DEPARTMENT OF THE ARMY
US ARMY PUBLIC HEALTH COMMAND (PROVISIONAL)
5158 BLACKHAWK ROAD
ABERDEEN PROVING GROUND MD 21010-5403

MCHB-TS-THE

MEMORANDUM FOR Environmental Acquisition and Logistics Sustainment Program (AMSRD-MSF\Mr. Erik Hangeland), USA RDECOM, Aberdeen Proving Ground, MD.

SUBJECT: Environmental Health Assessment for Work Unit RM 05-04, Toxicology Report No. 87-XE-074Z-09D, Low Signature Smokeless Rocket/Missile Environmentally Benign Propellant Formulations

1. Five copies of the subject report with Executive Summary are enclosed.

2. Please contact us if this report or any of our services did not meet your expectations.

3. The US Army Public Health Command (Provisional) point of contact is Dr. Valerie H. Adams, Directorate of Toxicology, Health Effects Research Program. She may be contacted at DSN 584-5063 or commercial (410) 436-5063.

FOR THE COMMANDER:

Encl

GLENN J. LEACH
Acting Director, Toxicology

U.S. Army Center for Health Promotion and Preventive Medicine

ENVIRONMENTAL HEALTH ASSESSMENT
FOR WORK UNIT RM 05-04
TOXICOLOGY REPORT NO. 87-XE-074Z-09D
LOW SIGNATURE SMOKELESS ROCKET/MISSILE
ENVIRONMENTALLY BENIGN PROPELLANT
FORMULATIONS
JUNE 2009

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Preventive Medicine Survey: 4005f1

CHPPM FORM 432-E (MCHB-CS-IPD), OCT 03

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Readiness Thru Health

REPORT DOCUMENTATION PAGE

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US Army Center for Health Promotion and Preventive Medicine
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14. ABSTRACT

This Environmental Health Assessment is part of an ongoing effort to assess the human health and environmental impact of items of Army materiel during the development process. The objective of the program is to reduce the human health and environmental impact of newly developed Army end items with concomitant reductions in overall costs, without sacrificing performance. The primary purpose of the RM 05-04 work unit is to eliminate lead from rocket and missile propellant formulations. Given the available data on the known or estimated properties of the substances, the amounts of projected use, and usage conditions, the compounds described in this assessment are not expected to pose significant human health or environmental concerns. Although there are data gaps for several of the compounds, there is sufficient evidence to support the use of these compounds as replacements for current lead-based formulations. It is recommended that this program progresses to the next stage and that the data gaps identified in this report be addressed.

15. SUBJECT TERMS

propellant, lead, lead-free, replacement, Environmental Health Assessment, rocket, missile

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Low Signature Smokeless Rocket/Missile
Environmentally Benign Propellant Formulations
Toxicology Report No. 87-XE-074Z-09D
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Data Requirement

Not Applicable

Authors

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US Army Center for Health Promotion and Preventive Medicine
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Toxicology Report No. 87-XE-074Z-09D, Oct 05-Jun 09

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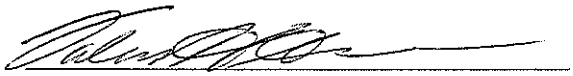

12 Nov 2009

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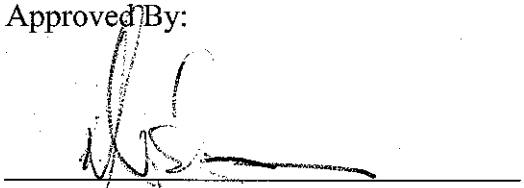

12 NOV 2009

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The authors would like to recognize the contribution of Howard T. Bausum to earlier versions of this report.

We would also like to acknowledge the support and encouragement provided to this effort by Mr. Erik Hangeland, Director, Environmental Acquisition and Logistics Sustainment Program, U.S. Army Research and Development Command and Dr. John Beatty of the Environmental Quality Technology Program Pollution Prevention Team.

