Literature-Based Toxicological Assessment of Xxxxxxxx and Xxxxxxxx

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

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Study Report Approval

Report Title: Literature-Based Toxicological Assessment of Xxxxxxxx and Xxxxxxxx

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

1. Xxxxxxxx.

Xxxxxxxx (X) is a heavy metal to which humans are minimally exposed, except in limited mining, smelting, industrial manufacturing, occasional product use, and unique military munitions applications. Perhaps the most notable human exposure to xxxxxxxx occurs when military war fighters or associated civilians are struck with xxxxxxxx shrapnel or are exposed to vaporized xxxxxxxx during missile attacks on targets of military interest. There is some recent evidence that chronic human dermal, oral or respiratory exposure to xxxxxxxx near military bases or industrial xxxxxxxx smelting operations may increase susceptibility to specific diseases, such as childhood leukemia and certain cancers (ATSDR, 2005). In these cases, the acute or chronic human exposure to xxxxxxxx is many times greater than would be expected during injection of the ocular system with drugs delivered in syringe barrels containing xxxxxxxx. The literature review would suggest that acute or chronic human exposure to xxxxxxxx during delivery of ocular drugs presents no human health risk.

2. Xxxxxxxx.

There has been extensive reported human exposure to xxxxxxxxs since the 1940s related to cosmetics, processed food, medical and commercial/industrial applications. For example, as many as 1 to 2.5 million women in the US may have been chronically implanted with xxxxxxxx gel-filled breast implants, shown to be susceptible to leaking into the body (Gem *et al.*, 2005). There have been reports of human health effects (e.g., immunotoxicity, arthritis, Chronic Fatigue Syndrome, fibromyalgia) associated with chronic systemic exposure to medically implanted xxxxxxxxs. However, the epidemiologic data obtained thus far have overwhelmingly concluded that no correlation exists between certain chronic symptoms patients and xxxxxxxx prosthesis (Perkins *et al.*, 1995; Liang, 1997; Gabriel, 1996; Edworthy *et al.*, 1998; Stein, 1999). This conclusion has been echoed by the expert panel report by the Institutes of Medicine (Siddiqui *et al.*, 1994). Additionally, there have been reports of human health effects associated with chronic industrial pulmonary exposure to xxxxxxxxs. However, there have been few reports of significant toxicity associated with dermal exposure to xxxxxxxxs used in cosmetics, other skin care products, or industrial xxxxxxxx sealants. More importantly, there have been few reports of significant toxicity associated with acute or chronic ocular exposure to xxxxxxxxs, including injection of xxxxxxxx oil into the anterior ocular chambers of patients undergoing retinal detachment surgeries. Exposure to the extremely small quantities of xxxxxxxx oil that would be expected with syringe injection of ocular drugs do not appear to present a human health risk.

3. Xxxxxxxx and Xxxxxxxx.

The literature search identified no research studies evaluating the potential of acute or chronic exposure to xxxxxxxx and xxxxxxxx to induce toxic responses. Thus, any

possible synergistic or additive effects of simultaneous exposure to xxxxxxxx and xxxxxxxx cannot be reported.

II. Introduction and Purpose

The purpose of this work was to conduct a toxicological assessment of xxxxxxxx and xxxxxxxx, whereby the xxxxxxxx is a component of the barrel of a syringe needle used for acute or repeated delivery of an ocular drug to the human eye and the xxxxxxxx is the predominant component of a xxxxxxxx oil used to lubricate the syringe barrel to minimize ocular trauma.

III. Scope

(A) The available literature regarding the possible toxicological implications for xxxxxxxx and xxxxxxxx is discussed in the Results and Discussion section (Section V), and is summarized for each target in Table 1 (Section VIII, Tables 1a and 1b).

(B) Information presented in Sections V and VIII is used to calculate, when possible, Reference Dose (RfD) and Acceptable Daily Intake (ADI) values for each target. This data is presented in Table 2. The exposure limits provided in Table 2 can be used to estimate human health risk from clinical use of the syringe to deliver the drug to the eye.

(C) Literature references are listed by target, in the Reference Section (Section IX).

IV. Experimental

(A) Literature Searches.

Literature searches were conducted using SciFinder Scholar, library resources 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; Klaassen, 1996; 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)

Where possible, an acceptable daily intake (ADI) for each compound was calculated from Reference Dose (RfD).

ADI (mg) = (RfD in mg/kg/d) x 50 kg body weight

V. Results and Discussion

1. Xxxxxxxx.

Xxxxxxxx Applications

Xxxxxxxx (X), known also as Xxxxxxx, is a naturally occurring heavy metal element that has been widely considered to be biologically "inert", although more recent evidence contradicts this assumption. Xxxxxxxx is most commonly released into the air as fine dust-like particles by weathering, and into groundwater from air contamination or erosion of soil containing xxxxxxxx. Emissions from xxxxxxxx mining and hard metal (xxxxxxxx/xxxxxxxx alloy) industries increase xxxxxxxx levels in the air and groundwater. The concentration of xxxxxxxx in ambient air has been estimated at <10 ng/m^3, and small quantities of xxxxxxxx have been measured in public water supplies and foods. Xxxxxxxx blood and urine levels of 1 to 6 and 0.085 µg/L, respectively, have been measured in the general public. Traditionally, xxxxxxxx has had a small number of industrial and commercial applications, and is generally used when extremely high tensile strength is required. Xxxxxxxx and its alloys are used as light bulb filaments, as the part of x-ray tubes where x-rays are formed, as a catalyst to speed up chemical reactions, as a component of steel in high-speed tools, in turbine blades, in phonographic needles, as welding electrodes, as gyroscope wheels, as aircraft counterbalance and fishing weights, in darts, in golf club components, and in ceramic pigments and fire retardant coatings. Due to the fairly limited number of applications, xxxxxxxx has been mined and smelted in only a small number of US and international locations. Most recently, xxxxxxxx has

been widely used by the militaries of the US and several other nations to replace lead or depleted uranium for a number of munitions applications. Human exposure to xxxxxxxx has increased due to the possibility of carrying xxxxxxxx bullets or shrapnel that cannot be removed from the muscle or other body tissues, or exposure to vaporized xxxxxxxx following explosion of xxxxxxxx-tipped missiles. There has been recent concern for civilians and military personnel living near military test ranges where xxxxxxxx munitions are commonly exploded and allowed to remain in the ground and groundwater sources (Masten, 2003; ATSDR, 2005).

Human Exposure Limits

NIOSH has established a recommended inhalation exposure limit (REL; 10-hr time weighted average) of 5 mg/m^3 and a short-term exposure limit (STEL; 15-min time weighted average) of 10 mg/m^3. OSHA has established permissible exposure limits (PELs; 8-hr time weighted average) for xxxxxxxx of 5 mg/m^3 (insoluble compounds) and 1 mg/m^3 (soluble compounds) for construction and shipyard industries (ATSDR, 2005).

Uptake, Metabolism and Elimination of Xxxxxxxx

There has been minimal study of the uptake of xxxxxxxx following oral administration. Sixteen adult mallards were orally dosed with eight xxxxxxxx-iron shot or eight BB-size xxxxxxxx-polymer shot and were maintained for 30 d. Small amounts of xxxxxxxx were detected in the femur and kidneys of two xxxxxxxx-polymer dosed ducks. Higher concentrations of xxxxxxxx were detected in the femur, liver, and kidneys of all xxxxxxxx-iron dosed ducks. Results indicated that xxxxxxxx-iron or xxxxxxxx-polymer shot orally administered to mallards did not adversely affect them during a 30-d trial (Kelly et al., 1998).

Xxxxxxxx ion in the body is not known to be metabolized. It has been postulated that xxxxxxxx may preferentially occupy enzyme sites normally reserved for the essential element, molybdenum, because xxxxxx xxxxxxxxx has been shown to antagonize the normal metabolic action of molybdate in its role as cofactor for the enzymes xanthanine dehydrogenase (Higgins *et al.*, 1956a, 1956b), sulfite oxidase, and aldehyde oxidase (Johnson and Rajagopalan, 1974), and xanthine oxidase secretion to milk (Owen and Proudfoot, 1968) in animal systems.

Once xxxxxxxx has been systemically distributed following inhalation, oral, or dermal exposure or parenteral injection, the pattern of elimination is similar across exposure routes. Information concerning elimination and excretion of xxxxxxxx in humans is limited to findings of measurable amounts of xxxxxxxx in urine of individuals exposed to xxxxxxxx (Barborik, 1972; Nicolaou *et al.*, 1987). Inhalation, oral, and parenteral injection studies in laboratory animals all indicate that absorbed xxxxxxxx is rapidly eliminated from the blood and quickly excreted in large quantities in the urine. Combined urinary and fecal excretion of radioxxxxxxxx from dogs following inhalation exposure to particulate aerosols of XXXXXX was described by three exponential components (Aamodt, 1975). Approximately 90% of the inhaled radioactivity was

removed with a biological half-life of about 14 hr; 6% with a half-life of 5.8 d, and 4% with a half-life of 63 d. The average urine to fecal ratio was 1.14 for the 100 d of post-exposure measurements. Radioxxxxxxxx was rapidly excreted from rats following oral dosing (Kaye, 1968). In a study of rats administered single gavage doses of 185W and followed for 72 hr, approximately 40% of the administered dose of radioxxxxxxxx had been eliminated in the urine in the first 12 hr post-administration; an additional 3% was eliminated during the subsequent 60 hr (ATSDR, 2005).

