Literature-Based Toxicological Assessment of Target Leachables

Prepared by:

SciScout LLC

Prepared for:

XXXXXXXXXXXXXXX

Study Report No.: XXX-XXXXXXX

XXXX XX, XXXX

(Specific data are replaced with "X" to maintain or accentuate confidentiality - www.sciscout.com)

TABLE OF CONTENTS

Study Report Approval

Report Title: Literature-Based Toxicological Assessment of Target Leachables

All data generated by SciScout LLC and described within this report were collected under the direction of the Study Director. This report accurately reflects the published data found in the references identified within this report.

James W. Lindsey, Ph.D. Date
Study Director
SciScout LLC

I. Executive Summary

A literature-based toxicological assessment of eight target leachables associated with the biomanufactured drug product XXXXXXXX™ was conducted to assess toxicological implications and to determine safe levels for the compounds. Reference doses were calculated from 'no observed adverse effect levels' or from 'lowest observed adverse effect levels' and used to determined acceptable daily intakes. Computed acceptable daily intakes for a 50 Kg human range in values from 2.5 mg (i.e., for xxxxxxxxxxxxxxxxxx) to 125 mg (i.e., for xxxxxxxxx). The toxicological assessment suggests that none of the target leachables would pose a human health risk from bodily exposure to levels at or below the computed acceptable daily intakes (where given) or from low mg levels for target leachables where acceptable daily intakes are not given (i.e., xxxxxxxxxxxxx, xxxxxxxxxxxx, xxxxxxxxxxxx, and xxxxxxxxxxxxx). For target leachables where acceptable daily intake values are specified (i.e., xxxxxxxxxxxxxxxxxx, xxxxxxx, xxxxxxxxx, and xxxxxxxxxxx), the analytical method for these target leachables is appropriate for detecting and quantifying their safe levels in the drug product.

II. Purpose

The purpose of this work was to conduct a toxicological assessment of eight target leachables associated with a biomanufactured drug product.

III. Scope

(A) The available literature regarding the possible toxicological implications for the target leachables in Table 1 will be summarized.

(B) The results from the literature search will be used to evaluate if the limits of detection and quantitation in Table 1 are appropriate, i.e., that the presence of these compounds at levels close to or below the limits of detection or quantitation would not be of concern.

Table 1. Limits of Detection (LOD) and Limits of Quantitation (LOQ) of Target Leachables

Target	LOQ (µg/mL)	LOD (µg/mL)
Xxxxxxx	X.XXX	X.XXX
xxxxxxxxxxxxxxxxxxx	X.XXX	X.XXX
Xxxxxxxxxxxxx	X.X	X.XXX

Table 1. Limits of Detection (LOD) and Limits of Quantitation (LOQ) of Target Leachables

Target	LOQ (µg/mL)	LOD (µg/mL)
Xxxxxxxxxxx	XX	X
Xxxxxxxxxx	XX	X.X
Xxxxxxxxxxxxx	XX	X
Xxxxxxxxxxx	XX	XX
Xxxxxxxxx	XXX	XX

IV. Introduction

The target leachables in XXXXXXXX™ drug product (Table 1) are tested by the XXXXXXXXXXXXXX analytical test method ATM-XXX-M0013. The limits of detection and quantitation of the method are listed in Table 1. The product vials contain a XX mg/mL solution of xxxxxx, and the maximum recommended dosing for the product is at XXX µg/Kg of body weight, administered twice daily by subcutaneous injection (Xxxxxx, XXXX). This corresponds with a maximum daily exposure to XX microliter of the product solution per kilogram of body weight. The purpose of this literature review is to determine the safe levels of target leachables in this product, and to assess if the method limits of detection and quantification are adequate to ensure the safety of the product.

V. Experimental

(A) Literature Searches.

Literature searches were conducted *via* library and database resources of the National Institute of Environmental Health Sciences (NIEHS), the Health Sciences Library of the University of North Carolina at Chapel Hill and the Internet (e.g., PubMed).

(B) Interspecies-Toxicity Extrapolation.

(Dourson, 1986; Hertzberg *et al.*, 1993; WHO, 1999)

The reference dose (RfD) is defined as an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is determined by use of the following equation: RfD=NOAEL or

LOAEL/(UF), where NOAEL is the 'no observed adverse effect level' and LOAEL is the 'lowest observed adverse effect level'. UF is called the uncertainty factor. UFs are products of 10 that are used to lower the NOAEL or LOAEL due to the uncertainty in the critical study. The following criteria are used to calculate UFs:

(i.) Use one factor of ten to account for the variation in sensitivity to the chemical among members of the human population.

(ii.) Use one factor of ten to account for the uncertainty of extrapolating data from animal studies to humans.

(iii.) Use one factor of ten to account for use of data from a subchronic study (less than 3 months).

(iv.) Use one factor of ten when the LOAEL is used instead of the NOAEL.

The reference concentration (RfC) is the inhalation counterpart of the RfD.

(C) Acceptable Daily Intake.

(Dourson, 1986; Hertzberg *et al.*, 1993; WHO, 1999)

Acceptable daily intake (ADI) values were calculated as follows:

ADI (mg) = RfD (mg/Kg/day) x Body Weight (Kg)

VI. Results and Discussion

(A) xxxxxxxxxxxxxxxxxxx (XXXXXX).

Compounds like XXXXXX (CAS No.: XX-XX-X) are commonly used in plastics and rubber products to minimize oxidation and as ultraviolet absorbers. These compounds may exhibit mild to pronounced antioxidant properties.

There is minimal animal and human toxicology data for the alkylphenol compound XXXXXX (Hirata-Koizumi *et al.*, 2005). The MSDS suggests that the compound may be harmful by ingestion, inhalation or dermal contact, and is an irritant (MSDS – XXXXXX, 2005). When delivered orally to infant rats from post-natal days 4 to 21, or to young rats (5- 6 weeks of age) for 28 days, XXXXXX was reported to induce histopathology and increased organ weights in the kidney and liver. Based on these results, the NOAEL for XXXXXX was concluded to be 5 and 20 mg/Kg/day for newborn and young rats, respectively (Hirata-Koizumi, 2005). In another study, male rats fed XXXXXX at a level of 2.27 micromolar percent in the diet for one week exhibited no significant clinical or histopathological signs (Takahashi and Hiraga, 1980). Finally, O'Malley *et al.* (1988) hypothesized that workers exhibiting unexplained depigmentation (vitiligo) may have been exposed to

xxxxxxxxxxxxxxxxxxx through handling of rubber associated with industrial pumps.

(B) Xxxxxxx.

Xxxxxxx (CAS No.: XXX-XX-X) is a volatile hydrocarbon that is widely present in fuels (gasoline, jet fuels, diesel fuels, etc.) and in a wide diversity of industrial chemicals (MSDS – Xxxxxxx, 2005). Xxxxxxx is also used to produce benzene and as a solvent in paints, coatings, synthetic fragrances, adhesives, inks, and industrial cleaning agents. Xxxxxxx is also used in the production of polymers used to make nylon, plastic soda bottles and polyurethanes and for pharmaceuticals, dyes, cosmetic nail products, and the synthesis of many organic chemicals.

