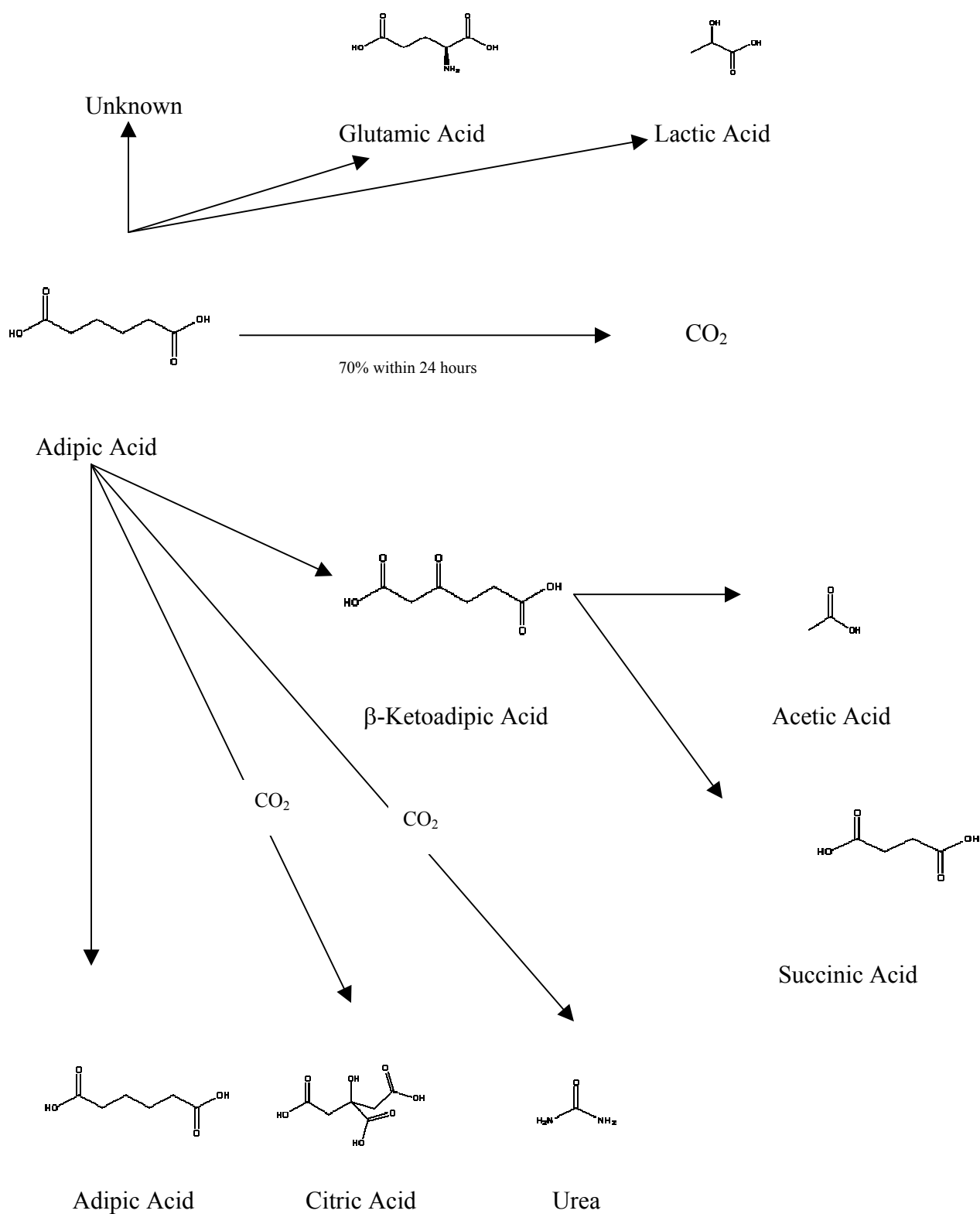


Figure 1. Adipic acid, conversion to carbon dioxide and urinary metabolites (based on Rusoff et al., 1960)

Bates (1989) measured expired $^{14}\text{CO}_2$ and urinary radioactivity for three hours after dosing groups of weanling, young adult, and adult Norwegian Hooded rats intragastrically with $[1,6\text{-}^{14}\text{C}]$ adipic acid. Measurements were made after the rats had been made riboflavin deficient through the diet and again after intragastric administration of flavin mononucleotide for tissue repletion. Percentages of the adipic acid dose in expired air for the riboflavin deficient and riboflavin repleted rats were, respectively, as follows: 13.1 and 23.7 for weanling rats; 16.4 and 30.0 for young adult rats; and 11.0 and 20.2 for adult rats. In all groups, riboflavin deficiency reduced the rate of adipic acid oxidation, which was restored by riboflavin repletion. Urinary radioactivity was significantly increased in riboflavin deficient rats of all ages, and was attributed to, although not positively identified as, unchanged adipic acid.

Kølvraa and Gregersen (1986) studied the metabolism of adipic acid *in vitro* using intact, purified female Wistar rat liver mitochondria and peroxisomes. Adipic acid was metabolized as far as succinic acid when formed intramitochondrially from higher dicarboxylic acids, but was not formed when added externally to the organelles. The authors concluded that either adipic acid could not be transported across the mitochondrial membrane, or that its K_m value of $980 \pm 90 \mu\text{mol/L}$ towards the acyl-CoA dehydrogenases was too high.

Haarhoff (1969) showed that adipic acid and other dicarboxylic acids were linear competitive inhibitors of the substrate pair 2-oxoglutarate/aspartate for aspartate aminotransferase. The author calculated K_1 , the value of the dissociation constant for adipic acid in competition with aspartate for the form of the enzyme with which it binds, and K_2 , the value of the dissociation constant for adipic acid in competition with 2-oxoglutarate. There was reasonable agreement between these calculated constants and those determined by other means.

Commercial cross-bred pigs fed a standard diet incorporating 1% adipic acid for seven days displayed significantly reduced plasma leucine, glutamine, alanine, and proline, as well as a significantly increased (18%) plasma lysine (van Kempen et al., 2001). In a second experiment (van Kempen et al., 2001) pigs were fed low lysine, low threonine, or low tryptophan diets (70% of the requirement for each) with or without incorporation of 1% adipic acid for seven days. Average daily food intake and average daily weight gain were significantly reduced for all three diets incorporating adipic acid when compared with the control diet or the deficient diets without adipic acid. The authors concluded that the effects on amino acid metabolism were not the result of inhibition of the lysine degradation pathway.

6.4 Elimination/Excretion

The metabolism experiments of Mori (1918) in rabbits showed that the average urinary recovery of unchanged adipic acid ranged from 48.73-63.80% in multiple dose experiments, and from 70.30-73.63% in single-dose experiments following subcutaneous injection of the chemical at 0.8-2.0 g (260-650 mg/kg). Enders (1941, as summarized in Informatics, Inc., 1974) dosed rabbits with 2.43 g/kg adipic acid by gavage daily for two days, and collected urine for six days following the initial dose. Urinary excretion of adipic acid accounted for 57% of the administered dose, with maximum excretion on the second day and no detectable excretion on the fifth or sixth days.