Mechanisms of Toxicity

Specific mechanisms of xxxxxxxx-induced toxicity have not been elucidated (ATSDR, 2005). In animals administered high levels of xxxxxxxx in combination with low dietary levels of molybdenum, the competitive agonistic properties of the two metals can be manifested by reduced levels of molybdenum and decreased activity of enzymes such as xanthine oxidase, sulfite oxidase and aldehyde oxidase, which normally incorporate molybdenum as a metal carrier (De Renzo, 1954; Higgins *et al.*, 1956a, 1956b**;** Johnson and Rajagopalan, 1974; Johnson *et al.*, 1974). Although these effects can be observed following exposure to elevated levels of xxxxxxxx, only very small amounts of supplemental molybdenum are required to reverse these xxxxxxxx-induced effects. The competitive agonistic properties of xxxxxxxx and molybdenum have not been associated with any observable signs of toxicity.

Health Effects from Exposure to Xxxxxxxx

General Human Health Effects

The Material Safety Data Sheet (MSDS) for xxxxxxxx suggests that the compound is irritating to the skin and eyes on contact. Inhalation may cause irritation to the lungs and mucus membrane. Irritation to the eyes will cause watering and redness. Reddening, scaling, and itching are characteristics of skin inflammation (MSDS, 1980, 2006). Pulmonary fibrosis, memory and sensory deficits, and increased mortality due to lung cancer have been attributed to occupational exposure to dusts generated in the hard metal industry. No reports were located in which cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular or dermal effects were associated with inhalation exposure of humans or animals to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). Hard metal is an alloy or encapsulated mixture that is composed of xxxxxxxx or xxxxxxxx carbide and cobalt (although the alloys may also contain thorium, copper, nickel, iron, or molybdenum). Based on the presence of xxxxxxxx oxide fibers in air samples taken at some hard metal facilities and demonstrations that xxxxxxxx oxide fibers are capable of generating hydroxyl radicals in human lung cells *in vitro*, it has been suggested that xxxxxxxx oxide fibers may contribute to the development of pulmonary fibrosis in hard metal workers. Historically, the respiratory and neurological effects observed in hard metal workers have been attributed to cobalt, not xxxxxxxx (ATSDR, 2005).

Human and Animal Mortality

No reports were located in which death in humans could be specifically associated with exposure to airborne xxxxxxxx or xxxxxxxx compounds. Information in animals is restricted to reports of no deaths during 14 d following single 4-hr exposure of rats to atmospheres of xxxxxx xxxxxxxxx dihydrate powder at a concentration of 5.01 mg/L (Huntingdon Life Sciences Ltd, 1999a) or xxxxxxxx metal powder at a concentration of 5.4 mg/L (Huntingdon Life Sciences Ltd, 1999b).

The toxicity of ingested xxxxxxxx in humans is not well known. In an early report, Kruger (1912) reported no adverse effects on patients administered 25 to 80 g of xxxxxxxx powder as a substitute for barium in radiological exams. Nausea, followed by seizure, 24-hour coma, temporary renal failure, and subsequent tubular necrosis and anuria were reported in a male subject who had accidentally consumed metallic xxxxxxxx in a mixture of beer and wine (Marquet *et al.* 1997). However, these effects could not be attributed to the consumption of xxxxxxxx *per se*, as the subject drank the xxxxxxxx from the hot barrel of a rifle. Acute oral exposure to xxxxxxxx does not appear to be a particular toxicity concern, based on acute oral LD50 values ranging from 240 to 11,300 mg/kg/d for several soluble xxxxxxxx compounds (ATSDR, 2005). Death was reported in guinea pigs following single oral (gavage) administration of xxxxxx xxxxxxxxx at doses ≥780 mg/kg (Karantassis, 1924). Concentrations of 2.0% xxxxxxxx (as xxxxxx xxxxxxxxx), 4% xxxxxxxx (as xxxxxxxx oxide), or 5.0% xxxxxxxx (as ammonium xxxxxxxxxxxxx), in the daily diet of rats resulted in 100% mortality within 10 d following the initiation of test diet (Kinard and Van de Erve, 1941). Diets containing the equivalent of 0.5% xxxxxxxx (as xxxxxx xxxxxxxxx, xxxxxxxx oxide, or ammonium xxxxxxxxxxxxx) resulted in mortality of 3/6 males and 4/6 females, 4/5 males and 5/5 females, and 0/5 males and 0/5 females, respectively. No deaths occurred in rats receiving 0.1% xxxxxxxx (as xxxxxx xxxxxxxxx or xxxxxxxx oxide) in the diet for 70 d. In another study, no deaths were reported in rats administered diets containing as much as 10% xxxxxxxx metal powder for 70 d (Kinard and Van de Erve, 1943). Approximately 15% decreases in longevity were observed in male, but not female, rats administered xxxxxxxx (as xxxxxx xxxxxxxxx) in the drinking water at a concentration of 5 mg/L for life (up to 3 years) (Schroeder and Mitchener, 1975a, 1975b).

No reports were located in which death in humans was associated with dermal exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). Available information in animals was limited to a single report of death in 0/2, 2/2, and 2/2 rabbits following dermal application of a 5% xxxxxxxx chloride solution in single doses of 100, 200, and 1,000 mg/kg, respectively (Dow Chemical Company, 1982).

Parenteral injection studies that have been performed using laboratory animals were designed to establish lethal doses of xxxxxxxx compounds and to assess the efficacy of methods to reduce toxicity. An LD50 value of 500 mg/kg was reported for intraperitoneally injected xxxxxxxx metal in rats. An LD50 was between 140 and 160 mg/kg for xxxxxxxx (as xxxxxx xxxxxxxxx) subcutaneously injected into 66-d old rats; younger rats appeared to be less sensitive (Kinard and Van de Erve, 1940). Intramuscular injection of a 10% aqueous solution of xxxxxx xxxxxxxxx in rats (Sivjakov and Braun,

1959) and rabbits (Lusky *et al.*, 1949) resulted in LD50 values of 220.6 and 105 mg/kg, respectively.

Ocular System Effects

Signs of slight conjunctival irritation were noted in rabbits following single ocular instillation of 100 mg of xxxxxx xxxxxxxxx dihydrate powder or xxxxxxxx metal powder (Huntingdon Life Sciences Ltd 1999c, 2000)**.** Instillation of a 5% xxxxxxxx chloride solution into the rabbit eye resulted in conjunctivitis, iritis, and corneal haziness that resolved within 14 d post instillation (Dow Chemical, 1982). No ocular toxicity has been reported in two studies in which xxxxxxxx metal was implanted intravitreally into the eyes of rabbits (Palanker *et al.*, 2002). When orally administered to streptozotocin-induced diabetic rats, xxxxxx xxxxxxxxx (0.7 mg/mL [2 mM] for the first three wk and then 2 mg/mL [7 mM] for the remainder of the eight month treatment period) in the drinking water prevented diabetes-induced morphological changes in the ocular lens (Barbera *et al.*, 2001). No reports were located in which ocular toxicity effects were associated with oral or dermal exposure of humans or animals to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005).

Carcinogenicity and Genotoxicity

No reports were located in which cancer in humans or animals could be associated with inhalation exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). Information regarding the carcinogenicity of ingested xxxxxxxx in humans is restricted to a single report of the Center for Disease Control (CDC, 2003) in which no statistically significant association (odds ratio 0.78, p-value 0.57) was found between exposure to xxxxxxxx in the drinking water and leukemia observed in a population of Churchill County (Fallon), NV. Recent evidence suggests that inhalation and/or oral ingestion of xxxxxxxx in Fallon, NV could be related to development of a childhood leukemia cluster. High levels of xxxxxxxx have been found in tree core samples and environmental air samples, as well as in blood samples collected from local residents (CDC, 2005). However, high levels of arsenic and various jet fuel hydrocarbon fractions have also been identified in the Fallon, NV area and may be similarly related to development of the leukemia cluster.

