12-21-04

Provisional Peer Reviewed Toxicity Values for

Octadecanoic Acid (Stearic Acid)

(CASRN 57-11-4)

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 Headquarters 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

Octadecanoic acid, an 18-carbon saturated fatty acid also known as stearic acid, is synthesized in the body and is a vital component of the cell membrane. It is a normal constituent of the diet found in vegetable oils and animal fats. Neither a subchronic nor chronic RfD for octadecanoic acid is listed on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997) or Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). The CARA list (U.S. EPA, 1991, 1994) does not report any relevant documents for octadecanoic acid. ATSDR (2002), IARC (2002) and WHO (2002) have not published review documents for octadecanoic acid. Computer literature searches of TOXLINE (1965-1994), TSCATS, and RTECS were initially performed in May, 1994. Update literature searches for the years 1993-2003 were conducted on TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK in January, 2003. The NTP (2002)

status report was also searched for relevant information. Additional literature searches were conducted by the NCEA-Cincinnati from February 2003 through May 2004 using TOXLINE, MEDLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT LITERATURE

Much of the research on the toxicity of fatty acids has focused on establishing a relationship between a high fat diet and coronary heart disease (CHD), 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, as 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 epidemiology studies, dietary intervention studies, and animal studies. A number of epidemiology 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 epidemiology 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 coronary heart disease risk. 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 who were at high risk for developing coronary heart disease were given stepped-care treatment for hypertension, counseling for quitting smoking, 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.

Several dietary studies in humans have reported that saturated fatty acids with 12, 14, or 16 carbons increase plasma cholesterol, whereas octadecanoic acid (with 18 carbons) has a neutral effect on plasma cholesterol (see Bonanome and Grundy, 1989; Emken et al., 1993; Grundy, 1994; Rhee et al., 1997; Snook et al., 1999 for reviews).

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). 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 (length of fatty acid carbon chain:number of double bonds, 16:0), followed by myristic acid (14:0), caprylic acid (8:0), octadecanoic acid (18:0), and lauric acid (12:0). 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.

In addition to the role dietary fatty acid plays in atherosclerosis, there are human and animal experimental 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 and animal studies have demonstrated that a high fat diet results in increased platelet turnover, platelet adhesiveness, and the formation of thrombi (Renaud et al., 1970; Baghurst and Truswell, 1979). 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).

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 man who smokes cigarettes, has a systolic blood pressure of 120 mm Hg and a blood cholesterol level of 210 mg/dl has a probability (per 1000) of 92 for developing cardiovascular disease in 8 years; if the individual did not smoke the probability would be 55 per 1000 (Castelli, 1983).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR OCTADECANOIC ACID

There is limited information on the toxicity of octadecanoic 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 nondietary (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 (Zöllner and Tato, 1992). Octadecanoic acid is just one of the many saturated fatty acids found in the diet. Without recommendations for safe dietary levels of octadecanoic acid, health-based guidelines for environmental ingestion (i.e., subchronic or chronic p-RfDs) of octadecanoic acid cannot be made.

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Octadecanoic Acid (Stearic Acid)

(CASRN 57-11-4)

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for relevant information. Additional literature searches were conducted by the NCEA-Cincinnati from February 2003 through May 2004 using TOXLINE, MEDLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No studies were located regarding inhalation exposure of humans to octadecanoic acid.

Animal Studies

No studies were located regarding inhalation exposure of animals to octadecanoic acid.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR OCTADECANOIC ACID

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

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Derivation of a Carcinogenicity Assessment

Superfund Health Risk Technical Support Center
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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

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PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR OCTADECANOIC ACID (STEARIC ACID, CASRN 57-11-4)
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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 Headquarters 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

Octadecanoic acid, an 18-carbon saturated fatty acid also known as stearic acid, is synthesized in the body and is a vital component of the cell membrane. It is a normal constituent of the diet found in vegetable oils and animal fats. A carcinogenicity assessment for octadecanoic is not available on IRIS (U.S. EPA, 2003), in the HEAST (U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2002). The CARA list (U.S. EPA, 1991, 1994) does not report any relevant documents for octadecanoic acid. IARC (2002), ACGIH (2002), and NTP (2002) have not assessed the carcinogenicity of octadecanoic acid. ATSDR (2002) and WHO (2002) have not published review documents for octadecanoic acid. Computer literature searches of TOXLINE (1965-1994), TSCATS, and RTECS were initially performed in May, 1994. Update literature searches for the years 1993-2003 were conducted on TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS,

GENETOX, DART/ETICBACK, and EMIC/EMICBACK in January, 2003. Additional literature searches were conducted by the NCEA-Cincinnati from February 2003 through May 2004 using TOXLINE, MEDLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT LITERATURE

Over 50 years ago, a relationship between a diet high in fat and an increased carcinogenic risk was first established in laboratory animals (Kristiansen et al., 1993; Boutwell, 1992). 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, as well as 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, intake of other macronutrients and micronutrients, and genetic factors (Boutwell, 1992; Birt, 1990; Carroll, 1991; Macrae, 1993).