DEPARTMENT OF THE ARMY
US ARMY CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE
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MCHB-TS-THE

EXECUTIVE SUMMARY
ENVIRONMENTAL HEALTH ASSESSMENT FOR WORK UNIT RM 05-04
LOW SIGNATURE, SMOKELESS ROCKET/MISSILE
ENVIRONMENTALLY BENIGN PROPELLANT FORMULATIONS
TOXICOLOGY REPORT NO. 87-XE-074Z-09D
JUNE 2009

1. PURPOSE. To provide environmental and occupational health information on new or replacement energetic compounds for Army use in the research, development, testing, and evaluation (RDT&E) of alternatives under the Environmental Quality Technology (EQT) program. This information is necessary for work-unit program evaluation.

a. Residues of explosives, propellants, pyrotechnics, and incendiaries that were part of mission-essential activities have been found in soil, air, surface, and groundwater samples, creating environmental problems and interfering with training activities. As a consequence, research, development, testing, training, and use of substances potentially less hazardous to human health and the environment is vital to the readiness of the U.S. Army. Safeguarding the health of Soldiers, civilians, and the environment requires an assessment of alternatives before they are fielded. Continuous assessment of the potential alternatives, begun early in the RDT&E process, can save significant time and effort during RDT&E, as well as over the life cycle of the items developed.

b. The Army EQT Ordnance Environmental Program (OEP) is dedicated to finding replacements for substances causing environmental and/or occupational risks to health. As part of this program, each work unit is evaluated for environmental and occupational health impacts. The primary purpose of this work unit (RM 05-04) is to eliminate lead from castable rocket and missile propellant formulations.

2. CONCLUSIONS. Based upon known or estimated properties of substances or structurally-similar surrogates, conditions, and amounts of projected use, this formulation is not expected to pose significant human health or environmental concerns. Toxicological and chemical-physical properties were obtained and reviewed for the individual chemicals used in this formulation to assess whether there were concerns relating to environmental quality or health from exposure. Based on this assessment, there is sufficient evidence to support the use of these compounds in replacing current lead-based formulations. There are, however, some data gaps that should be addressed as development continues.

3. RECOMMENDATIONS. Given the available data, the new formulation appears to be relatively, environmentally benign and has a low potential to adversely affect human health and the environment. The use of diisocynates has the potential to cause sensitization in occupational settings; however, it biodegrades rapidly in the environment. Toxicity data are needed for N-methyl-*p*-nitroaniline, but since this compound is used in very limited quantities, risks from exposures are suspected to be minimal. It is recommended that this program progress to further stages. Additional data are needed to fill the data gaps for the following compounds—

a. Butanetriol trinitrate (BTTN). Recommend *in vitro* genotoxicity and mutagenicity assays are conducted on this compound. Based on the aquatic toxicity of trinitrotoluene which is a structurally similar chemical, recommend a luminescent bacteria screen for acute aquatic toxicity.

b Diethyleneglycol dinitrate (DEGDN). An *in vitro* battery, to include Ames test and luminescent bacteria screen are recommended.

c. 2-Nitrodiphenylamine (2-NDPA). Due to potential risk to aquatic species, the luminescent bacteria screen, a surrogate for aquatic toxicity tests in fathead minnows, is recommended. This compound has the potential to reach ground water but is not volatile. Available information based on similar compounds suggests that 2-NDPA might be toxic to fish at the low parts-per-million level and has the potential to bioaccumulate.

d. N-methyl-*p*-nitroaniline (NMA). NMA is of low solubility, but physical properties suggest it can enter the vapor phase. Rat 50 percent lethal dose (or LD_{50}) and rat chronic lowest-observed adverse effect level (LOAEL) were estimated by QSAR to be 546 milligrams per kilograms (mg/kg) and 4.8 mg/kg-day, respectively. Information concerning cancer risk was not found, and QSAR estimates were equivocal. Although it is present in low amounts in this formulation, experimental work on this compound is desirable. A preliminary *in vitro* toxicological screen to include genotoxicity assays is recommended. Depending upon the outcome of the *in vitro* testing, a 14-day subacute rat study might also be indicated.

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LOW SIGNATURE, SMOKELESS ROCKET/MISSILE
ENVIRONMENTALLY BENIGN PROPELLANT FORMULATIONS
TOXICOLOGY REPORT NO. 87-XE-074Z-09B
JUNE 2009

1. REFERENCES. See Appendix A for a listing of references.

2. PURPOSE. To provide environmental and occupational health information on new or replacement energetic compounds for Army use in the Research, Development, Testing, and Evaluation (RDT&E) of alternatives under the Environmental Quality Technology (EQT) program. This information is necessary for work unit program evaluations.

3. AUTHORITY. This Environmental Health Assessment addresses, in part, the environmental safety and occupational health (ESOH) requirements outlined in Army Regulation (AR) 200-1 (AR 200-1, 2007), AR 40-5 (AR 40-5, 2007), and AR 70-1 (AR 70-1, 2003), Department of Defense Instruction (DODI) 4715.4 (DOD 4715.4), and Army Environmental Requirement and Technology Assessment PP-3-02-04, "Compliant Ordnance Lifecycle for Readiness of the Transformation and Objective Forces" (AERTA, 2007). It was conducted as part of an on-going effort by the US Army Research, Development and Engineering Command (RDECOM), Environmental Acquisition Logistics & Sustainment Program (EALSP; Mr. Erik Hangeland) and the Environmental Quality Technology, Pollution Prevention Team (EQT P2, Dr. John Beatty).