Gross tumor incidences in rats administered xxxxxxxx (as xxxxxx xxxxxxxxx) in the drinking water at a concentration of 5 mg/L for life were similar to those of controls (Schroeder and Mitchener, 1975a). Male rats administered xxxxxx xxxxxxxxx (100 ppm) in the drinking water for 19 or 30 wk did not exhibit treatment-related evidence of carcinoma in the esophagus or forestomach; nor did xxxxxx xxxxxxxxx treatment enhance the carcinogenic effect of *N*-nitrososarcosine ethyl ester, a chemical known to induce esophageal cancer in rats (Luo *et al.,* 1983). In a study designed to assess the effect of systemic sulfite on benzo[*a*]pyrene-induced lung carcinoma in rats, Gunnison *et al.* (1988) administered xxxxxx xxxxxxxxx to induce sulfite oxidase deficiency, thus increasing systemic sulfite. In this study, xxxxxx xxxxxxxxx did not statistically significantly affect the initiation of squamous cell carcinoma of the respiratory tract of benzo[*a*]pyrene-treated rats or incidences of mammary gland tumors. Results of Wei *et*

al. (1987) indicated that xxxxxxxx may act as a tumor promoter in rats administered 150 ppm of xxxxxxxx in the drinking water followed by intravenous injection of the known carcinogen, N-nitroso-N-methylurea. In one recent study, intramuscular implanted xxxxxxxx alloy (91.1% xxxxxxxx, 6.0% nickel, and 2.9% cobalt) was shown to rapidly cause aggressive tumors in rats. However, since both nickel and cobalt are known to cause tumors following intramuscular injection in rats, the carcinogenic role of xxxxxxxx itself was not determined Miller *et al.*, 2004). Results of *in vitro* testing by one group of investigators indicate the potential for synergistic effects following exposure to xxxxxxxx alloys such as xxxxxxxx-cobalt-nickel and xxxxxxxx-nickel-iron (ATSDR, 2005).

Kalinich *et al.* (2005) recently assessed the potential health consequences of intramuscularly implanted weapons-grade xxxxxxxx alloy pellets in male F344 rats. Within 4 to 5 months, all of the xxxxxxxx alloy-implanted (n=92) rats developed extremely aggressive localized tumors (high-grade pleomorphic rhabdomyosarcomas) that rapidly metastasized to the lungs, necessitating euthanasia. No tumors were found in a group of 46 rats implanted with an inert control metal (tantalum), even up to 12 months post-implantation. The xxxxxxxx alloy pellets consisted of 91.1% xxxxxxxx, 6% nickel, and 2.9% cobalt. Kalinich *et al.*, (2005) also embedded 36 rats with nickel pellets to serve as positive controls for the xxxxxxxx-alloy embedded rats since intramuscularly-injected nickel has previously been demonstrated to cause injection-site tumors (Heath and Daniel 1964). All of the nickel-embedded rats developed tumors similar to those observed in the xxxxxxxx alloy-embedded rats (Kalinich *et al.* 2005).

No information was located regarding xxxxxxxx-induced genotoxicity following inhalation, oral, or dermal exposure to xxxxxxxx or xxxxxxxx compounds in humans or laboratory animals (ATSDR, 2005). The genotoxic potential of xxxxxxxx and xxxxxxxx compounds has not been extensively assessed. Xxxxxx xxxxxxxxx demonstrated mutagenic activity in a bacterial bioluminescence test in *Photobacterium fischeri* (Pf-13) (Ulitzur and Barak, 1988). Xxxxxx xxxxxxxxx induced lambda prophage in *Escherichia coli* WP2s (λ) (Rossman *et al.*, 1984, 1991) and gene conversion at *trp* 5 and reverse mutation at *ilv* 1 in *Saccharomyces cerevisiae* strain D7 (Singh, 1983), and increased recombinant frequency in strain DIS13 (Sora *et al.*, 1986). Positive results were obtained for xxxxxxxxx anion in Chinese hamster lung V79 cells using the HGPRT forward mutation assay (Zelikoff *et al.*, 1986). Xxxxxx xxxxxxxxx did not increase sister chromatid exchanges in human whole blood cultures or cause chromosome aberrations in human lymphocytes or Syrian hamster embryo cells (Larramendy *et al.*, 1981). The chemical did not induce morphological transformation in Syrian hamster cells (DiPaolo and Casto, 1979). Dose- and time-dependent increases in DNA single strand breaks (comet and alkaline elution tests) and micronucleus induction were observed in human peripheral lymphocytes incubated in either xxxxxxxx carbide cobalt alloy or cobalt alone, but not in xxxxxxxx carbide alone (Anard *et al.*, 1997; Van Goethem, 1997). Using human osteoblast cells, Miller *et al.*, (2001) found that heavy metal-xxxxxxxx alloys composed of xxxxxxxx (92%), nickel (5%), and either cobalt (3%) or iron (3%) are capable of inducing neoplastic transformation (characterized by anchorage-dependent growth, tumor formation in nude mice, and expression of high levels of the K-*ras* oncogene), as well as increased DNA strand breakage and micronuclei at rates exceeding

that of nickel sulfide (a well-known transforming agent and carcinogen). More recently, Miller *et al*. (2004) demonstrated that pure xxxxxxxx is capable of inducing a similar effect, but at a significantly reduced magnitude relative to the heavy metal-xxxxxxxx alloys.

Reproductive System and Developmental Effects

No reports were located regarding reproductive or developmental effects in humans following inhalation exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). Decreased sperm motility (10 to12% lower than controls) was reported in male rats continuously exposed to atmospheres containing xxxxxx xxxxxxxxx powder for 17 wk at concentrations of 1.0 and 0.5 mg/m^3, but not at 0.1 mg/m^3 (Idiyatullina, 1981).

No information was located regarding reproductive or developmental toxicity in humans following oral exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). Information in animals is restricted to reported embryotoxicity (expressed as increased percentages of pre- and post-implantation losses, relative to controls) following oral administration of an unspecified xxxxxxxx compound to adult female rats at a single dose level of 0.005 mg/kg for up to 8 months before and during pregnancy (Nadeenko and Lenchenko, 1977; Nadeenko, *et al.* 1977, 1978).

No information was located regarding reproductive toxicity in humans or animals following dermal exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005).

Wide (1984) assessed the potential for xxxxxxxx to induce developmental toxicity in mice. Pregnant dams were administered a single intravenous injection (0.1 mL) of a 25 mM xxxxxx xxxxxxxxx solution on gestation d 8. Although there was no indication of xxxxxxxx-induced fetal malformations at examination on gestation day 17, a significantly increased incidence of resorptions was noted. Particular sensitivity to xxxxxxxx during fetal development and postnatal periods of nursing may be of concern since absorption of xxxxxxxx in pregnant animals can result in the accumulation of xxxxxxxx in fetal tissues (Wide *et al.*, 1986), and xxxxxxxx can enter the milk of xxxxxxxx-exposed animals (Mullen *et al.*, 1976). However, no information was located regarding the ability of xxxxxxxx to cross the placenta or enter the breast milk of humans (ATSDR, 2005).

Respiratory System Effects

No reports were located in which respiratory effects were associated with oral exposure of humans or animals to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005).

Respiratory effects were reported in workers who were occupationally exposed to airborne dusts containing xxxxxxxx trioxide, xxxxxxxx xxxxxxx, metallic xxxxxxxx, and xxxxxxxx carbide in areas where high tensile strength xxxxxxxx was prepared (Mezentseva, 1967). Of 54 workers examined, 5 exhibited early radiographic signs of pulmonary fibrosis after having been employed for 2 to 3 years (3 workers) or 19 or 24

years. Other potentially hazardous substances may have also been present in the workplace air. It is generally believed that the health effects observed in hard metal workers are the result of exposure to cobalt (or other metals (e.g., nickel), not xxxxxxxx. Few reports were located regarding respiratory effects in animals. Signs of mild pulmonary fibrosis were noted in rats exposed to atmospheres containing xxxxxxxx carbide at a concentration of 600 mg/m^3, 1 hr/d for 5 months (Mezentseva, 1967). Other rats exhibited similar signs of pulmonary fibrosis following intratracheal instillation of metallic xxxxxxxx, xxxxxxxx trioxide, or xxxxxxxx carbide and subsequent observations for up to 8 months post-instillation (Mezentseva, 1967). Guinea pigs that received 3 weekly doses of xxxxxxxx metal dust or xxxxxxxx carbide and carbon dust via intratracheal instillation were examined for up to 12 months post treatment (Delahant, 1955; Schepers, 1955a, 1955b). Gross histological examinations of the lungs revealed pigmented lung lesions that did not appear to involve lymphoid tissue; the results were not suggestive of pulmonary fibrosis. The lungs of mice exhibited no signs of a fibrotic response following intratracheal instillation of xxxxxxxx carbide (Lardot, *et al.* 1998). Lasfargues, *et al.* (1992) reported severe acute pulmonary edema in rats that had received hard metal (xxxxxxxx carbide and cobalt alloy) *via* intratracheal instillation, but not in rats similarly exposed to xxxxxxxx carbide or cobalt alone. In a subsequent study of repeated intratracheal instillation (Lasfargues *et al.,* 1995), it was demonstrated that intratracheally-instilled xxxxxxxx carbide and cobalt in combination, but not alone, induced interstitial pulmonary fibrosis.