There is a large amount of scientific literature describing effects in humans and animals from acute, subchronic or chronic exposure to xxxxxxx (inhalation or gavage) (Ritchie *et al.*, 2001, 2003). However, as humans cannot be ethically exposed chronically to xxxxxxx in the laboratory, interpretation of human studies of xxxxxxx toxicity are frequently complicated by the fact that many industrial workers viewed as subjects have been chronically exposed to xxxxxxx as well as to a number of other potentially toxic industrial chemicals (e.g., benzenes, xylenes, naphthalenes). Xxxxxxx can be readily absorbed through the lungs, skin and eyes. Consumers are commonly exposed to xxxxxxx when purchasing or using gasoline (Ritchie *et al*., 2003, 2005). Animal studies often report the effects of gavage exposure to xxxxxxx, although this route is extremely uncommon for human industrial exposures. Xxxxxxx has been shown in four major reviews of animal or human studies to induce toxicity in a diversity of body systems (Low *et al.*, 1988; Ritchie *et al.*, 2001, 2003; ATSDR, 2004). In the studies reviewed there wide were variations in NOAEL values as a function of species, sex, exposure route, duration of exposure and toxicological endpoint. In the ATSDR review, for example, NOAEL values varied from 40 to 5000 ppm (ATSDR, 2004). Hillefors-Berglund *et al*. (1995) exposed rats by inhalation to xxxxxxx (40 to 320 ppm; 6 hr/d; 5 days/week for 4 weeks) and reported statistically a significant decrease in the wet weights of the subcortical caudate-putamen area of rats exposed to 80 ppm (but not 40 ppm) compared to controls. The NOAEL calculated in this study was 40 ppm. The ATSDR review also listed the calculated NOAELs for a number of oral administration studies, ranging generally from 105 to 2500 mg/Kg/d. Hsieh *et al.* (1989) reported that the NOEAL for mice exposed to xxxxxxx in the drinking water for 4 weeks was approximately 105 mg/Kg for the endpoints of increases in liver weight and decrease in thymus mass. In a study where the exposure was xxxxxxx without benzene or xylene, rotogravure printers and assistants were occupationally exposed for about 3 years while their blood constituents and bone marrow were consistently monitored (Banfer, 1961). No evidence of hematopoietic problems was observed. The acute effects of an xxxxxxx exposure include a narcotic effect, as well as impaired cognitive and neuromuscular function. Similar effects, albeit often to a lesser degree, are found to persist following exposure. The data for human health effects overall suggest the effects of xxxxxxx are primarily neurobehavioral

effects. For instance, a 6 hr exposure to 100 ppm xxxxxxx caused deficits in visual perception, the ability to discriminate colors, and the ability to do multiplication calculations (Baelum *et al.*, 1985). Similar exposures have resulted in deficits in some, but not all, tests of short-term memory (Echeverria *et al.*, 1991). In the Echeverria *et al.* (1991) study, no differences were reported for tasks of sensory motor skills such as reaction time, hand-eye coordination, finger tapping, or critical tracking. The most carefully controlled exposure to xxxxxxx was conducted with 3 volunteers who were exposed to different concentrations of xxxxxxx for 8 hr, twice/wk for 3 months (von Oettingen *et al*, 1942a, 1942b). No myelotoxic effects were observed in these volunteers, however, neurobehavioral effects were apparent. In general, the effects during exposure consisted of fatigue, headaches, incoordination and muscle weakening, with a worsening of symptoms as the concentrations increased from 50-800 ppm. At the highest doses, neurobehavioral effects such as mental confusion, exhilaration, and lack of self control were reported. There were no lasting effects at concentrations up to 100 ppm. However, lasting problems with fatigue, general confusion, headaches, insomnia and skin paresthesia were evident following exposures at higher doses. Evidence from animal models of neurobehavior following xxxxxxx exposure also suggests deficits with several different tests of cognitive processing (Ritchie *et al*., 2001, 2003). Xxxxxxx exposure also has reproductive and teratological effects. Lemasters *et al.* (1997) reported a small but statistically significant increase in the frequency of sister chromatid exchanges, as well as in micronucleus frequency (MN) in the sperm of sheet metal workers or painters exposed to occupational xxxxxxx for up to 30 wk. In female xxxxxxx abusers, an absence of effects on menstruation variables was reported (Ng *et al.*, 1992a), consistent with an increase in spontaneous abortions (Ng *et al.*, 1992b). In males, hormonal changes have been reported, although there was not a systematic analysis of the effects on fertility (Svensson *et al.*, 1992a, 1992b). The effects were reductions in luteinizing hormone, follicular stimulating hormone (FSH), and testosterone. Infants of mothers who abuse xxxxxxx often have craniofacial features that resemble those of children with fetal alcohol syndrome, even if the mother did not consume alcohol during pregnancy (Ritchie *et al.*, 2001, 2003). Other effects on the embryos and infants include digital hypoplasia, urinary tract anomalies, intrauterine growth retardation, prenatal microencephaly, and developmental delays (Ritchie *et al.*, 2001, 2003).

(C) Xxxxxxxxxxxxx (Xxxxxx).

Xxxxxxxxxxxxx (Xxxxxx Xxxxxxxxx Xxxxxxxxx) (CAS No.: XXXX-XX-X)) is commonly used in laboratory buffer solutions for molecular biology applications.

There is little human or animal toxicity data for xxxxxxxxxxxxx. Exposure to xxxxxxxxxxxxx may result in eye, dermal or respiratory irritation and toxicity (MSDS – Xxxxxxxxxxxxx Xxxxxxxxx, 2006).

(D) Xxxxxxxxx.

Xxxxxxxxx (CAS No: XXX-XX-X) is an additive permitted in adhesives used in food packaging, a slip agent in polyethylene films, and a slip and mold release agent in some rubber products.

There is limited scientific literature and no significant reported toxicity effects related to low dose exposures to xxxxxxxxx. Xxxxxxxxx is a skin, eye and respiratory irritant (MSDS-Xxxxxxxxx, 2003). It may be naturally present in low concentrations in blood plasma and in a number of body organs (e.g., identified in the pig and rat). Xxxxxxxxx may be involved in regulation of fluid volumes in organs including the lung, liver spleen and brain, although the mechanism is unknown (Hamberger and Stenhagen, 2003). The fatty acid amide xxxxxxxxx has been shown to exhibit angiogenic functions in bovine mesentery (Wakamatsu *et al.*, 1990) and in a rat cornea-micropocket assay (Mitchell *et al.*, 1996). No mortalities occurred and no signs of toxicity were observed during a 14-day observation period where one group of Wistar rats, comprising of five males and five females, received a total oral dose of xxxxxxxxx at 5000 mg/Kg body weight twice within 24 hours. Post-mortem examination of all animals did not reveal any changes that were considered to have arisen as a result of treatment (IUCLID, 2000). No significant clinical effects were observed from a study where five young rats were fed 10% xxxxxxxxx in their diet (10-36 g/Kg/d) for four weeks. Feed consumption and body weight were decreased, possibly due to diet unpalatability. There were no effects on the gross appearance of organs, or on blood composition or clinical chemistry (IUCLID, 2000). A 60 mg quantity of xxxxxxxxx resulted in slight to diffuse redness of the conjunctivae and slight chemosis when applied to one of the eyes of each of three albino rabbits. A 500 mg quantity of xxxxxxxxx caused very slight erythema in three albino rabbits when applied to the flank skin of each of the three animals (IUCLID, 2000).

(E) Xxxxxxxxxxx (Xxxxxxxxxxxxxxx).