4. BACKGROUND.

a. Current regulations require assessment of human health and environmental effects arising from exposure to substances in soil, surface water, and ground water. Applied after an item has been fielded, these assessments can reveal the existence of adverse environmental and human health effects that must be addressed, often at substantial cost. It is more efficient to begin the assessment of exposure, effects, and environmental transport of military-related compounds/substances early in the RDT&E process in order to avoid unnecessary costs, conserve physical resources, and sustain the health of our forces and others potentially exposed.

b. In an effort to support this preventive approach, the US Army Center for Health Promotion and Preventive Medicine (USACHPPM) has been tasked with creation of a phased process to reduce adverse ESOH effects impacting readiness, training, and development costs. This is an ongoing effort, and this report represents the status of information available as of the date of publication. Summary interpretations of preliminary information for this work unit were provided to the sponsor for use at Ordnance Environmental Program Internal Work Area Reviews. The Principle Investigator for this Work Unit is Mr. Lawrence Warren of the US Army Aviation and Missile Research, Development and Engineering Center (USAAMRDEC), Huntsville, Alabama.

c. The USAAMRDEC has already received two patents for isocyanate-cured propellants that use bismuth citrate as ballistic modifiers and is in the process of acquiring US Army Program Executive Office—Missile and Space endorsements. A similar formulation is used in the present program.

5. STATEMENT OF PROBLEM. Lead is currently used as a ballistic-modifier compound in rocket and missile propellant formulations. It is a toxic metal that is environmentally persistent and mobile, with well understood modes and mechanisms of action. Lead is easily absorbed via ingestion and inhalation. Exposure to lead used in the propellant formulations of small rockets has the potential to affect the health of Soldiers and unborn children. Lead exposure has been shown to damage the circulatory, nervous, alimentary, and reproductive systems, as well as being a known teratogen and developmental toxicant. The objective of this work unit is to find replacements for lead in these formulations without impairing the performance of the weapons systems.

6. METHODS.

a. In order to determine the human health and ecological impacts of compounds employed in these formulations, it is necessary to correctly and unambiguously identify each compound and determine its physical, chemical, and toxicological properties. The primary means of identification employed for each compound in this program is its Chemical Abstracts Service Registry Number (CASRN) (see Table 1).

Table 1. Individual Chemicals, Their Representative Formulation Proportions, and Their Function.

Chemical Substance	CAS number	Percentage	Function
Butanetriol trinitrate (BTTN)	6659-60-5	51.74	energetic/oxidizer plasticizer
Pelletized nitrocellulose or Plastisol nitrocellulose (PNC)	9004-70-0	26	binder/fuel/oxidizer
Diethyleneglycol dinitrate (DEGDN)	693-21-0	13.05	energetic/oxidizer plasticizer
Desmodur® hexamethylene diisocyanate (N3200)*	28182-81-2 822-06-0	1.5	binder/fuel
Bismuth sub-salicylate	14882-18-9	1.5	ballistic modifier
2-nitro-diphenyl amine (2-NDPA)	119-75-5	1	Stabilizer
N-Methyl-p-nitroaniline (MNA)	100-15-2	1	Stabilizer
Polycaprolactone polymer (CAPA)	depends upon polymer	0.75	Binder
Polyethylene glycol (PEG)	25322-68-3	0.75	Binder
Carbon	7440-44-0	0.6	ballistic modifier
Aluminum	7429-90-5	0.5	ballistic modifier
Dibutyltin dilaurate (DBTDL)	77-58-7	0.01	cure catalyst

*Desmodur® is a registered trademark of the Bayer Materials Science Corporation; N3200 specifies the formulation.

While all compounds do not necessarily have a single CASRN, the CASRN is an unambiguous way of accessing information for chemical substances. The CASRN is regularly used as a keyword for searching online databases, and is often cross-referenced with both systematic and trivial (i.e., "common") names for chemical substances. In some cases, synonyms and trade names are also used to identify structures.

b. This report addresses compounds investigated as part of this work unit through the end of fiscal year 2009. Basic physical and chemical properties are usually determined by consulting authoritative tertiary sources when such information is available. The properties necessary to assess fate and transport in the environment (FTE) include—

(1) Molecular weight (MW).

(2) Henry's law constant (K_H).

(3) Octanol-water partition coefficient (log K_{OW}).