Cardiovascular and Hematological Systems

No reports were located regarding cardiovascular effects in humans or animals following multi-route exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). The results of Kalinich, *et al.* (2005) indicate the potential for xxxxxxxx alloy induced hematotoxicity (expressed by increases in leukocyte and erythrocyte counts, hemoglobin, and hematocrit) in rats. However, since the xxxxxxxx alloy pellets consisted of nickel and cobalt in addition to xxxxxxxx, the role of xxxxxxxx in the observed effects is not known.

Endocrine and Urinary System Effects

Available information in humans is restricted to an account of temporary renal failure and subsequent tubular necrosis and anuria in a male subject 1 d following the accidental consumption of metallic xxxxxxxx in a mixture of beer and wine that had been poured into the hot barrel of a 155-mm gun (Marquet *et al.,* 1997). The author estimated the absorbed dose of xxxxxxxx to be in the range of 5 to12 mg/kg. No information was located regarding renal effects in animals following oral, inhalation or dermal exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005).

No information was located regarding the potential of xxxxxxxx or xxxxxxxx compounds to disrupt endocrine function in humans or animals (ATSDR, 2005).

Dermal System Effects

No reports were located in which dermal exposure to xxxxxxxx compounds in humans could be associated with skin effects. Although dermatitis has been reported among employees of the hard metal industry, results of patch testing implicated cobalt, not xxxxxxxx (Schwartz *et al.*, 1945; Skog, 1963). In the only located report of dermal effects in animals following dermal exposure to xxxxxxxx, single or repeated dermal application of a 5% xxxxxxxx chloride solution in rabbits resulted in contact dermatitis (Dow Chemical Company, 1982). No studies were located regarding absorption of xxxxxxxx in humans or animals following dermal exposure to xxxxxxxx or xxxxxxxx compounds. However, the report of death in rabbits following dermal application of a 5% xxxxxxxx chloride solution in single doses of 100 to 1000 mg/kg (Dow Chemical Company 1982) indicates that dermal absorption of xxxxxxxx occurs.

Nervous System and Special Sense Organ Effects

No human data were located in which neurological signs could be associated with inhalation, oral, or dermal exposure to xxxxxxxx. Signs of memory and sensory deficits have been reported among workers in the hard metal industry who were exposed to atmospheres of hard metal dusts (Jordan *et al.*, 1990**;** Kaplun and Mezentseva, 1959; Vengerskaya and Salikhodzhaev, 1962); however, these effects likely reflect exposure to cobalt, not xxxxxxxx. No studies were located regarding neurological effects in animals following inhalation exposure to xxxxxxxx or xxxxxxxx compounds. Results of available animal studies indicated clinical signs of neurotoxicity following acute oral dosing at levels resulting in death (Karantassis, 1924) and learning deficits and brain lesions following repeated oral dosing (Nadeenko, 1966) at sublethal doses. However, clinical signs at lethal doses are not a reliable indicator of primary neurotoxicity and the report of Nadeenko (1966) was not designed to adequately assess neurotoxicity end points. Available early animal data indicate that orally administered xxxxxxxx may induce neurological effects. Guinea pigs exhibited clinical signs that included trembling and abnormal locomotor behavior following single oral (gavage) administration of xxxxxx xxxxxxxxx at ultimately lethal doses (≥780 mg/kg) (Karantassis, 1924). Decreased blood cholinesterase activity and impaired conditioned reflexes were reported in rats orally exposed to xxxxxx xxxxxxxxx at doses in the range of 0.05 to 5.0 mg/kg/d for 7 months (Nadeenko, 1966).

Immune System Effects

No information was located concerning xxxxxxxx-induced immunotoxicity in humans or animals following inhalation, oral, or dermal exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). A single report was located in which a marked inflammatory response characterized by infiltration of leukocytes in the lungs of mice following intratracheal instillation of water-insoluble xxxxxxx xxxxxxxxx powder (Peao *et al.*, 1993). The inflammatory response was likely the result of local irritation rather than an adverse immunological effect. The results of Kalinich *et al.* (2005) indicate the potential for xxxxxxxx alloy-induced immunotoxicity (expressed by increased spleen weight and decreased thymus weight). However, since the xxxxxxxx alloy pellets

consisted of nickel and cobalt in addition to xxxxxxxx. Results of *in vitro* testing by one group of investigators (Miller *et al.* 2001, 2002) indicate the potential for synergistic effects following immunotoxicity exposure to xxxxxxxx alloys such as xxxxxxxx-cobalt-nickel and xxxxxxxx-nickel-iron.

No reports were located regarding immunological or lymphoreticular effects in humans or animals following inhalation exposure to xxxxxxxx or xxxxxxxx compounds. Intratracheal instillation of 250 µg of water-insoluble xxxxxxx xxxxxxxxx crystals (in saline) in mice resulted in a marked inflammatory response characterized by infiltration of leukocytes with cellular peaks at d 1 and 14 post-instillation (Peao *et al.*, 1993). The inflammatory response was likely the result of local irritation rather than an adverse immunological effect.

2. Xxxxxxxx.

Xxxxxxxx Applications

Xxxxxxx (XX) is a non-metallic element with an atomic weight of XX. The term "xxxxxx" is used to refer to naturally occurring materials composed principally of xxxxxxx xxxxxxx (XXXX), whereas "xxxxxxxx"(xxxxxxxxxxxxxx) refers to man-made xxxxxxxx xxxxxxxx based on a structure of alternating xxxxxxx-oxygen units and organic side groups. Xxxxxxxx was developed in the 1930s, and was considered to be less bioactive than xxxxxx. The methyl side groups were thought to shield the XX-X (xxxxxxxx) backbone from biological and chemical activity, resulting in what was thought to be an essentially inert compound. The term xxxxxxxx includes a large number of compounds based on xxxxxxxxxxxxxxxxxxxs, with xxxxxxxxxxx and xxxxxxxxxxx being the better known in the pharmaceutical world. Xxxxxxxx technology reaches beyond xxxxxxxxxxxxxxxxxxxxs. Xxxxxxxx xxxxxxxx such as xxxxxxxx gums, xxxxxxxx elastomers, xxxxxxxx waxes or xxxxxxxx emulsifiers are commonly used for topical pharmaceutical applications (Siddiqui *et al.*, 1994).

Xxxxxxxxs are used for a very large variety of cosmetics, pharmaceutical/ nutraceutical, medical, medical product delivery, processed food, and commercial and industrial applications. Human exposure to hundreds of products and applications containing xxxxxxx occurs through all common routes. Medical use of xxxxxxxx began in the 1940s, initially as a waterproof wound dressing. The first xxxxxxxx gel-filled breast implant was developed in the 1960s. Approximately 1 to 2.5 million US women have been medically/cosmetically treated with xxxxxxx gel-filled breast implants, which have been found in some cases to leak xxxxxxxx into the body (Gem *et al*., 2005).

General Toxicity of Xxxxxxxx

Based on the extensive human exposure to xxxxxxxx with minimal reports of health effects, xxxxxxxx is generally thought to present minimal human health risk. The LD50 for xxxxxxxx oil for rats is very high, > 5 g/kg (MSDS, 1997). The PAN Database –

Pesticides reports that xxxxxxxx may induce a cough when ingested into the lungs, and may cause reversible skin redness with prolonged dermal exposure (Pan Database, 2006).

A xxxx(xxxxxxxxxxxxxxxx) type xxxxxxxx oil containing xxxxxxxxxxxxxx groups was evaluated for acute toxicity. Acute inhalation, oral and dermal toxicity, primary skin irritation, skin sensitization, eye irritation, and human patch testing studies failed to demonstrate any toxicity response to this oil. Transient eye irritation and barely perceptible skin irritation were among the observations (Parent, 1979c). A xxxxxxxx-functional xxxx(xxxxxxxxxxxxxxxx) xxxxxxxx oil vapor (0.15 and 0.45 mg/L) was generated by passage of air through the heated oil and rats were subjected to these vapors over a 90-d period. An extensive pathological, clinical and hematological workup failed to demonstrate any significant effects of this exposure. In addition, weight gains over the experimental period were comparable to controls (Parent, 1979b).

Ocular Effects

Human ocular exposure to xxxxxxxx can occur through daily use of xxxxxxxx hydrogel contact lenses, through permanent injection of xxxxxxxx oil into the anterior chamber of the eye during various ocular surgeries, or through exposure to xxxxxxxx oil lubricating the barrels of syringes during ocular drug injections. According to the MSDS, exposure of the cornea to xxxxxxxx oil results in a temporary cloudiness, reversed when the eye is cleansed of the toxicant (MSDS, 1997).