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 potential for a high fat diet to promote cancer (Carroll, 1991). 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; Carroll, 1991). Increases in the incidence of spontaneous tumors have also been observed in animals fed high fat diets, suggesting that dietary fat may be a complete carcinogen. The results from older studies suggested that unsaturated fatty acids were tumorigenic and a diet 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 complex and that the concentration of essential fatty acids in the diet, the degree of unsaturation, and the 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 in the diet. Several studies have shown that caloric restriction reduces the incidence of spontaneous and chemically-induced tumors in animals fed high fat diets (Boutwell, 1992). Animal studies examining the carcinogenicity of a high fat diet, where the principal fatty acid was octadecanoic acid, are discussed below. The objective of most of these studies was to examine the carcinogenic potential of octadecanoic acid in a particular tissue, and other tissues were not examined histologically. Complete histological examinations were conducted in the Kristiansen et al. (1993) study.

Kristiansen et al. (1993) examined the influence of a diet high in saturated fat on the incidence of spontaneous tumors. Groups of 110 male and 110 female Wistar rats were fed a basal diet which was supplemented with saturated fatty acids (total fat content was 16%) for 129-134 weeks. The saturated fat was 85% octadecanoic acid and 13% hexadecanoic acid; the diet also contained 4% soybean oil and provided recommended essential fatty acids. The control group (59/sex) received the basal diet, which had a fat content of 4% (from soybean oil). No unusual clinical signs or increase in mortality were observed. Body weight, weight gain and food consumption were similar for the two groups. From week 38 to the end of the study, an increase in the number of neutrophils and a decrease in the number of lymphocytes were observed in the female rats fed the high fat diet (the differences were statistically significant beginning at week 87); no change in the number of total leukocytes were observed. No significant differences in time to occurrence of organ-specific tumors were observed between the two groups. A statistically significant increase in the incidence of fibroadenomas of the mammary gland was observed in the female rats fed the high fat diet; when the incidence of benign mammary tumors (adenomas and fibroadenomas) were combined, the difference between the groups was no longer statistically different. In the male control group, significant increases in the incidence of adenoma of the parathyroid gland and medullary carcinoma of the adrenal gland were observed.

Swern et al. (1970) conducted a series of 7 experiments to determine the carcinogenicity of octadecanoic acid using female BALB/c or Swiss Webster mice. Using the following dosing schedule, groups of BALB/c mice received repeated subcutaneous injections of octadecanoic acid in tricaprylin in approximately the same site of the inguinal and axillary regions: 10 mice received 82 doses of 1 mg, 2 times per week; groups of 10 mice received 114 doses of either 0.05 or 0.5 mg, 2 times/week; and 15 mice received 0.05 mg doses administered twice weekly for 104 injections. Swiss Webster mice were similarly exposed using the following protocols: 15 mice received 10 doses of 1.0 mg, 3 times/week; and groups of 16 mice received 26 doses of either 0.05 or 0.5 mg administered once a week. Control groups consisting of untreated mice or mice receiving the tricaprylin vehicle only were similarly exposed. The incidences of subcutaneous sarcomas, pulmonary tumors, breast cancers, lymphomas and other tumors for mice alive at 6 months (data collapsed across experimental groups) were 4/83, 3/83, 0/83, 1/83, and 1/83, respectively, as compared to 1/104, 5/104, 2/104, 0/104, and 4/104 in the vehicle control group. The 4 sarcomas seen in the octadecanoic acid exposed mice were seen in mice exposed to 0.05 mg twice weekly for a total of 114 doses; sarcomas were not seen in mice similarly exposed to higher concentrations. The authors could not find an explanation for this finding and noted that these animals were housed in the same cage (with 4 other animals).

