6-7-05

Provisional Peer Reviewed Toxicity Values for

Hexadecanoic acid

(CASRN 57-10-3)

Derivation of Subchronic and Chronic Oral RfDs

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

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
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
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
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 inhalation reference concentration**
p-RfD	**provisional oral reference dose**
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

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Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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 (PPRTV) 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 Table (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 Integrated Risk Information System (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 multi-program 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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript 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

Hexadecanoic acid, also called palmitic acid, is a saturated long hydrocarbon chain carboxylic acid. This 16-carbon saturated fatty acid is found in practically all vegetable oils and animal fats (Anonymous, 1987). A subchronic or chronic RfD for hexadecanoic acid is not available on IRIS (U.S. EPA, 2003), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). No relevant documents were located on the CARA list (U.S. EPA, 1991, 1994). ATSDR (2003), NTP (2003), IARC (2003), and WHO (2003) have not produced documents regarding hexadecanoic acid. Literature searches of the following databases were conducted in 1991 for hexadecanoic acid: TOXLIT (1965-1991), TOXLINE (1981-1991), MEDLINE (1980-1991), CANCER (1963-1991), ETIC, HSDB, and RTECS. Literature searches of TOXLINE, RTECS, and TSCATS were conducted again in May 1994. Update literature searches from 1994 through June 2003 were conducted in the following

databases: TOXLINE (supplemented with BIOSIS and NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. Additional literature searches from June 2003 through July 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

No data were located on the health effects of hexadecanoic acid itself in humans. However, there is an extensive database establishing a link between a diet high in saturated fatty acids and an increased risk of coronary heart disease, and in particular atherosclerosis. Atherosclerosis is characterized by the presence of plaques in the intimal layer of large and medium-sized arteries. In the developing atherosclerotic lesion, there is an accumulation of lipids, especially cholesterol and cholesterol esters. The etiology of atherosclerosis is equivocal, but is generally believed to be multifactorial. The primary risk factors are hypertension, elevated blood lipid levels, and smoking. Age, heredity, sex, lack of exercise, and personality type are also risk factors (Barna and Biro, 1989; Castelli, 1983). Both the total intake of dietary fat and the type of fat can influence plasma cholesterol levels. As reviewed by Connor and Connor (1990), a positive correlation has been established between dietary saturated fatty acids and plasma cholesterol levels (discussed below). The rise in plasma cholesterol levels associated with dietary saturated fatty acids is primarily due to an increase in low density lipoprotein (LDL) cholesterol. Dietary saturated fatty acids suppress hepatic LDL receptor activity and decrease the removal of LDL from blood, resulting in an increase in LDL cholesterol levels in the blood.

As reviewed by Nordoy and Goodnight (1990), Connor and Connor (1990), and Zemel and Sowers (1990), the evidence relating diet to atherosclerosis is largely based on epidemiological studies, dietary intervention studies, and animal studies. A number of epidemiological studies have been conducted. For the most part, these studies have found significant correlations between mortality from coronary-heart disease and dietary intake of saturated fats and cholesterol. One of the largest epidemiological studies comparing different populations was the Seven Countries Study, conducted by Keys (1970). Using men aged 40-59 years from 18 communities in Finland, Greece, Italy, Japan, Netherlands, United States, and Yugoslavia, the rate of coronary heart disease (myocardial infarction and death from coronary heart disease) was compared to components of the diet (dietary information was collected from 7-day food records). A positive statistically significant correlation was found between coronary heart disease rate, serum cholesterol, and dietary intake of saturated fat. In another study (Kato et al., 1973), referred to as the Ni-Hon-San study, dietary habits and coronary heart disease mortality were examined in men of Japanese ancestry living in Nissei (Japan), Honolulu, and San Francisco. The percentage of calories from saturated fat was 7% in Nissei, 12% in Honolulu, and

14% in San Francisco. The lowest rate of mortality from coronary heart disease was found in the men living in Nissei. The mortality rate was 1.7 times higher in the Honolulu population and 2.8 times higher in the San Francisco population. These findings suggest an association between intake of saturated fatty acids and coronary heart disease.

A number of large-scale dietary intervention studies have been performed to assess the role of dietary changes in the reduction of serum cholesterol and risk of coronary heart disease. Dietary intervention studies are designed to determine if experimentally manipulating the diet (e.g., decreasing cholesterol and saturated fatty acid intake, or increasing intake of polyunsaturated fatty acids) will result in a decrease in coronary heart disease. Studies such as the Multiple Risk Factor Intervention Trial (MRFIT) have suggested that a reduction in serum cholesterol by changes in the diet is associated with a lower mortality from coronary heart disease (Kannel et al., 1986). In the MRFIT study, approximately 6500 men aged 35-57 years at high risk for developing coronary heart disease were given stepped-care treatment for hypertension, counseling for smoking cessation, and dietary advice for lowering blood cholesterol. A similar control group was referred to usual sources of health care in the community. The men were followed for 7 years (Multiple Risk Factor Intervention Trial Research Group, 1982). The dietary intervention studies are often difficult to interpret because most of the studies involve the simultaneous reduction of several risk factors and the study population is typically individuals who had an initial increased risk of coronary heart disease.