It has been pointed out that the xxxxxxxx oil tamponade can result in complications such as corneal damage, elevation of intraocular pressure and retinal toxicity against. The effect of xxxxxxxx oil on the ocular tissues was investigated histopathologically by injecting xxxxxxxx oil into the anterior chamber of the eyes of rabbits. In addition, in order to study its effect on the retina, xxxxxxxx oil was injected into the vitreous cavity after vitrectomy. The eyes were extracted 3, 6, 9, 12 and 18 months after injection and various tissues were observed by light and electron microscopy. Xxxxxxxx oil particles were first observed in the retro-corneal membrane 18 months after injection. In the trabecular meshwork, xxxxxxxx oil particles were seen for the first time 12 months after injection. Migrating cells engulfing xxxxxxxx oil particles were attached to the internal limiting membrane of the retina three months after injection. Twelve and 18 months after injection, xxxxxxxx oil particles passed through the internal limiting membrane and were engulfed by Mueller cells (Suzuki et al., 1990).

A study presented a two year-follow up of 105 eyes operated on retinal detachment by xxxxxxxx oil injection after pars plana vitrectomy. All cases of retinal detachment were of bad prognosis. Cataract was a constant complication when xxxxxxxx oil had not been removed within the first 6 months. Intraocular hypertension developed frequently. Other complications that occurred less frequently were corneal edema, conjunctival hyperemia and uveitis. These complications were attributed to the consequence of xxxxxxxx oil toxicity and/or the mechanical effects of intraocular oil (Roussat *et al.*, 1984). However, in another study eight eyes were examined histologically after xxxxxxxx oil injection. Intraretinal deposits suggestive of xxxxxxxx were not present in attached retinas, but

were frequently observed in detached retinas when subretinal xxxxxxxx occurred. This may possibly be due to defects in the horizontal conducting structures of the retina such as those occurring in persistent detachment with disorganization of the retina. Morphologically, the retina was essentially normal 3.5 years after the xxxxxxxx injection. This observation contradicts the idea that xxxxxxxx oil has a toxic effect, unless other retinal complications exist (Kirchof *et al*., 1986).

In a similar finding, Wang *et al*. (1996) reported on histopathologic findings from 10 eyes of 10 patients with previous xxxxxxxx oil injection related to retinal detachment surgery. The globes were enucleated 4 to 27 months after xxxxxxxx oil injection. Paraffin sections were made for light microscopic examination. The retinas showed severe degeneration, pre- and sub-retinal membranous fibrous tissue proliferation. Round empty vacuoles formed by xxxxxxxx oil could be seen in the proliferative membrane. It is demonstrated that xxxxxxxx oil has a toxic effect to the detached retina and it may stimulate the development of proliferative vitreoretinopathy.

It has been hypothesized that retinal toxicity associated with injection of xxxxxxxx oils may be attributable to the toxicity of specific additives, proven to increase corneal endothelial permeability. These compounds were added to a purified xxxxxxxx oil, and exchanged for the vitreous humor of rabbits to assess their effects on the retina. Blood-ocular barrier permeability was measured with fluorophotometry after i.v. dye, and retinal function was measured using dark-adapted electroretinography (ERG). Each parameter was determined at 8-wk intervals. The fluorescein concentrations in different ocular compartments indicated a non-statistically significant increased aqueous humor fluorescein concentration after pure xxxxxxxx oil or oil plus long chain additive (a significant 240% increase). After oil plus a linear series of additive compounds, both aqueous humor (2000%) and anterior vitreous humor fluorescence (8000%) was statistically significantly increased, indicating a breakdown of the blood-aqueous barrier. The height of the b-wave of the ERG was unaffected by any oil in the presence or absence of additives. In summary, overt changes were minimal with oil alone, were increased with oil containing a linear chain additive, and were extensive with oil containing a long chain additive (Green *et al*., 1993). In another study, it was shown that xxxxxxx oil contaminants, long-chain xxxxxxx-terminated xxxxxxxxxxxxxxxxxxxx (1000 cps) at 2 mg/mL, tetramethylammonium siloxanolate (a catalyst) at 1 mg/mL and a mixture of a series of linear compounds (MM through MD10M) each at 10 mg/mL, all caused a large corneal endothelial permeability increase (Green *et al.*, 1992). A mixture of two short-chain xxxxxxx-terminated compounds was less damaging, as was a mixture of a cyclic series.

In a rabbit study of corneal epithelium permeability, animals were perfused *in vivo* with non-toxic oil containing one or more common xxxxxxx oil low molecular weight contaminants at concentrations of from 1 to 25 mg/kg. While several of the contaminants induced minor increases in epithelial permeability, the majority of the contaminants tested were without effect or decreased corneal permeability (Green *et al*., 1988). Long-term assessment of eyes in which xxxxxxxx oil injection had been used in the treatment of retinal detachment was undertaken in 92 patients. While a high incidence of

complications, particularly cataract, was confirmed, this study concluded that they were probably caused not by any toxic effect of xxxxxxxx oil but by obstruction of normal metabolic exchange at the xxxxxxxx-tissue interface. The incidence of complications causing deterioration of vision or serious symptoms was not found to be high, and navigating vision was well preserved (Leaver *et al*., 1979).

Six African green monkeys underwent vitrectomy and vitreous replacement with Vitreon (perfluorophenanthrene) or Vitreon plus xxxxxxxx. Vitreon alone and in combination remained optically clear and allowed fundus examination up to 162 d. No toxic effects to the retina were detectable (Peyman *et al*., 2001).

Several studies have suggested that xxxxxxxx oil may be toxic to the retina or may stimulate periretinal proliferation. Emulsified or nonemulsified xxxxxxxx oil was injected into rabbit eyes that had undergone mechanical vitrectomy. Retinal changes were compared by light microscopy at 1, 4, and 12 wk after intraocular injection. Emulsified xxxxxxxx oil was found to penetrate the inner retina at 1 wk and cause epiretinal membrane formation as early as 4 wk after injection. Nonmulsified oil produced no histologic changes in the retina. No cytotoxic effects were observed in eyes treated with ether emulsified or nonemulsified xxxxxxxx oil. It is concluded that emulsified xxxxxxxx oil can both penetrate the retina and stimulate epiretinal membrane formation in the vitrectomized rabbit eye (Ohira *et al*., 1991).

Clinical and morphological changes were studied in the corneas of rabbits and cats when the anterior chamber was filled with xxxxxxxx oil. Within 6 d, wide-field specular microscopy showed a 40% reduction in endothelial diameter in the area of the xxxxxxxx oil bubble in both groups. Progressive stromal thinning occurred in the rabbit cornea, with gradual development of a retrocorneal membrane at the junction of xxxxxxxx-endothelial cell contact. In contrast, persistent stromal edema, peripheral vascularization, irregular plaques on the endothelium, and eventual epithelial ulceration and corneal thinning occurred in cat eyes (Sternberg *et al.,* 1985).

Genotoxicity and Carcinogenicity

Dow Corning published a study assessing the potential adverse effects of xxxxxxxx breast implant envelope elastomer on general reproduction and fetal development in rats and rabbits. One control and one treatment group of 30 male and 30 female Charles River CD rats and 25 inseminated New Zealand white rabbits per group were used in the one-generation reproductive and developmental toxicity studies, respectively. Two 1.2-cm discs of xxxxxxxx elastomer were subcutaneously implanted in one site in the left flank and one site in the right-flank of the treated group of rats, while four 2.5-cm discs were implanted in two sites in the left flank and two sites in the right flank of the treated group of rabbits. The size of the elastomer implants was chosen to approximate the expected body burden of women with breast implants. The control and test articles were implanted in the male and female rats at 61 and 47 d, respectively, prior to mating (in the rat reproduction study) and approximately 42 d prior to insemination of female rabbits (in the rabbit developmental toxicity study). Subcutaneously implanted discs of xxxxxxxx

breast implant envelope elastomer did not induce maternal or developmental toxicity before or during pregnancy or during lactation, did not cause any adverse effects on the parents or neonates, and did not impair reproductive performance in the rat reproduction study (Sene *et al.,* 2002). No maternal toxicity or adverse developmental effects, including teratogenicity, were observed in the treated groups in the rabbit developmental toxicity study (Siddiqui *et al*., 1994).

Two xxxxxxxx fluids (Dow Corning Q7-9120 Xxxxxxxx Fluids and ST-Xxxxxxxxxxxxx 5-NF) have received extensive testing by the manufacturer (Sene *et al*., 2002). An effect for Q7-9180 Xxxxxxxx Fluid was an early onset of testicular tumors in rats; this effect was not considered applicable to humans (Sene *et al*., 2002). None of the materials were genetically active in a bacterial reverse mutation assay (Sene *et al*., 2002).