Xxxxxxxxxxx (CAS No.: XX-XX-X) is a saturated aliphatic carboxylic acid used in the manufacturing of rubber, latex and plastics, greases and lubricants, waterproofing materials, food additives, pharmaceuticals, cosmetics, soaps and toiletries, and in the synthesis of metallic palmitates. It occurs as a major component of many natural fats and oils in the form of a glycerol ester (e.g., palm oil) and most commercial grade stearic acid. Xxxxxxxxxxx is a normal component of many foods, and additive to many commercial products that are ingested, and occurs naturally in the body. Xxxxxxxxxxx is stored in fatty tissues of the body, or metabolized by oxidation or conversion to other long-chain fatty acids.

Human and animal studies have reported mild skin, eye and respiratory irritation from exposure to xxxxxxxxxxx. High concentrations of xxxxxxxxxxx in dust may induce coughing and mild, temporary respiratory irritancy in humans. Xxxxxxxxxxx is not a skin irritant or sensitizer (MSDS – Xxxxxxxxxxx, 2003). Xxxxxxxxxxx is not an eye irritant in animals (Briggs *et al.*, 1976). Repeated application of 0.04 mL of a 0.5 or 1 M solution to the eye for 10 days did not

produce irritation in humans (Stillman *et al*., 1975). Ji *et al*. (2004) reported that xxxxxxxxxxxx delivered to human hepatocytes at 0.2-0.4 mmol/L resulted in cell death, possibly *via* mitochondria-mediated apoptosis. The oral LD50 for rats is > 10 g/Kg, while the intravenous LD50 for mice is 57 mg/Kg (MSDS – Xxxxxxxxxxxx, 2003). There is no reported evidence for carcinogenicity induced by repeated exposure to low doses of xxxxxxxxxxxx (CCOHS, 1996).

(F) Xxxxxxxxxxxx (*n*-Xxxxxxxxxxx).

Xxxxxxxxxxxx (CAS No.: XXX-XX-X), also known as Xxxxxxxxxxx, is the carboxylic acid derived from hexane with the formula X_XX_XXXXX. It is a fatty acid found naturally in various animal fats and oils (e.g., certain seed oils rich in medium-chain fatty acids). It comprises 1-2% of the totals fatty acids in ruminant milk triacylglycerols. It is used in cutting oils and specialty soaps, and may be present in very low concentrations in some plastics products.

As there is little opportunity for exposure to toxic concentrations of xxxxxxxxxxxx except during manufacturing, there has been minimal animal or human toxicology research conducted on this compound. At appropriately high concentrations, xxxxxxxxxxxx is a corrosive that is especially destructive of mucous membranes. Xxxxxxxxxxxx is harmful by ingestion, inhalation or skin absorption, and is readily absorbed through skin (MSDS – Xxxxxxxxxxxx, 2002). The oral LD50 in mouse for xxxxxxxxxxxx is 5 g/Kg (MSDS – Xxxxxxxxxxxx, 1997).

Traul *et al.* (2000) conducted a review of the toxicological properties of medium-chain triglycerides (MCTs), composed mainly of caprylic (C_8, 50-80%) and capric fatty acids (C_{10}, 20-50%) with traces of caproic (C_6, 1-2%) and lauric (C_{12}, 1-2%) fatty acids. The review concluded that MCTs exhibits very low levels of toxicity in a variety of laboratory animals and humans when administered orally, parenterally or dermally. There is no evidence that MCTs are sensitizers and they show little evidence that they are ocular or dermal irritants. The data strongly suggest that MCTs would pose little or no risk from toxicity when consumed as a supplement in a balanced diet at levels up to 15% of the dietary calories or about 50% of the dietary fat. For example, 10 human volunteers ingested 100 mL (approximately 95 g) of a synthetic fat (a triglyceride of 74% lauric, 17% cupric, 5% caprylic, 3% myristic, and a trace of caproic), eight had no chylomicrons in their sera, and none developed diarrhea or had fat in their feces. All had increased levels of free fatty acids in their sera. These results support other data which show that MCTs are readily metabolized in the intestine and are absorbed primarily as free fatty acids without adverse effects (CTFA, 1980).

(G) Xxxxxxxxxxx (Xxxxxx).

Xxxxxxxxxxx (CAS No: XXX-XX-X) is an intermediate used primarily in the manufacture of synthetic fibers, especially of Xxxxxx (MSDS – Xxxxxxxxxxx, 1998). Xxxxxxxxxxx is also used in brush bristles, textile stiffeners, film coatings,

synthetic plastics, plasticizers, paint vehicles, cross-linking for polyurethanes and in the synthesis of lysine.

The most probable routes of human exposure are dermal contact during manufacturing, inhalation of emissions and effluents in the environment, and ingestion of contaminated water sources (US EPA, 1988; US DHHS, 1993). Acute exposure of humans to xxxxxxxxxxx may result in irritation and burning of the eyes, nose, throat, and skin. Headaches, malaise, confusion, and nervous irritation have been observed in workers exposed repeatedly to xxxxxxxxxxx by inhalation. Chronic (long-term) exposure of workers to xxxxxxxxxxx has been observed to cause peeling of the hands and some eye, nose, and throat irritation, but no other effects on general health (US EPA, 1988).

In an animal study, male and female rats were exposed to feeding diets containing 3,750 or 7,500 ppm xxxxxxxxxxx for 103 weeks. Rats and mice exposed in the feed to xxxxxxxxxxx at or near the MTD exhibited depressed body weights, but no evidence of carcinogenicity and unexpected histopathology in any of the organ systems evaluated (US EPA 1988, 1999). Serota *et al.* (1988) fed groups of rats diets containing xxxxxxxxxxx at 0, 1000, 5000 or 10,000 ppm for three-generations. No treatment related effects were observed in the parental animals with respect to mortality, clinical signs, reproductive performance or gross pathology findings. Consistently (and generally statistically significant) lower body weights were noted in the P2 (generation 2) and P3 mid- and high-dose males and females. Consistently lower mean food consumption values were noted in the P2 and P3 mid- and high-dose males and the high-dose females. Mean body weights and food consumption were reduced in both parental generations at 5000 and 10,000 ppm. Body weights of offspring were also reduced at these dietary concentrations. Gad *et al.* (1987) further evaluated the developmental toxicity of xxxxxxxxxxx, using both rats and rabbits. Rats were orally dosed on gestation days 6 to 15 with 100, 500 or 1000 mg/Kg/d xxxxxxxxxxx, while rabbits were dosed with 50, 150 or 250 mg/Kg/d. Maternal survival rate was significantly lower in the 1000 mg/Kg/d rat group, and in the high dose (250 mg/Kg/d) rabbit group as compared to controls. No embryotoxicity or teratogenicity occurred at any dose level.

(H) Xxxxxxxxxxxxxx (Xxxxxxxxxx).

Xxxxxxxxxxxxxx (CAS No: XXX-XX-X) is used in alkyd resins, wetting agents, soaps, detergents, cosmetics, emulsifiers, lubricants, carriers, insecticides and food additives (CCOHS, 1997). *n*-Xxxxxxxxxxxxxx is one of the three most widely distributed naturally occurring saturated carboxylic acids and is found naturally (as glycerides) in many vegetable fats, especially in coconut, palm kernel and laurel oils. Xxxxxxxxxxxxxx is a normal component of the body, and it may be metabolized in several ways in the body. It has been shown to rapidly absorb from the blood in rats and may be oxidized or incorporated into fatty tissues. In addition, it may also be

converted to higher molecular weight acids, myristic, palmitic and stearic acids.(Katz *et al.*, 1994).