Although the evidence associating a diet high in saturated fatty acids to an increased risk of coronary heart disease is fairly strong, a cause and effect relationship has not be established. The etiology of coronary heart disease is likely to be multifactorial. The Framingham Study and other large prospective studies have identified a number of risk factors for coronary heart disease. The Framingham Study followed approximately 5000 men and women over a period of 18 years (Castelli, 1983). This study identified the following risk factors for coronary heart disease: elevated blood cholesterol levels, low high density lipoprotein (HDL) cholesterol, elevated LDL cholesterol, hypertension, left ventricular hypertrophy, high serum glucose levels, excess body weight, cigarette smoking, lack of exercise, and Type A personality type. The Framingham Study also demonstrated interactions between the risk factors. For example, a 50 year old man who smokes cigarettes, with a systolic blood pressure of 120 mm Hg, and a blood cholesterol level of 210 mg/dl has a probability of 92/1000 for developing cardiovascular disease in 8 years; if the individual did not smoke, the probability would be 55 per 1000 (Castelli, 1983).

In addition to the role dietary fatty acid plays in atherosclerosis, there are human data linking dietary saturated fatty acids with thrombosis and impaired platelet function (Nordoy and Goodnight, 1990; Connor and Connor, 1990). Thrombosis is intimately related to atherosclerosis. It contributes to the progression of atherosclerotic lesions and is also responsible for many of the clinical complications of atherosclerosis (i.e., a thrombus may occlude a coronary artery). A diet high in saturated fatty acids may influence platelet and endothelial cell function

by altering the fatty acid composition of these cells. Saturated fatty acids with a carbon chain length of 12 or higher appear to be thrombogenic, activating the coagulation cascade and aggregating platelets (Nordoy and Goodnight, 1990; Connor and Connor, 1990). Human studies have demonstrated that a high fat diet results in increased platelet turnover, platelet adhesiveness, and the formation of thrombi (Baghurst and Truswell, 1979).

Animal Studies

The association between dietary saturated fatty acids and atherosclerosis has also been demonstrated in animals studies. Hypercholesterolemia and atherosclerotic lesions were observed in animals fed diets high in saturated fatty acids (as reviewed by Nordoy and Goodnight, 1990; Kritchevsky, 1991). Atherosclerotic lesions were noted in rats fed 6% hexadecanoic acid for 16 weeks (Sullivan and Krieger, 1992). Saturated fatty acids of different carbon chain lengths are not equally hypercholesterolemic. In a study conducted in rats by Renaud (1968), the most hypercholesterolemic fatty acid (as measured by blood cholesterol levels) was hexadecanoic acid (saturated, length of carbon chain, 16), followed by myristic acid (14), caprylic acid (8), octadecanoic acid (18), and lauric acid (12). Although a relationship between dietary saturated fatty acid intake and atherosclerotic lesions has been established in animal models, Nordoy and Goodnight (1990) caution against extrapolating from animal models because the animal studies typically use diets that have a very high lipid content, much higher than seen in human diets. There are also animal experimental data linking dietary saturated fatty acids with thrombosis and impaired platelet function (Nordoy and Goodnight, 1990; Connor and Connor, 1990). A high fat diet produced increased platelet turnover, platelet adhesiveness, and the formation of thrombi in rats (Renaud et al., 1970). In a study comparing the thrombotic activity in rats fed diets high in several saturated fatty acids, octadecanoic acid produced the shortest clotting time and the most severe thrombosis, followed (in decreasing order) by hexadecanoic acid, caprylic acid, lauric acid, and myristic acid (Renaud, 1968).