Developmental Toxicity and Reproductive System

No studies of human or animal developmental toxicity could be identified. In 29 of 35 studies of reproductive system toxicity, no effects on the male gonads were found. The summary document, without providing references however, mentions that some xxxxxxxxxxxxxxxxxxx (XXXX) fluids given by gavage at 3.3 ml/kg for six d were associated with reduced seminal vesicle weights, whereas others, given for up to 20 d at similar doses, had no such effects. Spermatogenic depression was found in two of ten rabbits treated with 2 ml/kg XXXX for 20 d. Dermal application of 2 ml/kg for 28 d decreased testicular weight. In the case of one XXXX fluid (not characterized), a no-observable-adverse-effect level (NOAEL) of 50 mg/kg/d for a 28-d exposure was established. All of these dose levels are orders of magnitude greater that could be achieved in women with breast implants on a milliliter- or milligram-per-kilogram body weight basis (Institute of Medicine, 1999).

Respiratory System Effects

The PAN Database – Pesticides reports that xxxxxxxx may induce a cough when ingested into the lungs (Pan Database, 2006).

Cardiovascular and Hematological Systems

A xxxxxxxx-functional xxxx(xxxxxxxxxxxxxxxx) xxxxxxxx oil vapor (0.15 and 0.45 mg/L) was generated by passage of air through the heated oil and rats were subjected to these vapors over a 90-d period. An extensive pathological, clinical and hematological workup failed to demonstrate any significant effects of this exposure (Parent, 1979).

Dermal System Effects

The PAN Database – Pesticides reports that xxxxxxxx may cause reversible skin redness with prolonged dermal exposure (Pan Database, 2006). Xxxxxxxx oil applied to shaved backs of mice at approximately 50 mg/animal, 3 times/wk for 18 months did not alter weight gain or cause systemic toxicity, but did cause lymphosarcomas and lung

adenomas in 4 and 8%, respectively, of the animals. No skin papillomas developed in the test animals but various nonneoplastic lesions developed which were not attributable to the treatment (Parent, 1979b).

Two xxxxxxxx fluids (Dow Corning Q7-9120 Xxxxxxxx Fluids and ST-Xxxxxxxxxxxxxx 5-NF) have received extensive testing by the manufacturer (Sene *et al*., 2002). Q7-9180 applied to skin did not elicit effects if it was allowed to evaporate, however, occlusive conditions produced minimal irritation. Q7-9180 and ST-Xxxxxxxxxxxxxx 5 were tested for dermal absorption *in vivo* in rat skin, and *in vitro* in human skin; absorption varied from 0.04 to 1.38%. The Dow Corning xxxxxxxx polymer product ST-Xxxxxxxxxxxx 40 was shown to be dermally nonirritating and nonsensitizing; was not toxic upon repeated ingestion; and was not genetically active in a bacterial reverse mutation assay (Sene *et al.,* 2002). ST-Xxxxxxxxxxxx 40, ST-Elastomer 10, Silky Wax 10, and Emulsifier 10, Dow Corning xxxxxxxx products, were also tested for toxicity. None of the materials were toxic if ingested or placed on the skin, and none were irritating or sensitizing to the skin.

Immune System Effects

A study was undertaken to determine the immunotoxicological potential of long-term exposure to the principal constituents of breast implants: xxxxxxxx fluid, xxxxxxxx gel and xxxxxxxx elastomer. An alternative covering for devices containing xxxxxxxx gels and polyurethane was also included in the study. Xxxxxxxx fluid and gel were injected subcutaneously (s.c) into female mice (1 mL/mouse) and 6-mm disks of xxxxxxxx elastomer or polyurethane were implanted s.c. There were no treatment-related deaths or overt signs of toxicity during a 180-d exposure. None of the tested materials had notable effects on body or organ weights, erythrocytes or leukocytes in the blood, or blood chemistries. The cellularity of the bone marrow was normal. The xxxxxxxxs and polyurethane tested marginally reduced the level of Lg+ cells in the spleen but did not consistently alter the distribution of T cell surface markers. The antibody response to sheep erythrocytes was not markedly altered, nor were proliferative responses to Con A, phytohemagglutinin, lipopolysaccharide or allogeneic cells. Reticuloendothelial function was normal, as was phagocytosis of chicken erythrocytes and Covaspheres by adherent peritoneal cells. Natural killer cell activity was modestly depressed in all xxxxxxxx treatment groups and in mice implanted with polyurethane. No xxxxxxxx or polyurethane treatment group displayed altered susceptibility to a challenge with *Listeria monocytogenes*, *Streptococcus pneumoniae* or the B16F10 tumor (Bradley *et al.*, 1994).

There have been numerous reports of human health effects (e.g., immunotoxicity, arthritis, Chronic Fatigue Syndrome, fibromyalgia) associated with chronic systemic exposure to medically implanted xxxxxxxxs. The epidemiologic data obtained thus far have overwhelmingly concluded that no correlation exists between certain chronic symptoms patients and xxxxxxxx prosthesis (Perkins *et al.*, 1995; Liang, 1997; Gabriel, 1996; Edworthy *et al.*, 1998; Stein, 1999). This conclusion has been echoed by the expert panel report by the Institutes of Medicine (Siddiqui *et al*., 1994).

Xxxxxxxx-gel breast implants have been associated with a myriad of autoimmune and connective tissue disorders by anecdotal reports and small observational series. These responses have been expressed as autoimmune diseases (e.g., arthritis, Chronic Fatigue Syndrome, fibromyalgia, etc.), but there has been little medical documentation demonstrating a causative relationship between xxxxxxx-gel breast implants and autoimmune responses. However, a possible mechanism to explain xxxxxxx gel-related autoimmunity has been hypothesized. In short, xxxxxxxx gel bleeding results in the coating of the implant with hydrophobic xxxxxxxx xxxxxxxx. Activation of macrophages occurs through adherence contact with amorphous xxxxxx and/or production of xxxxxx from xxxxxxxx. The development of a fibrotic capsule can ensue. Macrophages may degrade xxxxxxxx elastomers by the release of reactive oxygen species (ROS), resulting in pH changes. Migration of xxxxxxxx may occur trough transportation in macrophages or following implant rupture. Xxxxxxxx may be presented as antigens to lymphocytes, resulting in an anti-xxxxxxxx immune responses. Complexes of xxxxxxxx and host molecules may render the latter more immunogenic. Chronic inflammatory response may lead to long-term release of oxidants. Preferential inactivation or apoptosis of CD8 T-cells by the pro-oxidant shift may result in the loss of immunological tolerance (Yoshida *et al.,* 1994).

Hepatic System

Two xxxxxxxx fluids (Dow Corning Q7-9120 Xxxxxxxx Fluids and ST-Xxxxxxxxxxxxxx 5-NF) have received extensive testing by the manufacturer (Sene *et al*., 2002). One of the few toxicology effects noted was a transient liver weight, hypothesized to be due to adaptation of the animals to Q7-9180.

VI. Conclusions

Small quantities of xxxxxxxx oil are expected to be used to lubricate the barrels of syringes delivering human interocular drugs. There is little or no evidence in the published literature that any acute or persisting toxicology effects should result from one or more ocular injections in which exposure to the lubricating oil occurs. The widespread belief that leaking xxxxxxxx gel breast implants have induced significant immunotoxicity in women has not been substantiated by major epidemiological investigations (Gem *et al*., 2005). The majority of ocular toxicity effects observed in patients following clinical injection of xxxxxxxx oil into the anterior chamber are not caused by any toxic effect of xxxxxxxx oil, but by obstruction of normal metabolic exchange at the xxxxxxxx-tissue interface. The only possible concerns might be chronic introduction of xxxxxxxx oils into clinically abnormal eyes in which xxxxxxxx oil could become embedded behind the retina, or long-chain xxxxxxx oil additives could induce unpredicted toxic responses. However, the xxxxxxxx oil concentrations/quantities required for a toxicologically significant effect are expected to be many times those used in the clinical operation of interest (ppm level).

Similarly, extremely small quantities of xxxxxxxx (if in a soluble form) are expected to be released from the barrels of syringes delivering human interocular drugs. There is

little or no evidence in the published literature that any acute or persisting toxicology effects should result from one or more ocular injections in which exposure to xxxxxxxx occurs. There is limited evidence of reproductive system and embryotoxicity in rats exposed repeatedly to xxxxxxxx compounds, although one of the relevant studies did not specify the exact test compound evaluated, and no similar health effects have been reported in humans. There is some recent evidence that chronic implantation of 1 mm diameter pellets containing xxxxxxxx and other metals into the muscles of rodents reliably results in carcinogenicity (Miller *et al.,* 2001, 2002 2004; Kalinich *et al*., 2005). It is unknown if xxxxxxxx, the other pellet metals, or synergism/additivity among the pellet constituents are responsible for the carcinogenicity effects observed. However, the xxxxxxxx concentrations/quantities required for a toxicologically significant effect are expected to be many times those used in the clinical operation of interest (ppm level).