The oral LD50 for rats is very high, and is listed as 12 g/Kg. Xxxxxxxxxxxxx was only mildly irritating to skin of the rabbit when 500 mg were applied. At high concentrations, xxxxxxxxxxxxx is an eye, nose, throat, skin and respiratory irritant in humans, although there is no evidence of skin sensitization (MSDS – Xxxxxxxxxxxxx, 2002). Mild skin and eye irritation were observed in rabbits *via* the skin and eye standard Draize tests at doses of 500 mg (skin) and 100 mg (eye) (RTECS No. OE9800000). The oral LD50 in rat is 12 g/Kg, and the intravenous LD50 in mouse is 131 mg/Kg (RTEC No. OE9800000). Stillman *et al.* (1975) reported no skin irritation in volunteers 24 hours after application of 1 M n-xxxxxxxxxxxxx in propanol under a cover preventing evaporation, although n-xxxxxxxxxxxxx dust induced mild irritation when applied to the sweaty skin of workers (Stillman *et al.*, 1975). Eye irritation was reported in workers exposed to airborne *n*-xxxxxxxxxxxxx (Stillman *et al.*, 1975). Apol *et al.* (1981) reported coughing, sneezing and difficult breathing in workers exposed to unspecified concentrations of airborne *n*-xxxxxxxxxxxxx dust.

VII. Conclusion

XXXXXXXX™ (xxxxxxxxxx [xxxx xxxxxx] injection) is a pharmaceutical product candidate with an amino acid sequence identical to that of xxxxxxxxxx xxxxx xxxxxxx-xxxx xxxxxx xxxxxx-x (xxx-x). XXXXXXXX™ is being tested for long-term treatment of xxxxxx xxxxxxx xx xxxxxxxx xxxx xxxxxx xxxxxxx xxx-x xxxxxxxxxx or with xxxxxx xxxxxxx (XX) xxxx xxxxxxxx who have developed neutralizing antibodies to XX. XXXXXXXX™ is an aqueous solution containing XX mg/mL xxxxxxxxxx, X mg/mL xxxxxx xxxxxxx, X.XX mg/mL xxxxxx xxxxxxxx, X mg/mL xxxxxxxxxxx XX and X.XXM xxxxxxx at a pH of approximately X.X. In clinical studies, XXXXXXXX™ was injected xxxxxxxxxxxxx (XX) twice daily at doses generally ranging from X.XX to X.XX mg/Kg (X to X mg/subject/day in a XX Kg adult individual). The maximum recommended daily exposure to the solution is XX µL/Kg body weight (approximately X.X mL in a XX Kg subject) (Xxxxxxx, XXXX). The eight target leachables reviewed in this report are thought to be associated with the XXXXXXXX™ solution.

While the bioavailability of XXXXXXXX™ has not been determined, the bioavailability of xxxxxx (xxxxxxxxxx-xxxx xxxxxx xxxxxx produced by xxxxxxxxxxx XXX technology) is known to be nearly 100% when administered XX to healthy human subjects (Xxxxxxx, XXXX). Thus, in the present report it was assumed that the bioavailability of XXXXXXXX™ and its target leachables is nearly 100% (worst case scenario for target leachables), although no scientific studies have yet been conducted to warrant this conclusion. The majority of studies reviewed in this report to evaluate the possible toxicity of the target leachables utilized oral or dermal routes of exposure. The toxicity of a chemical may or may not depend on the route of administration. For compounds with no appreciable biotransformation in the liver, toxicity should be independent of the route of administration if the rates of absorption are equal (Klaassen,

1996). Each of the target leachables reviewed in this report are expected to be bioavailable at very small quantities when XXXXXXXX™ is dosed XX at X to X mg/subject/day (up to approximately X.X mL/subject/day). Where available, acceptable daily intakes of target leachables range in values from X.X mg (i.e., for XXXXXX) to XXX mg (i.e., for xxxxxxxxx). This equates to dosing concentrations of X.X mg/mL to XXX mg/mL if dosing occurs at maximum drug product dose volume of X.X mL/subject/day and if target leachables are present in this dose volume at acceptable daily intake levels. These dosing levels are significantly higher than the LODs and LOQs (Table 1) of the analytical test method (ATM-XXX-M0013) for the target leachables, suggesting that the sensitivity of the analytical method is appropriate for detecting and quantifying safe levels of the target leachables in the drug product. Except for xxxxxxx, there are no available scientific data to evaluate possible accumulation of the target leachables in specific organ systems with repeated administrations. It is known that xxxxxxx and possibly metabolites of xxxxxxx exhibit minimal accumulation in the blood with repeated administration (Cocheo *et al.*, 1982; Ghantous *et al.*, 1990).

Xxxxxxx would appear to present the most significant human toxicology risk among the target leachables examined in this report. It is well known that acute exposure to relatively low concentrations of xxxxxxx induces a wide range of neurobehavioral effects (in a dose-dependent manner) including initial exhilaration followed by fatigue, changes in activity levels, headache, mental confusion, short-term memory and learning deficits, mild ataxia, and sensory deficits. Xxxxxxx is often abused by human subjects and can result in histopathological changes in the brain. There is evidence from both human and animal studies that long-term exposure to xxxxxxx can result in reproductive toxicity in both males and females, and in teratological and developmental toxicity (Ritchie *et al.*, 2001, 2003). xxxxxxxxxxxxxxxxxx is an antioxidant that is not expected to result in human toxicity unless doses sufficient to induce tissue irritancy are administered. Very low doses of XXXXXX might be expected to be protective against oxidative stress induced by normal metabolic processes or effects of other xenobiotics. There is virtually no published toxicology data for Xxxxxxxxxxxx**.** Significant toxicity effects were not observed from acute oral toxicity and repeated dose toxicity studies in animals, and *in vitro* genetic toxicology studies of xxxxxxxxx (IUCLID, 2000). Xxxxxxxxx has been shown to occur naturally in several mammalian species and may be involved in maintenance of homeostatic fluid balance in several organs systems and in angiogenesis. Xxxxxxxxxxxx is a normal component of many foods, an additive to many commercial products that are ingested, and occurs naturally in the body. There is no evidence of human toxicity except when large oral or dermal doses are administered that can result in mild tissue irritation. The oral LD50 for rats is > XX g/Kg. The toxicity of xxxxxxxxxxxx appears limited to its capacity to induce corrosive damage to tissues including the skin, eyes and gastrointestinal tract . Xxxxxxxxxxxxx is a normal constituent of many foods including vegetable oils and is used as a food additive. Animal studies indicated it is very low in oral toxicity. Human studies conclude that xxxxxxxxxxxxxx is a mild irritant to skin, eyes and the respiratory system. There are no published studies suggesting antagonistic, additive or synergistic toxicology effects among any of the target leachables reviewed in this report. It is concluded that human

exposure to the target leachables at or below the Rfd or RfC values should not result in any significant human toxicity.