Other Studies

In an *in vitro* study (Nonagaki et al., 1994), mouse embryos cultured in medium containing 50 μm of hexadecanoic acid showed significant inhibition of mouse pronuclear and two-stage embryo development compared to controls. None of the zygotes exposed to hexadecanoic acid reached the four-cell stage of cell division.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR HEXADECANOIC ACID

There is limited information on the toxicity of hexadecanoic acid. However, there is an extensive database establishing a link between a diet high in saturated fatty acids and an

increased risk of coronary heart disease. A cause and effect relationship has not been established for coronary heart disease, largely because the etiology of coronary heart disease is multifactorial. A number of dietary (e.g., high intake of saturated fatty acids, low intake of polyunsaturated fatty acids) and non-dietary (e.g., hypertension, cigarette smoking, lack of exercise) factors contribute to the overall risk for coronary heart disease. The data are not adequate to make population-based dietary recommendations for saturated fatty acids (Zoller and Tato, 1992). Hexadecanoic acid is one of the many saturated fatty acids found in the diet; the lack of data to set recommendations for total saturated fatty acids precludes setting recommendations for a particular saturated fatty acid. Without recommendations for safe dietary levels of hexadecanoic acid, provisional values (RfDs, subchronic or chronic) for ingestion of hexadecanoic acid cannot be calculated.

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INTRODUCTION

Hexadecanoic acid, also called palmitic acid, is a saturated long hydrocarbon chain carboxylic acid. This 16-carbon saturated fatty acid is found in practically all vegetable oils and animal fats (Anonymous, 1987). Hexadecanoic acid is a solid at room temperature with a low vapor pressure (10 mm Hg); therefore, the potential for vapor inhalation exposure is low. However, there is a potential for inhalation exposure to particulate during the manufacture and process handling of the powder form (U.S. EPA, 1990). A subchronic or chronic RfC for hexadecanoic acid is not available on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997). No relevant documents regarding hexadecanoic acid were located in the CARA list (U.S. EPA, 1991, 1994). ATSDR (2003), NTP (2003), IARC (2003), and WHO (2003) have not produced documents regarding hexadecanoic acid. ACGIH (2003), NIOSH (2003), and OSHA (2003) have not recommended occupational exposure limits for hexadecanoic acid. Literature searches

of the following databases were conducted in 1991 for hexadecanoic acid: TOXLIT (1965-1991), TOXLINE (1981-1991), MEDLINE (1980-1991), CANCER (1963-1991), ETIC, HSDB, and RTECS. Literature searches of TOXLINE, RTECS, and TSCATS were conducted again in May 1994. Update literature searches from 1994 through June 2003 were conducted in the following databases: TOXLINE (supplemented with BIOSIS and NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. Additional literature searches from June 2003 through July 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT DATA

Human Studies

No data regarding the toxicity of hexadecanoic acid to humans following inhalation exposure were located. However, there is some information on the toxicity of airborne lauric acid. Lauric acid is a 12-carbon saturated fatty acid. In a NIOSH Health Hazard Evaluation report (as reviewed in Anonymous, 1987), 7 workers reported eye, nose, throat, and skin irritation following exposure to airborne lauric acid. The workers were involved in the flaking and bagging operation at a manufacturing facility. It is not known if hexadecanoic acid would have similar irritative effects.

Animal Studies

No data regarding the toxicity of hexadecanoic acid to animals following inhalation exposure were located.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR HEXADECANOIC ACID

In the absence of subchronic or chronic inhalation data on the toxicity of hexadecanoic acid, derivation of a provisional subchronic or chronic RfC is precluded.

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Provisional Peer Reviewed Toxicity Values for

Hexadecanoic acid
(CASRN 57-10-3)

Derivation of a Carcinogenicity Assessment

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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
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
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
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 inhalation reference concentration**
p-RfD	**provisional oral reference dose**
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

7-15-05

PROVISIONAL PEER REVIEWED TOXICITY VALUE FOR HEXADECANOIC ACID (CASRN 57-10-3)
Derivation of a Carcinogenicity Assessment

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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 (PPRTV) 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 Table (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 Integrated Risk Information System (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 multi-program 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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript 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

Hexadecanoic acid, also called palmitic acid, is a saturated long hydrocarbon chain carboxylic acid. This 16-carbon saturated fatty acid is found in practically all vegetable oils and animal fats (Anonymous, 1987). A carcinogenicity assessment for hexadecanoic acid is not available on IRIS (U.S. EPA, 2003), the HEAST (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). No relevant documents were located in the CARA list (U.S. EPA, 1991, 1994). ATSDR (2003), NTP (2003), IARC (2003), and WHO (2003) have not produced documents regarding hexadecanoic acid. Literature searches of the following databases were conducted in 1991 for hexadecanoic acid: TOXLIT (1965-1991), TOXLINE (1981-1991), MEDLINE (1980-1991), CANCER (1963-1991), ETIC, HSDB, and RTECS. Literature searches of TOXLINE, RTECS, and TSCATS were conducted again in May 1994. Update literature searches from 1994 through June 2003 were conducted in the following

databases: TOXLINE (supplemented with BIOSIS and NTIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, DART/ETICBACK, EMIC/EMICBACK, RTECS and TSCATS. Additional literature searches from June 2003 through July 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT DATA