(4) Water solubility.

(5) Boiling point (bp).

(6) Organic carbon partition coefficient (log K_{OC}).

(7) Vapor pressure (vp).

c. Available information on combustion, explosion, and thermal decomposition products is also collected, if available. Toxicological information needed to estimate potential human health risks includes reported toxicity effects of acute, subacute, subchronic, and chronic exposures; potential for mutagenesis and carcinogenesis; and mode(s) and mechanisms of toxicity. Toxicological information is derived directly from primary sources whenever possible.

d. Hardcopy sources used in this search included publications from the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR), and *The Merck Index* (O'Neil, 2006). The Chemical Propulsion Information Agency's (CPIA), *Hazards of Chemical Rockets and Propellants* (CPIA, 1985), and the U.S. Environmental Protection Agency's (USEPA) *Drinking Water Health Advisory: Munitions* (USEPA, 1992), American Conference of Governmental Industrial Hygienists, Inc (ACGIH®) *Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices,* Code of Federal Regulations (CFR), the National Research Council's (NRC) *Drinking Water and Health,* were also consulted. Commercial suppliers are sometimes contacted for results of in-house research that may not appear in the open literature. (ACGIH® is a registered trademark of the American Conference of Governmental Industrial Hygienists.)

e. Online sources include the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), the International Chemical Safety Cards (ICSC) developed by the National Institute for Occupational Safety and Health (NIOSH), and the U.S. National Library of Medicine's Toxicology Data Network (TOXNET®) that provides access to information from the National Institutes of Health (NIH)and the US Environmental Protection Agency (USEPA). The TOXNET is a suite of individual databases including ChemIDplusLite® (CIDPL) and ChemIDplus® Advanced (i.e., chemical and registration numbers, and chemical identification and structure, searches respectively), Hazardous Substances Data Bank (HSDB®), Chemical Carcinogenesis Research Information System (CCRIS), Developmental and Reproductive Toxicology (DART/ETIC), Directory of Information Resources Online (DIRLINE®), Genetic Toxicology (GENE-TOX), Haz-Map (database linking chemicals, jobs and diseases), Household Products Databank (HPD) (potential health effects of chemicals in common household products), Integrated Risk Information System (IRIS), International Toxicity Estimates for Risk (ITER), Toxicology. Information Online (TOXLINE®), Toxic Release Inventory (TRI), and Lactation Database (LactMed) (database of drugs and other chemicals to which breastfeeding mothers may be exposed). The USEPA ECOTOXicology Database System (ECOTOX®) and the National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program (NTP) databases were used. Primary sources are identified and retrieved using PubMed®, the Ovid® Technologies Journals, and the EBSCOhost® Research Database. (TOXNET®, ChemIDplusLite®, ChemIDplus®, DIRLINE®, TOXLINE®, PubMed®, are registered trademarks US National Library of Medicine; OVID®, is a registered trademark of Ovid Technologies, Inc.; and EBSCOhost® is a registered trademark of EBSCO Publishing).

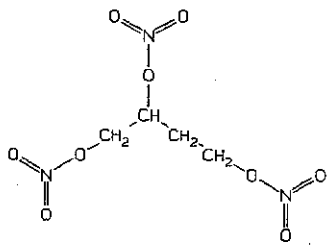
f. Persistence, bioaccumulation, human health toxicity, and ecotoxicity are assigned to general categories of risk (e.g., low, moderate, and high) using criteria modified from Howe et al. (2006). Table 2 describes the criteria used in the categorization, though the relative proportions of each substance were also factored into the final assessment.

7. RESULTS.

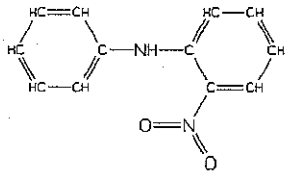
a. Physical and Chemical Properties. Physical and chemical properties are summarized in Table 3. When data were not found, "nd" (no data) is inserted. In some cases the property named is not applicable ("n/a") to the substance being described. For example, if the compound is a non-volatile solid or an inorganic salt, vapor pressure, K_{OW}, K_{OC}, and the Henry's Law constant (K_H) are typically negligible.

b. Summaries. The summaries of the physical and chemical properties are in Table 4; animal toxicity data are in Table 5. Summaries of human health and environmental toxicology for each of the formula components are presented in Tables 6 and 7, respectively. Each characterization is generally based on the criteria set forth in Table 2. The final risk characterization also incorporates assessment of the uncertainty associated with available data, the amount of each compound present in the formulation, and the nature of potential exposure associated with use of

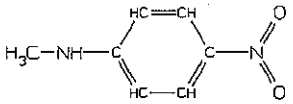
the end item.