VIII. Definitions

ADI: Acceptable daily intake

ASTDR: Agency for Toxic Substances and Disease Registry

CAS: Chemical Abstracts Service

CCOHS: Canadian Center for Occupational Health and Safety

CNS: Central nervous system

d: Day

DHHS: Department of Health and Human Services

EPA: Environmental Protection Agency

FSH: Follicular stimulating hormone

g: Gram

IVN: Intravenous

Kg: Kilogram

LD50: Lethal Dose; the dose at which 50% of animals experience lethality

LOAEL: Lowest observed adverse effect level

LOD: Limit of detection

LOQ: Limit of quantitation

M: Molar

mg: milligram

mL: milliliter

mM: millimolar

MSDS: Material Safety Data Sheet

MTD: Maximal tolerated dose

NIEHS: National Institute of Environmental Health Sciences

NOAEL: No observed adverse effect level

ORL: Oral

ppm: parts per million

RfC: Reference concentration

RfD: Reference dose

SAP: Serum alkaline phosphatase

SC: Subcutaneous

SGP**:** Serum glutamic pyruvic transaminase

UF: Uncertainty factor

WHO: World Health Organization

wk: Week

IX. Tables

Table 2a. Literature-Based Toxicological Findings for **xxxxxxxxxxxxxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Genotoxicity and Carcinogenicity	No reported effects.
Developmental Toxicity	Infant rats exposed from postnatal days 4-21 by oral gavage to XXXXXX and young rats (5 to 6 weeks of age) exposed to XXXXXX exhibited hepatic and renal toxicity effects (histopathological changes and increased organ weights) (Hirata-Koizumi *et al.*, 2005).
Respiratory System	No reported effects.
Cardiovascular System	No reported effects.
Endocrine and Urinary Systems	Infant rats exposed from postnatal days 4-21 by oral gavage to XXXXXX and young rats (5 to 6 weeks of age) exposed to XXXXXX exhibited hepatic and renal toxicity effects (histopathological changes and increased organ weights) (Hirata-Koizumi *et al.*, 2005).
Reproductive System	No reported effects.
Nervous System and Special Sense Organs	No reported effects.
Other	Antioxidant effects, generally without cytotoxicity (Saito *et al.*, 2001; Yoon *et al.*, 2006). Unexplained depigmentation (vitiligo) in industrial workers possibly exposed to

Table 2a. Literature-Based Toxicological Findings for **xxxxxxxxxxxxxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	xxxxxxxxxxxxxxxxxxx through handling of rubber associated with industrial pumps (O'Malley *et al.*, 1988).

[a]RfD, RfC and ADI values are provided in Table 3.

Table 2b. Literature-Based Toxicological Findings for **Xxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Genotoxicity and Carcinogenicity	Experimental results for human and animal genotoxicity and carcinogenicity from xxxxxxx exposure are equivocal, and generally fail to support the hypothesis that xxxxxxx exposure is direct related to these consequences (ATSDR, 2004). Bauchinger *et al.* (1982) reported increases in sister-chromatid exchanges and chromosome breaks in workers chronically exposed to xxxxxxx. Lemasters *et al.* (1997, 1999) reported a small but statistically significant increase in the frequency of sister chromatid exchanges, as well as in micronucleus frequency (MN) in the sperm of sheet metal workers or painters exposed to occupational xxxxxxx for up to 30 wk.
Developmental Toxicity	A number of studies of women who abused xxxxxxx during pregnancy suggest that high level exposure to xxxxxxx can be detrimental to the developing fetus. Results of animal studies indicate that repeated exposure to levels of xxxxxxx (133 to 750 ppm by inhalation) sufficient to induce maternal toxicity also result in developmental toxicity in offspring, including reduced fetal survival and retardation of fetal growth and skeletal development (ATSDR, 2004). Infants of mothers who abuse xxxxxxx often have craniofacial features that resemble those of children with fetal alcohol syndrome, even if the mother did not consume alcohol during pregnancy (Ritchie *et al*., 2001, 2003). Other effects on the embryos and infants include digital hypoplasia, urinary tract anomalies, intrauterine growth retardation, prenatal microencephaly, and developmental delays (review in Ritchie *et al.*, 2001, 2003).
Respiratory System	Acute, subchronic or chronic exposure to xxxxxxx vapor (< 100 ppm) results in irritation of the upper airway and nasal epithelium degeneration in humans (ATSDR, 2004). Inflammation of the nasal mucosa, erosion and metaplasia of the olfactory epithelium, and degeneration of the respiratory epithelium were reported in rats

Table 2b. Literature-Based Toxicological Findings for **Xxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	exposed to 600 or 1200 ppm for two years (ATSDR, 2004).
Cardiovascular System	A number of human and animal studies have indicated that high-level inhalation exposure to xxxxxxx can be associated with development of cardiac arrhythmias in some subjects. However, chronic inhalation exposure of animals to xxxxxxx (300-1200 ppm) did not result in histopathology (ATSDR, 2004).
Endocrine and Urinary Systems	There is limited human data related to endocrine system changes related to chronic xxxxxxx exposure. Rats and mice exposed to xxxxxxx by inhalation (1200-3000 ppm) for up to two years exhibited no histopathological changes in the pancreas, adrenal or thyroid glands (ATSDR, 2004). There are no toxicologically significant studies indicating consistent changes in the urinary systems of humans or animals exposed to non-lethal doses of xxxxxxx (ATSDR, 2004).
Reproductive System	In female xxxxxxx abusers, an absence of effects on menstruation variables was reported (Ng *et al.*, 1992a), consistent with an increase in spontaneous abortions (Ng *et al.*, 1992b). In males, hormonal changes have been reported, although there was not a systematic analysis of the effects on fertility (Svensson *et al.*, 1992a, 1992b). The effects were reductions in luteinizing hormone, follicular stimulating hormone (FSH), and testosterone.
Nervous System and Special Sense Organs	High-dose human exposure to xxxxxxx has been shown to result in severe CNS depression and possible lethality. Lower-dose acute exposures to xxxxxxx may result in headache, dizziness, fatigue, disorientation, and altered decision-making. Chronic exposure to xxxxxxx can result in ataxia, drowsiness, tremors, nystagmus, impaired speech and hearing, and eventual cerebral atrophy. Animals exposed orally to a single

Table 2b. Literature-Based Toxicological Findings for **Xxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	dose of xxxxxxx (2610-5250 mg/Kg) exhibited a variety of neurobehavioral and neurological changes including increased locomotor activity, lacrimation and salivation, and a dose-dependent increase in ataxia. In some cases, these changes persisted for a number of days (ATSDR, 2004). Single doses of 250-1000 mg/Kg xxxxxxx administered orally resulted in reduced flash evoked potential wave pattern amplitudes (ATSDR, 2004).
Other	There are no animal or human studies indicating significant changes in the hepatic system following exposure to xxxxxxx (ATSDR, 2004).

[a]RfD, RfC and ADI values are provided in Table 3.

Table 2c. Literature-Based Toxicological Findings for **Xxxxxxxxxxxx (Xxxxxx)**

Target System and Non-Target System Toxicity	[a]Literature Findings
Genotoxicity and Carcinogenicity	No effects reported (MSDS – Xxxxxxxxxxxx, 2006).
Developmental Toxicity	No effects reported (MSDS – Xxxxxxxxxxxx, 2006).
Respiratory System	Inhalation of Xxxxxxxxxxxx should be avoided (MSDS – Xxxxxxxxxxxx, 2006).
Cardiovascular System	No effects reported (MSDS – Xxxxxxxxxxxx, 2006).
Endocrine and Urinary Systems	No effects reported (MSDS – Xxxxxxxxxxxx, 2006).
Reproductive System	No effects reported (MSDS – Xxxxxxxxxxxx, 2006).
Nervous System and Special Sense Organs	Ocular contact with Xxxxxxxxxxxx should be avoided (MSDS – Xxxxxxxxxxxx, 2006).
Other	Dermal contact with Xxxxxxxxxxxx should be avoided (MSDS – Xxxxxxxxxxxx, 2006).