The literature search identified no research studies evaluating the potential of acute or chronic exposure to xxxxxxxx and xxxxxxxx to induce toxic responses. Thus, any possible synergistic or additive effects of simultaneous exposure to xxxxxxxx and xxxxxxxx cannot be reported.

VII. Abbreviations and Definitions

ADI: Acceptable Daily Intake

ACGIH: The American Conference of Governmental Industrial Hygienists

ATSDR: Agency for Toxic Substances and Disease Registry

BW: Body weight

CDC: Center for Disease Control

Chronic Exposure: Exposure to a chemical for 365 days or more

d: Day

EPA: Environmental Protection Agency

ERG: Electroretinography

FDA: Food and Drug Administration

g: Gram

Ig: Immunoglobulin

In Vitro: Isolated from the living organism and artificially maintained, as in a test tube

In Vivo: Occurring within the living organism

i.v.: Intravenous

kg: Kilogram

LC50: Lethal Concentration(50) (LC50). A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

LD50: Lethal Dose(50) (LD50). The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

LOAEL: Lowest-Observed-Adverse-Effect Level. The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

mg: Milligram

mL: Milliliter

mM: Millimolar

MSDS: Material Safety Data Sheet

NIOSH: National Institute for Occupational Safety and Health

NOAEL: No-Observed-Adverse-Effect Level. The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

NTP: National Toxicology Program

OSHA: Occupational Safety and Health Administration

PEL: Permissible Exposure Limit. An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

XXXX: Xxxxxxxxxxxxxxxxxxxx

ppm: Parts per million

REL: Recommended Exposure Limit. A NIOSH time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

RfC: Reference Concentration. An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime.

RfD: Reference Dose. An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime.

s.c.: Subcutaneous

SML: Specific Migration Limit

STEL: Short-Term Exposure Limit. The ACGIH maximum concentration to which workers can be exposed for up to 15 minutes continually.

TDI: Tolerable daily intake

TLV: Threshold Limit Value. An ACGIH concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

TWA: Time-Weighted Average. An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

UF: Uncertainty Factor. A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data.

wk: Week

WHO: World Health Organization

VIII. Tables

Table 1a. Literature-Based Toxicological Findings for (1) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Ocular System	Human No reports were located in which ocular toxicity effects were associated with oral or dermal exposure of humans or animals to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). The Material Safety Data Sheet (MSDS) for xxxxxxxx suggests that the compound is irritating to the eyes on contact (MSDS, 1980, 2006). Animal Signs of slight conjunctival irritation were noted in rabbits following single ocular instillation of 100 mg of xxxxxx xxxxxxxxx dihydrate powder or xxxxxxxx metal powder (Huntingdon Life Sciences Ltd 1999c, 2000). Instillation of a 5% xxxxxxxx chloride solution into the rabbit eye resulted in conjunctivitis, iritis, and corneal haziness that resolved within 14 d post instillation (Dow Chemical, 1982).
Genotoxicity and Carcinogenicity	Human No reports were located in which cancer in humans could be associated with inhalation exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). No information was located regarding xxxxxxxx-induced genotoxicity following inhalation, oral, or dermal exposure to xxxxxxxx or xxxxxxxx compounds in humans (ATSDR, 2005). Animal In one recent study, intramuscular implanted xxxxxxxx alloy (91.1% xxxxxxxx, 6.0% nickel, and 2.9% cobalt) was shown to rapidly cause aggressive tumors in rats. However, since both nickel and cobalt are known to cause tumors following intramuscular injection in rats, the carcinogenic role of xxxxxxxx itself was not determined Miller *et al.*, 2004). Kalinich *et al.* (2005) recently assessed the potential health consequences of

Table 1a. Literature-Based Toxicological Findings for (1) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	intramuscularly implanted weapons-grade xxxxxxxx alloy pellets in male F344 rats. Within 4 to 5 months, all of the xxxxxxxx alloy-implanted (n=92) rats developed extremely aggressive localized tumors (high-grade pleomorphic rhabdomyosarcomas) that rapidly metastasized to the lungs. No information was located regarding xxxxxxxx-induced genotoxicity following inhalation, oral, or dermal exposure to xxxxxxxx or xxxxxxxx compounds in humans or laboratory animals (ATSDR, 2005).
Developmental Toxicity and Reproductive System	Human No reports were located regarding reproductive or developmental effects in humans following exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). Animal Decreased sperm motility (10 to 12% lower than controls) was reported in male rats continuously exposed to atmospheres containing xxxxxx xxxxxxxxx powder for 17 wk at concentrations of 1.0 and 0.5 mg/m^3, but not at 0.1 mg/m^3 (Idiyatullina, 1981). Information in animals is restricted to reported embryotoxicity (expressed as increased percentages of pre- and post-implantation losses, relative to controls) following oral administration of an unspecified xxxxxxxx compound to adult female rats at a single dose level of 0.005 mg/kg for up to 8 months before and during pregnancy (Nadeenko and Lenchenko, 1977; Nadeenko, *et al.* 1977, 1978). Wide (1984) assessed the potential for xxxxxxxx to induce developmental toxicity in mice. Pregnant dams were administered a single intravenous injection (0.1 mL) of a 25 mM xxxxxx xxxxxxxxx solution on gestation d 8. Although there was no indication of xxxxxxxx-induced fetal malformations at examination on gestation day

Table 1a. Literature-Based Toxicological Findings for (1) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	17, a significantly increased incidence of resorptions was noted.
Respiratory System	Human The Material Safety Data Sheet (MSDS) for xxxxxxxx suggests that inhalation may cause irritation to the lungs and mucus membrane (MSDS, 1980, 2006). Animal Signs of mild pulmonary fibrosis were noted in rats exposed to atmospheres containing xxxxxxxx carbide at a concentration of 600 mg/m^3, 1 hr/d for 5 months (Mezentseva, 1967). Other rats exhibited similar signs of pulmonary fibrosis following intratracheal instillation of metallic xxxxxxxx, xxxxxxxx trioxide, or xxxxxxxx carbide and subsequent observations for up to 8 months post-instillation (Mezentseva, 1967).
Cardiovascular/Hematological System	Human No reports were located regarding cardiovascular effects in humans following multi-route exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). Animal No reports were located regarding cardiovascular effects in animals following multi-route exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005).
Endocrine and Urinary Systems	Human Available information in humans is restricted to an account of temporary renal failure and subsequent tubular necrosis and anuria in a male subject 1 d following the accidental consumption of metallic xxxxxxxx in a mixture of beer and wine that had been poured into the hot barrel of a 155-mm gun (Marquet *et al.*, 1997). The xxxxxxxx was thought to be contaminated with other metals.

Table 1a. Literature-Based Toxicological Findings for (1) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	No information was located regarding the potential of xxxxxxxx or xxxxxxxx compounds to disrupt endocrine function in humans (ATSDR, 2005). Animal No information was located regarding renal effects in animals following oral, inhalation or dermal exposure to xxxxxxxx or xxxxxxxx compounds (ATSDR, 2005). No information was located regarding the potential of xxxxxxxx or xxxxxxxx compounds to disrupt endocrine function in animals (ATSDR, 2005).
Dermal System	Human The Material Safety Data Sheet (MSDS) for xxxxxxxx suggests that the compound is irritating to the skin contact (MSDS, 1980, 2006). Animal In the only located report of dermal effects in animals following dermal exposure to xxxxxxxx, single or repeated dermal application of a 5% xxxxxxxx chloride solution in rabbits resulted in contact dermatitis (Dow Chemical Company, 1982).
Nervous System and Special Sense Organs	Human No human data were located in which neurological signs could be associated with inhalation, oral, or dermal exposure to xxxxxxxx. Animal No studies were located regarding neurological effects in animals following inhalation exposure to xxxxxxxx or xxxxxxxx compounds. Results of available animal studies indicated clinical signs of neurotoxicity following acute oral dosing at levels resulting

Table 1a. Literature-Based Toxicological Findings for (1) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	in death (Karantassis, 1924) and learning deficits and brain lesions following repeated oral dosing (Nadeenko, 1966) at sublethal doses. These studies, however, failed to identify the xxxxxxxx compound used as the test article.
Immune System	Human No information was located concerning xxxxxxxx-induced immunotoxicity in humans following inhalation, oral, or dermal exposure to xxxxxxxx or xxxxxxxx compounds. Animals A single report was located in which a marked inflammatory response characterized by infiltration of leukocytes in the lungs of mice following intratracheal instillation of water-insoluble xxxxxxx xxxxxxxxx powder (Peao *et al.*, 1993). The inflammatory response was likely the result of local irritation rather than an adverse immunological effect.
Hepatic System	Human No significant results were identified (ATSDR, 2005) Animal No significant results were identified (ATSDR, 2005)
Other	Human No significant results were identified. Animal No significant results were identified.

[a]Where applicable, RfD, RfC, PEL and ADI values are provided in Table 2.