In a replication of the Swern et al. (1970) study, groups of 15 female ICR/Ha Swiss Millerton mice and 16 female Swiss Webster were exposed to 0.05 or 0.5 mg/day octadecanoic acid in tricaprylin (Van Duuren et al., 1972). The four groups of mice received subcutaneous injections in the inguinal area once a week for 26 weeks. Of the mice that were alive after 6 months, no injection site sarcomas were observed, and 3/15 ICR mice exposed to 0.05 mg/day

and 1/14 ICR mice exposed to 0.5 mg/day had tumors at other sites. In the vehicle only control groups, the incidences of injection site sarcomas were 0/16 and 0/15 for the ICR and Swiss Webster mice, respectively, and the incidences of other tumors were 0/16 and 1/15, respectively.

Herting and Harris (1959) examined the incidence of lipogranulomas in groups of 4 male and 4 female Holtzman rats fed high fat diets containing 50.4% octadecanoic acid for 24 weeks. After the exposure period, the rats were fed a diet containing 20% corn oil for 24 weeks. The control group were fed diets containing 4% corn oil and 10% triacetin (supplying acetyl equivalent to that in a diet containing 54% of distilled partially acetylated monoglycerides) for 48 weeks. The incidences of lipogranulomas in perigonadal fat after 8, 16, or 24 weeks on the octadecanoic acid diet were 5/7, 3/6, and 5/5, respectively. After 8, 16, or 24 weeks on corn oil diet, the incidences of lipogranulomas were 1/4, 3/5, and 2/5, respectively. No lipogranulomas were seen in the control group. The lipogranulomas observed in the rats exposed to the diet high in octadecanoic acid are not considered neoplastic.

Groups of 26 female weanling A/St mice and 23 adult (11.5 months of age) were placed on a high fat diet (13.1% of the diet consisted of octadecanoic acid, and the total fat content was 15%) (Bennett, 1984). The comparison groups were 27 weanling female mice and 65 adult female mice fed a low fat diet (total dietary fat was 4.5% with 0.3% octadecanoic acid). By age 24 months, 17/26 mice placed on the high fat diet at weaning developed mammary adenocarcinomas, and the average age at tumor development was 15.7 months. In the weanling control group, 20/27 mice developed tumors by 24 months of age and the average age at tumor development was 12.7 months. The age at tumor development was significantly higher in the high fat diet group as compared to the low fat diet group. The length of time to tumor development was also significantly higher in the adult mice fed the high fat diet (tumors developed after an average of 5.0 months) compared to the adult low fat group (tumor development after 3.0 months).

In a study designed to examine the potential for octadecanoic acid to induce pancreatic carcinogenesis, groups of 10 male Leed rats were fed a high fat diet (22% fat) for 6 months (Khoo et al., 1991). The octadecanoic acid content of the diet was 20.05% (87.63% of the total fat). The control group (10 male rats) was fed a standard diet containing a fat content of 2.5% (0.06% octadecanoic acid). The animals fed octadecanoic acid weighed significantly less (9.4%) than the control rats. No significant alterations in the incidence of atypical acinar cell foci (apparent precursors of acinar cell adenomas and carcinomas) were observed. Another group of 10 rats received repeated intraperitoneal injections of azaserine (30 mg/kg) at age 14, 21, and 28 days, after which they received the high fat diet for 6 months. No significant alterations in acidophilic acinar cell foci were observed in this group.

The genotoxicity of octadecanoic acid was tested using the spot test, a qualitative form of the Salmonella/microsome test (Blevins and Taylor, 1982). Negative results were found, with

and without S9 activation, using *Salmonella typhimurium* strains TA1538, TA1537, TA1535, TA100, and TA98.

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

Although the results in humans are inconsistent, animal data suggest that a high fat diet may increase the susceptibility to cancer. Although many variables may be responsible, the degree of unsaturation of the dietary fat is an important determining factor (Birt, 1990). No human studies examining the influence of octadecanoic acid on the carcinogenic potential of a high fat diet were located. Animal studies have shown that under the conditions tested, an increased carcinogenic risk is not associated with a diet high in octadecanoic acid. The usefulness of most of the animal studies for assessing carcinogenicity is limited because a very small number of tissues were histologically examined and the animals were exposed for less than a lifetime. The Kristiansen et al. (1993) study involved lifetime exposure and histological examination of most tissues and/or organs; however the results were inconclusive with regard to the carcinogenic potential of octadecanoic acid.

Under the proposed U.S. EPA (1999) cancer guidelines, the available data are inadequate for an assessment of human carcinogenic potential.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Lack of adequate human or animal cancer data precludes derivation of quantitative estimates of cancer risk for octadecanoic acid.

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