[a]RfD, RfC and ADI values are provided in Table 3.

Table 2d. Literature-Based Toxicological Findings for **Xxxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Genotoxicity and Carcinogenicity	No significant effects reported (IUCLID, 2000).
Developmental Toxicity	No significant effects reported (IUCLID, 2000).
Respiratory System	No significant effects reported (IUCLID, 2000).
Cardiovascular System	Xxxxxxxxx has been identified as an angiogenic agent in bovine mesentery (Wakamatsu *et al.,* 1990) and in a rat cornea-micropocket assay (Mitchell *et al*., 1996).
Endocrine and Urinary Systems	No significant effects reported (IUCLID, 2000).
Reproductive System	No significant effects reported (IUCLID, 2000).
Nervous System and Special Sense Organs	Xxxxxxxxx has been shown to cause very slight erythema when applied to skin of albino rabbits (IUCLID, 2000). Xxxxxxxxx has been shown to result in slight diffuse redness of the conjunctivae and slight chemosis in albino rabbits (IUCLID, 2000).
Other	May be involved in maintaining fluid balance in a number of organ systems (rat and pig) (Hamberger and Stenhagen, 2003).

[a]RfD, RfC and ADI values are provided in Table 3.

Table 2e. Literature-Based Toxicological Findings for **Xxxxxxxxxxx (Xxxxxxxxxxxxxxx)**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Genotoxicity and Carcinogenicity	No reported effects.
Developmental Toxicity	No reported effects.
Respiratory System	High concentrations of dust containing xxxxxxxxxxx may result in coughing and mild, temporary respiratory irritancy in humans (MSDS – Xxxxxxxxxxx, 2003).
Cardiovascular System	No reported effects.
Endocrine and Urinary Systems	No reported effects.
Reproductive System	No reported effects.
Nervous System and Special Sense Organs	Animal and human studies indicate that xxxxxxxxxxx is not an eye or dermal irritant (Briggs *et al.*, 1976).
Other	Cell death in human hepatocytes possibly *via* mitochondria-mediated apoptosis (Ji *et al.*, 2005).

[a]RfD, RfC and ADI values are provided in Table 3.

Table 2f. Literature-Based Toxicological Findings for **Xxxxxxxxxxxx (*n*-Xxxxxxxxxxx)**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Genotoxicity and Carcinogenicity	No reported effects (Traul *et al.*, 2000; MSDS – Xxxxxxxxxxx, 2002).
Developmental Toxicity	No reported effects (Traul *et al.*, 2000; MSDS – Xxxxxxxxxxx, 2002).
Respiratory System	No reported effects (Traul *et al.*, 2000; MSDS – Xxxxxxxxxxx, 2002).
Cardiovascular System	No reported effects (Traul *et al.*, 2000; MSDS – Xxxxxxxxxxx, 2002).
Endocrine and Urinary Systems	No reported effects (Traul *et al.*, 2000; MSDS – Xxxxxxxxxxx, 2002).
Reproductive System	No reported effects (Traul *et al.*, 2000; MSDS – Xxxxxxxxxxx, 2002).
Nervous System and Special Sense Organs	Irritating to the eyes at high concentrations (MSDS – Xxxxxxxxxxx, 2002).
Other	Irritating to skin and mucous membranes at high concentrations (MSDS – Xxxxxxxxxxx, 2002). May cause gastrointestinal distress at high concentrations (MSDS – Xxxxxxxxxxx, 2002).

[a]RfD, RfC and ADI values are provided in Table 3.

Table 2g. Literature-Based Toxicological Findings for **Xxxxxxxxxx (Xxxxxx)**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Genotoxicity and Carcinogenicity	No significant increase in tumor incidence was reported to F344 rats and B6C3F1 mice exposed to xxxxxxxxxx in their diet at or near the MTD (US DHHS, 1982).
Developmental Toxicity	Depressed fetal body weights were observed in the offspring of rats and mice exposed to xxxxxxxxxx in their diets, and in rabbits exposed by gavage (US DHHS, 1993; US EPA, 1988).
Respiratory System	No reported effects.
Cardiovascular System	No reported effects.
Endocrine and Urinary Systems	Body weight depression and increased kidney weights in rats exposed chronically to xxxxxxxxxx in the diet (US EPA, 1988).
Reproductive System	Alterations in ovarian-menstrual functions and condition have been reported in ferrets exposed to xxxxxxxxxx vapors/dust (US EPA, 1999). Adverse effects on spermatogenesis have been observed in rats following inhalation (US EPA, 1999).
Nervous System and Special Sense Organs	Acute exposure to xxxxxxxxxx may result in irritation and burning of the eyes, nose and skin humans. Chronic exposure may result in dermal peeling (US EPA, 1988; 1993). Headaches, malaise, confusion and nervous system irritation have been observed in workers exposed to xxxxxxxxxx by inhalation (US EPA, 1993). Fever and grand mal seizures were reported in one man exposed to high concentrations of xxxxxxxxxx for 3 days (US EPA, 1993).

Table 2g. Literature-Based Toxicological Findings for **Xxxxxxxxxxx (Xxxxxx)**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Other	Body weight gain depression and increased liver weights in rats exposed chronically to xxxxxxxxxxx in the diet (US EPA, 1988).

[a]RfD, RfC and ADI values are provided in Table 3.

Table 2h. Literature-Based Toxicological Findings for **Xxxxxxxxxxxxx (Xxxxxxxxxx)**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Genotoxicity and Carcinogenicity	There is no human information available. In one animal study, application to skin following an exposure to a known carcinogen caused increased tumors (Holsti, 1959).
Developmental Toxicity	No reported effects (CHEMINFO, 1997).
Respiratory System	Dusts or mists can cause irritation of the nose and throat. High concentrations may cause coughing, sneezing and difficult breathing. Irritation of the nose and throat was reported by workers exposed to unspecified concentrations of airborne *n*-xxxxxxxxxxxxx dust (Apol *et al.*, 1981).
Cardiovascular System	No reported effects (CHEMINFO, 1997).
Endocrine and Urinary Systems	No reported effects (CHEMINFO, 1997).
Reproductive System	No reported effects (CHEMINFO, 1997).
Nervous System and Special Sense Organs	Eye irritation has been reported by workers occupationally exposure to airborne n-xxxxxxxxxxxxx dust. (Apol *et al.*, 1981).
Other	Repeated or prolonged skin contact with dusts or solutions can cause irritation of the skin. Irritation was observed in 6/10 volunteers after application of *n*-xxxxxxxxxxxxx for 4 days (24 hours/day) using a patch which prevented evaporation (Stillman *et al.*, 1975). However, no sensitization was observed following repeated application of a 1% aqueous solution of a liquid soap containing

Table 2h. Literature-Based Toxicological Findings for **Xxxxxxxxxxxxxx (Xxxxxxxxxx)**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	1.95% *n*-xxxxxxxxxxxxxx to intact and abraded skin of human volunteers (Cosmetic, Toiletry and Fragrance Association, 1987).

[a]RfD, RfC and ADI values are provided in Table 3.

Table 3. Reference Values and Acceptable Daily Intake for Target leachables.