Human Studies

No data regarding the possible carcinogenicity specifically in humans for hexadecanoic acid were located. Over 50 years ago, a relationship between a diet high in fat and an increased carcinogenic risk was first established in laboratory animals. Subsequently, a large number of human and animal studies have been conducted to establish the role of the level and nature of dietary fat in the susceptibility to cancer. The epidemiology studies, including case-control and cohort studies, do not provide conclusive evidence for an association between dietary fat and cancer incidence (Birt, 1990; Carroll, 1991). The lack of consistent results from the human studies may be due to confounding variables such as the difficulty in assessing dietary fat intake (particularly previous intake); differences in lifestyle (e.g., exercise, smoking); total caloric intake and intake of other macronutrients and micronutrients; and genetic factors (Boutwell, 1992; Birt, 1990; Carroll, 1991; Macrae, 1993).

Animal Studies

A large number of animal studies have found a positive correlation between the amount of fat in the diet and the incidence of cancer. A majority of the studies have examined the relationship between dietary fat and chemically-induced tumors. Increases in the incidence of chemically-induced tumors of the skin, mammary glands, lungs, intestinal tract, liver and pancreas have been observed in animals fed high fat diets (Kristiansen et al., 1993). Increases in the incidence of spontaneous tumors have also been observed in animals fed high fat diets. The results from older studies suggested that unsaturated fatty acids were tumorigenic and diets high in saturated fats did not result in increased incidences of cancer (reviewed in Birt, 1990 and Carroll, 1991). More recent studies have shown that the relationship between dietary fat and carcinogenesis is more complex, and dependent on more than just the degree of saturation and may depend on the cancer model under investigation. The concentration of essential fatty acids in the diet, the degree of unsaturation, and the structural location of the unsaturation are all important determining factors (Birt, 1990). Additionally, a number of investigators have provided evidence on the importance of energy balance, rather than the percentage of fat. Several studies have shown that caloric restriction reduces the incidence of spontaneous and chemically-induced tumors in animals fed high fat diets (Boutwell, 1992).

Few studies specifically conducted on hexadecanoic acid were located. Swern et al. (1970) administered to two groups of 16 female Swiss Webster mice hexadecanoic acid in tricaprylin at doses of 1.0 mg/day, 3 times/week for 10 subcutaneous injections in the inguinal area, or 5.0 mg/day, 2 times/week for 25 subcutaneous injections in the inguinal and axillary regions. There was no increase in tumors associated with injection of hexadecanoic acid at the injection site or internally. Of the 26 mice that survived at least 6 months (collapsed across groups), 2 subcutaneous sarcomas, 2 pulmonary tumors, 3 breast cancers, and 1 lymphoma were observed. In the tricaprylin control group (consisting of 104 Swiss Webster and BALB/c mice that survived at least 6 months), 1 subcutaneous sarcoma, 5 pulmonary tumors, 2 breast cancers, 0 lymphomas, and 4 other tumors were observed. The untreated control group (202 Swiss Webster and BALB/c mice that survived at least 6 months) included 1 mouse with subcutaneous sarcoma, 11 with pulmonary tumors, 14 with breast cancers, 4 with lymphomas, and 2 with other tumors. Herting et al. (1959) found that male and female Holtzman rats fed high fat diets containing 50% hexadecanoic acid for 24 weeks developed lipogranulomas in the perigonadal fat. The lipogranulomas were not seen in controls. The lipogranulomas were reversible upon diet substitution and were not considered to be neoplastic.

Other Studies

In a dietary study conducted by Record et al. (1992), 17 adult men (aged 32-63 years) with mild hypercholesterolemia were given dietary supplements (margarine, biscuits, and potato crisps) high in different oils. The frequency and distribution of micronuclei in peripheral blood lymphocytes were determined after 3 weeks on the test diets. No significant alterations were observed in the subjects ingesting diets high in hexadecanoic acid.

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

The human and animal data suggest that a diet high in fat may increase susceptibility to cancer, but are not conclusive. The limited evidence specifically on hexadecanoic acid are negative for genotoxicity and carcinogenicity. Under the U.S. EPA (2005) cancer guidelines, the data are inadequate to assess the carcinogenic potential of hexadecanoic acid. The animal study described above (Swern et al., 1970) relies on an unconventional approach. The time frame, method of application (subcutaneous administration), and range of doses individually and collectively render this study unacceptable for generating a risk assessment.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for hexadecanoic acid is precluded by the lack of data demonstrating carcinogenicity associated with hexadecanoic acid exposure.

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