Table 1b. Literature-Based Toxicological Findings for (2) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Ocular System	Human According to the MSDS, exposure of the cornea to xxxxxxxx oil results in a temporary cloudiness, reversed when the eye is cleansed of the toxicant (MSDS, 1997). Animal A study presented a two year-follow up of 105 eyes operated on retinal detachment by xxxxxxxx oil injection after pars plana vitrectomy. All cases of retinal detachment were of bad prognosis. Cataract was a constant complication when xxxxxxxx oil had not been removed within the first 6 months. Intraocular hypertension developed frequently. Other complications that occurred less frequently were corneal edema, conjunctival hyperemia and uveitis. These complications were attributed to the consequence of xxxxxxxx oil toxicity and/or the mechanical effects of intraocular oil (Roussat *et al*., 1984). However, in another study eight eyes were examined histologically after xxxxxxxx oil injection. Intraretinal deposits suggestive of xxxxxxxx were not present in attached retinas, but were frequently observed in detached retinas when subretinal xxxxxxxx occurred. This may possibly be due to defects in the horizontal conducting structures of the retina such as those occurring in persistent detachment with disorganization of the retina. Morphologically, the retina was essentially normal 3.5 years after the xxxxxxxx injection. This observation contradicts the idea that xxxxxxxx oil has a toxic effect, unless other retinal complications exist (Kirchof *et al*., 1986). In a similar finding, Wang *et al*. (1996) reported on histopathologic findings from 10

Table 1b. Literature-Based Toxicological Findings for (2) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	eyes of 10 patients with previous xxxxxxxx oil injection related to retinal detachment surgery. The globes were enucleated 4 to 27 months after xxxxxxxx oil injection. Paraffin sections were made for light microscopic examination. The retinas showed severe degeneration, pre- and sub-retinal membranous fibrous tissue proliferation. Round empty vacuoles formed by xxxxxxxx oil could be seen in the proliferative membrane. It is demonstrated that xxxxxxxx oil has a toxic effect to the detached retina and it may stimulate the development of proliferative vitreoretinopathy. In a rabbit study of corneal epithelium permeability, animals were perfused *in vivo* with non-toxic oil containing one or more common xxxxxxx oil low molecular weight contaminants at concentrations of from 1 to 25 mg/kg. While several of the contaminants induced minor increases in epithelial permeability, the majority of the contaminants tested were without effect or decreased corneal permeability (Green *et al*., 1988). Long-term assessment of eyes in which xxxxxxxx oil injection had been used in the treatment of retinal detachment was undertaken in 92 patients. While a high incidence of complications, particularly cataract, was confirmed, this study concluded that they were probably caused not by any toxic effect of xxxxxxxx oil but by obstruction of normal metabolic exchange at the xxxxxxxx-tissue interface. Clinical and morphological changes were studied in the corneas of rabbits and cats when the anterior chamber was filled with xxxxxxxx oil. Within 6 d, wide-field specular microscopy showed a 40% reduction in endothelial diameter in the area of the xxxxxxxx oil bubble in both groups. Progressive stromal thinning occurred in the rabbit cornea, with gradual development of a retrocorneal membrane at the junction of xxxxxxxx-endothelial cell contact. In contrast, persistent stromal edema, peripheral vascularization, irregular plaques on the endothelium, and eventual epithelial

Table 1b. Literature-Based Toxicological Findings for (2) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	ulceration and corneal thinning occurred in cat eyes (Sternberg *et al.,* 1985).
Genotoxicity and Carcinogenicity	Human No significant effects reported. Animal An effect for Q7-9180 Xxxxxxxx Fluid was an early onset of testicular tumors in rats; this effect was not considered applicable to humans (Sene *et al*., 2002). None of the materials were genetically active in a bacterial reverse mutation assay (Sene *et al*., 2002).
Developmental Toxicity and Reproductive System	Human No studies of human developmental or reproductive toxicity could be identified. Animal No studies of animal developmental toxicity could be identified. In 29 of 35 studies of reproductive system toxicity, no effects on the male gonads were found. Xxxxxxxxxxxxxxxxxxx XXXX fluids given by gavage at 3.3 ml/kg for six d were associated with reduced seminal vesicle weights, whereas others, given for up to 20 d at similar doses, had no such effects. Spermatogenic depression was found in two of ten rabbits treated with 2 ml/kg XXXX for 20 d. Dermal application of 2 ml/kg for 28 d decreased testicular weight.
Respiratory System	Human The PAN Database – Pesticides reports that xxxxxxxx may induce a cough when ingested into the lungs (Pan Database, 2006).

Table 1b. Literature-Based Toxicological Findings for (2) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
Cardiovascular/Hematological Systems	Animal No significant effects reported. Human No significant effects reported. Animal A xxxxxxxx-functional xxxx(xxxxxxxxxxxxxxxx) xxxxxxxx oil vapor (0.15 and 0.45 mg/L) was generated by passage of air through the heated oil and rats were subjected to these vapors over a 90-d period. An extensive pathological, clinical and hematological workup failed to demonstrate any significant effects of this exposure (Parent, 1979).
Endocrine and Urinary Systems	Human No significant effects reported. Animal No significant effects reported.
Dermal System	Human The PAN Database – Pesticides reports that xxxxxxxx may cause reversible skin redness with prolonged dermal exposure (Pan Database, 2006). Animal Xxxxxxx oil applied to shaved backs of mice at approximately 50 mg/animal, 3 times/wk for 18 months did not alter weight gain or cause systemic toxicity, but did

Table 1b. Literature-Based Toxicological Findings for (2) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	cause lymphosarcomas and lung adenomas in 4 and 8%, respectively, of the animals. No skin papillomas developed in the test animals but various nonneoplastic lesions developed which were not attributable to the treatment (Parent, 1979b). Two xxxxxxxx fluids (Dow Corning Q7-9120 Xxxxxxxx Fluids and ST-Xxxxxxxxxxxxx 5-NF) have received extensive testing by the manufacturer (Sene *et al*., 2002). Q7-9180 applied to skin did not elicit effects if it was allowed to evaporate, however, occlusive conditions produced minimal irritation. None of the materials were toxic if ingested or placed on the skin, and none were irritating or sensitizing to the skin.
Nervous System and Special Sense Organs	Human No significant effects reported. Animal No significant effects reported.
Immune System	Human There have been numerous reports of human health effects (e.g., immunotoxicity, arthritis, Chronic Fatigue Syndrome, fibromyalgia) associated with chronic systemic exposure to medically implanted xxxxxxxxs. The epidemiologic data obtained thus far have overwhelmingly concluded that no correlation exists between certain chronic symptoms patients and xxxxxxxx prosthesis (Perkins *et al.*, 1995; Liang, 1997; Gabriel, 1996; Edworthy *et al.*, 1998; Stein, 1999). This conclusion has been echoed by the expert panel report by the Institutes of Medicine (Siddiqui *et al*., 1994).

Table 1b. Literature-Based Toxicological Findings for (2) **Xxxxxxxx**.

Target System and Non-Target System Toxicity	[a]Literature Findings
	Animal A study was undertaken to determine the immunotoxicological potential of long-term exposure to the principal constituents of breast implants: xxxxxxxx fluid, xxxxxxxx gel and xxxxxxxx elastomer. Natural killer cell activity was modestly depressed in all xxxxxxxx treatment groups and in mice implanted with polyurethane. (Bradley *et al.*, 1994).
Hepatic System	Human No significant results were identified.
	Animal Two xxxxxxxx fluids (Dow Corning Q7-9120 Xxxxxxxx Fluids and ST-Xxxxxxxxxxxxxx 5-NF) have received extensive testing by the manufacturer (Sene *et al*., 2002). One of the few toxicology effects noted was a transient liver weight, hypothesized to be due to adaptation of the animals to Q7-9180.
Other	Human No significant effects reported.
	Animal No significant effects reported.

[a]Where applicable, RfD, RfC, PEL and ADI values are provided in Table 2.

Table 2. Reference Values, Permissible Exposure Limit and Acceptable Daily Intake for Targets.

Target Compound	RfD [mg/kg/day]	RfC or PEL [mg/m^3]	ADI [mg]	[a]Comments
1) Xxxxxxxx	N/A	1	N/A (see PEL)	Based on 8-hr time-weighted average PEL of 1.0 mg/m^3 (for soluble xxxxxxxx compound) (ATSDR, 2005)
2) Xxxxxxxx	50 mg/kg x 10^{-3} RfD = 0.05	N/A	2.5	Based on no observed effect for male reproductive system effects when a XXXX fluid was dosed at 50 mg/kg/d for 28 d (Institute of Medicine, 1999)

[a]ADI (mg) = (RfD in mg/kg/day) x 50 kg body weight. RfD = (NOAEL or LOAEL)/(UF). See section IV for equations.

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X. Appendix A

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