Compound	RfD [mg/Kg/day]	RfC [ppm]	ADI [mg]	[a]Comments
xxxxxxxxxxxxxxxxxx (XXXXXX)	X.XX	N/A	X.X	Based on NOAEL of X mg/Kg/day for renal and hepatic effects in infant and young rats exposed to XXXXXX during development (Hirata-Koizumi *et al.*, 2005)
Xxxxxxx	X.X	X.X	X	The RfD is based on a NOAEL of XXX mg/Kg/g for changes in liver and thymus weights with repeated oral dosing (Hsieh *et al.*, 1989). The RfC is based on a NOAEL of XX ppm in a study of decreased brain weight in male rats (Hillefors-Berglund *et al.*, 1995)
Xxxxxxxxxxxx (Xxxxxx)	N/A	N/A	N/A	There is virtually no toxicology data available for Xxxxxxxxxxxx (MSDS – Xxxxxxxxxxxx, 2006)
Xxxxxxxxx	X.X	N/A	XXX	Based on NOAEL of XXXX mg/Kg from acute oral toxicity study (IUCLID, 2000).
Xxxxxxxxxxx (Xxxxxxxxxxxxxxx)	N/A	N/A	N/A	ORL-RatLD50 > XX g/Kg ORL-Mouse LD50 = XXXX mg/Kg
Xxxxxxxxxxx (*n*-Xxxxxxxxxx)	N/A	N/A	N/A	ORL Mouse LD50 = X g/Kg Dermal LD50 Guinea Pig = X mL/Kg Draize Rabbit = XXX microgram

Table 3. Reference Values and Acceptable Daily Intake for Target leachables.

Compound	**RfD [mg/Kg/day]**	**RfC [ppm]**	**ADI [mg]**	**[a]Comments**
				(severe) No LOAEL, NOAEL, RfD or RfC values are available.
Xxxxxxxxxxx (Xxxxxx)	X.X	N/A	XX	XX mg/Kg/d NOAEL based on reduced offspring body weight in rats US EPA, 1988, 1999
Xxxxxxxxxxxxx (Xxxxxxxxxx)	N/A	N/A	N/A	ORL-Rat LD50 = XX g/Kg IVN-Mouse = XXX1 mg/Kg

[a]ADI (mg) = (RfD in mg/Kg/day) x 50 Kg body weight. RfD = NOAEL or LOAEL/(UF). ORL = Oral. IVN = Intravenous. See section V for equations.

X. References

General.

Dourson ML. New Approaches in the Derivation of Acceptable Daily Intake (ADI). Comments Toxicology. 1986;1(1):35-48.

Hertzberg RC and Dourson ML. Using Categorical Regression Instead of a NOAEL to Characterize a Toxicologist's Judgment in Noncancer Risk Assessment. Toxicology of Chemical Mixtures: Case Studies, Mechanisms and Novel Approaches, RSH Yang, Ed. Academic Press, 1993.

Klaassen CD. Casarett and Doull's Toxicology: The Basic Science of Poisons. Fifth Edition. McGraw-Hill, 1996.

Xxxxxxx, Inc. XXXXXXXX™ (mecasermin [rDNA origin] injection) Product Package Insert, 2005.

World Health Organization (WHO). Principles for the assessment of risks to human health from exposure to chemicals. World Health Organization, Geneva, Environmental Health Criteria (210), 1999.

xxxxxxxxxxxxxxxxxx (xxxxxx).

Hirata-Koizumi M, Hamamura M, Furukawa H, *et al.* Elevated susceptibility of newborn as compared with young rats to 2-tert-butylphenol and xxxxxxxxxxxxxxxxxx toxicity. Congenit Anom (Kyoyo). 2005;45(4):146-153.

MSDS – xxxxxxxxxxxxxxxxxx, 2005. http://physchem.ox.ac.uk/MSDS/DI/xxxxxxxxxxxxxxxxxx.html.

O'Malley MA, Mathias CG, Priddy M, Molina D, Grote AA and Halperin WE. Occupational vitiligo due to unsuspected presence of phenolic antioxidant byproducts in commercial bulk rubber. J Occup Med. 1988;30(6):512-516.

Saito M, Atsumi T, Satoh K, *et al*. Radical production and cytotoxic activity of tert-butyl-substituted phenols. In Vitr Mol Toxicol. 2001;14(1):53-63.

Takahashi O, Hiraga K. 4-tert-butyl-2,6-diisopropylphenol: Another phenol inducing hemorrhage in rats. Toxicol Lett. 1980;5(2):147-150.

Yoon MA, Jeong TS, Park DS, *et al.* Antioxidant effects of quinoline alkaloids and 2,4-di-tert-butlyphenol isolated from Scolopendra subspinipes. Biol Pharm Bull. 2006; 29(4):735-739.

Xxxxxxx.

Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Xxxxxxx (Update), 2004.

Baelum J, Andersen I, Lundqvist GR *et al.* Response of solvent-exposed printers and unexposed controls to six-hour xxxxxxx exposure. Scand J Work Enviro. Health. 1985;1:271-280.

Banfer W. Studies on the effect of pure xxxxxxx on the blood picture of photogravure printers and helper workers. (Ger) Zentralbl Arbeitsmed. 1961;11:35-40.

Bauchinger M, Schmid E, Dresp J, Kolin-Gerresheim J, Hauf R and Suhr E. Chromosome changes in lymphocytes after occupational exposure to xxxxxxx. Mutat Res. 1982;102(4):439-445.

Cocheo V, Silvestri R, Bombi GG and Perbellini L. Purge and Trap analysis of xxxxxxx in blood: comparison with the Head Space method. Am Ind Hyg Assoc J. 1982;43(12):938-941.

Echeverria D, Fine L, Langolf G, Schork T and Sampaio C. Acute behavioral comparisons to xxxxxxx and ethanol in human subjects. Brit. J. Ind. Med. 1991;48:750-761.

Ghantous H, Dencker L, Gabrielsson J, Danielsson BR and Bergman K. Accumulation and turnover of metabolites of xxxxxxx and xylene in nasal mucosa and olfactory bulb in the mouse. Pharmacol Toxicol. 1990;66(2):87-92.

Hillefors-Berglund M, Liu Y and von Euler G. Persistent, specific and dose-dependent effects of xxxxxxx exposure on dopamine D2 agonist binding in the rat caudate-putamen. Toxicology. 1995;26;100(1-3):185-194.

Hsieh GC, Sharma RP and Parker RD. Immunotoxicological evaluation of xxxxxxx exposure via drinking water in mice. Environ Res. 1989;49(1:93-103.

Lemasters GK, Livingston GK, Lockey JE, *et al.* Genotoxic changes after low-level solvent and fuel exposure on aircraft maintenance personnel. Mutagenesis. 1997;12(4):237-243.

Lemasters GK Olsen DM, Yin, DH *et al.* Male reproductive effects of solvent and fuel exposure during aircraft maintenance. Reprod Toxicol. 1999;13:155-166.

Low LK Meeks JR, and Mackerer, CR. Health effects of the alkylbenzenes. I. Xxxxxxx. Toxicol Ind Health. 1988;4(1):49-75.

MSDS – Xxxxxxx, 2005

http://physchem.ox.ac.uk/MSDS/TO/xxxxxxx.html.

Ng TP, Foo SC and Yoong, T. Menstrual function in workers exposed to xxxxxxx. Brit J Ind Med. 1992a;49:799-803.

Ng TP, Foo SC and Yoong T. Risk of spontaneous abortion in workers exposed to xxxxxxx. Brit J Ind Med. 1992b;49:804-808.

Ritchie GD, Still KR, Alexander WK, Nordholm AF, Wilson CL, Rossi J 3rd and Mattie DR. A review of the neurotoxicity risk of selected hydrocarbon fuels. J Toxicological Environ Health B. 2001;4:223-312.

Ritchie GD, Still KR, Rossi J 3rd, Bekkedal MYV, Bobb A and Arfsten D. Biological and health effects of exposure to kerosene-based jet fuels and performance additives. J Toxicol Environ Health B. 2003;357-451.

Svensson BG, Nise G, Erfurth EM, Nilsson A and Skerfving S. Hormone status in occupational xxxxxxx exposure. Am J Ind Med. 1992a;22:99-107.

Svensson BG, Nise G, Erfurthm EM and Olsson H. Neuroendocrine effects in printing workers exposed to xxxxxxx. Brit J Ind Med.1992b;9:402-408.

US Environmental Protection Agency (US EPA). Integrated Risk Information System (IRIS) on Xxxxxxx. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. 1999.

von Oettingen WF, Neal PA and Donahue DD. The toxicity and potential dangers of xxxxxxx: Preliminary report. JAMA. 1942a;118:579-584.

von Oettingen WF, Neal PA, Donahue DD, *et al.* The toxicity and potential dangers of xxxxxxx with special reference to its maximal permissible concentration, bulletin 279. Public Health Service, 1942b:50.

Xxxxxxxxxxxx (Xxxxxx).

MSDS – Xxxxxxxxxxxxx (Xxxxxx Xxxxxxxxx Xxxxxxxxx Xxxxxxxxx), 2006 http://www.sigmaaldrich.com/catalog/search/ProductDetail/SIGMA/XXXXX.

Xxxxxxxxx.

Hamberger A and Stenhagen G. Xxxxxxxxx as a modulator of water balance: new function of a fatty acid amide. Neurochem Res. 2003;28(2):177-185.

European Commission – European Chemical Bureau (IUCLID). IUCLID Dataset – Substance ID: 112-84-5, 2000.

Mitchell CA, Davies MJ, Grounds MD, *et al.* Enhancement of neovascularization in regenerating skeletal muscle by the sustained release of xxxxxxxxx from a polymer matrix. J Biomater Appl. 1996;10(3):230-249.

MSDS – Xxxxxxxxx, 2003. http://physchem.ox.ac.uk/MSDS/ER/xxxxxxxxx.html.

Wakamatsu K, Masaki T, Itoh F, Kondo K and Sudo K. Isolation of fatty acid amide as an angiogenic principle from bovine mesentery. Bichem Biophys Res Commun. 1990; 168(2):423-429.

Xxxxxxxxxxx (Xxxxxxxxxxxxxxx).

Briggs GB, *et al.* Safety studies on a series of fatty acids. Amer Industrial Hygiene Association J. 1976:251-253.

Canadian Center for Occupational Health and Safety (CCOHS). CHEMINFO Record #542 – Xxxxxxxxxxx, 1996.
http://www.intox.org/databank/documents/chemical/palmitic/cie542.htm.

Ji J, Zhang L, Wang P, *et al*. Saturated free fatty acid, xxxxxxxxxxx, induces apoptosis in fetal hepatocytes in culture. Exp Toxicol Pathol. 2005;56(6):369-376.

MSDS – Xxxxxxxxxxx, 2003. http://www.jtbaker.com/msds/englishhtml/p0011.htm.

Stillman MA, *et al.* Relative irritancy of free fatty acids of different chain length. Contact Dermatitis. 1975:65-69.

Xxxxxxxxxxx (*n*-Xxxxxxxxxx).

MSDS – Xxxxxxxxxxx, 1997
http://avogadro.chem.iastate.edu/MSDS/caproic_acid.htm.

MSDS – Xxxxxxxxxxx, 2005.
http://physchem.ox.ac.uk/MSDS/HE/hexanoic_acid.html.

Traul KA, Driedger A, Ingle DL and Nakhasi D. Review of the Toxicologic Properties of Medium-chain Triglycerides. Food and Chemical Toxicology. 2000;38:79-98.

Xxxxxxxxxx (Xxxxx).

MSDS – Xxxxxxxxxx, 1998.
http://avogadro.chem.iastate.edu/MSDS/xxxxxxxxxx.htm.

Gad SC, Robinson K, Serota DG and Colpean BR. Developmental toxicity studies of xxxxxxxxxxx in the rat and rabbit. J Appl Toxicol. 1987;7(5):317-326.

Serota DG, Hoberman AM, Friedman MA and Gad SC. Three-generation reproduction study with xxxxxxxxxxx in rats. J Appl Toxicol. 1988;8(4):285-293.

US Department of Health and Human Services (US DHHS), National Toxicology Program. Carcinogenesis Bioassay of Xxxxxxxxxxx (CAS No. XXX-XX-X) F344 Rats and B6C3F1 Mice (Feed Study). NIH Report No. 81-1770, 1982.

US Environmental Protection Agency (US EPA). Health and Environmental Effects Profile for Xxxxxxxxxxx. ECAO-CIN-G018. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Cincinnati, OH, 1988.

US Environmental Protection Agency (US EPA). Integrated Risk Information System (IRIS). Xxxxxxxxxxx. National Center for Environmental Assessment, Office of Research and Development, Washington, DC, 1999.

US Department of Health and Human Services (US DHHS). Hazardous Substances Data Bank (HSDB, online database, Capriotic Acid). National Toxicology Information Program, National Library of Medicine, Bethesda, MD. 1993.

Xxxxxxxxxxxxxx.

Apol AG, *et al.* Health hazard evaluation report no. HHE 80-160-897. Emery Industries Inc., Los Angeles, California. National Institute of Occupational Safety and Health (NIOSH), 1981.

Briggs GB *et al.* Safety studies on a series of fatty acids. Amer Industrial Hyg Assn J. 1976;37(4);251-253.

Canadian Center for Occupational Health and Safety (CCOHS). CHEMINFO Record #556 – n-Xxxxxxxxxxxxxx, 1997.
http://www.intox.org/databank/documents/chemical/dodecacd/cie556.htm.

Cosmetic, Toiletry and Fragrance Association. Final report on the safety assessment of oleic acid, Xxxxxxxxxx, xxxxxxxxxxxx, myristic acid and stearic acid. J Am College of Toxicol. 1987;6(3):321-401.

Holsti, P. Tumor promoting effects of some long chain fatty acids in experimental skin carcinogenesis in the mouse. Acta Pathologica et Microbiologica Scandinavica. 1959;46:51-58.

Katz GV., *et al*. Aliphatic carboxylic acids. In: Patty's Industrial Hygiene and Toxicology. Edited by GD Clayton *et al*. 4th edition. Volume II. Toxicology. Part E. John Wiley and Sons, 1994. p. 3523-3526, 3566- 3567, 3646-3671.

MSDS – Xxxxxxxxxxxxxx, 2002.
http://www.pgchemicals.com/resources/msds/C1299.pdf.

Registry of Toxic Effects of Chemical Substances (RTECS). RTECS Number: OE9800000. CAS Number: XXX-XX-X. Last Revision Date: 200502.

Stillman MA, *et al.* Relative irritancy of free fatty acids of different chain length. Contact Dermatitis. 1975;1(2)1:65-69.

XI. Appendix A

Appendix removed.

XII. Appendix B

Appendix removed.