1,2,4-Butanetriol trinitrate



2-Nitro diphenylamine



N-methyl-para-nitroaniline

Figure 1: Structures for Selected Compounds

Table 2. Categorization Criteria used in the Development of Environmental Safety and Occupational Health Severity.

	LOW	MODERATE	HIGH
PERSISTANCE	Readily biodegrades (<28 days)	Degradation ½ life: water <40 days , soil <120 days	Degradation ½ life: water >40 days soil > 120 days
TRANSPORT	Water sol. < 10 mg/L log K_{OC} > 2.0	Water sol. 10-1000 mg/L log K_{OC} 2.0-1.0	Water sol. > 1000 mg/L log Koc <1.0
BIOACCUMULATION	log K_{OW} <3.0	log K_{OW} 3.0-4.5	log K_{OW} >4.5
TOXICITY	No evidence of carcinogenicity/ mutagenicity; Subchronic LOAEL > 200 mg/kg-day	Mixed evidence for carcinogenicity/mutagenicity (B2, 2); Subchronic LOAEL 5-200 mg/kg-d	Positive corroborative evidence for carcinogenicity /mutagenicity; LOAEL < 5 mg/kg-d
ECOTOXICITY	Acute LC_{50}/LD_{50} >1 mg/L or 1500 mg/kg; Subchronic EC_{50} >100 µg/L or LOAEL >100 mg/kg-d	Acute LC_{50}/LD_{50} 1-0.1 mg/L or 1500-150 mg/kg; Subchronic EC_{50} 100-10 µg/L or LOAEL – 10-100 mg/kg-d	Acute LC_{50}/LD_{50}<100 µg/L or <150 mg/kg; Subchronic LOAEL <10 mg/kg-d
mg/L - milligrams per liter; LOAEL - lowest-observed adverse effect level; LC_{50} – concentration expected to result in 50% lethality to a population of test animals; mg/kg - milligram per kilogram; µg/L - microgram per liter			

c. Compound Characterizations.

(1) Butanetriol trinitrate (BTTN). There are virtually no data on BTTN available in the open scientific literature.

(a) Acute Oral. BTTN was evaluated in rats using a sequential stage-wise probit methodology. The LD50 was determined to be >2000 mg/kg (USACHPPM, 2008).

(b) Subacute Oral. As reported by USACHPPM, BTTN was administered orally 7 days/week for 14 days (USACHPPM, 2008). No pre-term lethality was observed at dosages up to 1000 mg/kg-day in female rats. Clinical signs of toxicity, including diarrhea, squinting, and hunched posture, were observed in 500 and 1000 mg/kg-day dose groups. A 14-day LOAEL was determined to be 500 mg/kg-d and the NOAEL 250 mg/kg-d.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. No chronic oral experimental data could be found. Chronic oral toxicity could not be reliably modeled; TOPKAT predicts a 78 percent probability of developmental toxicity with a low degree of confidence.

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal. No data found.

(j) Reproduction and Development. No data found.

(k) Mutagenicity. No experimental data are available. QSAR were employed to estimate the mutagenicity of BTTN. Modeling predicts that BTTN will be mutagenic with a moderate degree of confidence. Note that the structurally similar glyceryl trinitrate (nitroglycerine) gives a positive Ames test for mutagenicity, yet exhibits negative results in laboratory animals (Ellis et al. 1978).

(l) Carcinogenicity. No experimental data are available. QSAR modeling predicts a 25 percent probability that BTTN will be carcinogenic, with a low degree of confidence.

(m) Ecotoxicology. No data are available on ecotoxicity of BTTN. The closely related nitroglycerin is toxic to fish (LC_{50}) in the 1-7 mg/L range and also has demonstrated toxicity for algae and water insects, indicating a potential for environmental impact (USEPA, 1992).

(2) Pelletized nitrocellulose (PNC). Military grade nitrocellulose contains 13.5 percent nitrogen by mass, and approaches the trinitrated form of the glucose monomer. Nitrocellulose does not appear to be absorbed into the body by any route (Hartley et al., 1992). In addition to its explosives/propellant applications, less-fully nitrated nitrocellulose in solution finds use with ethyl alcohol and diethyl ether as a topical adhesive and protectant for cuts and small burns (Budavari et al., 1996). The US Food and Drug Administration (FDA) recognizes collodion (a formulation containing nitrocellulose) as an indirect food additive to be used only as a component of packaging adhesives. When burned as a propellant component, nitrocellulose can potentially form toxic oxides of carbon and nitrogen, and hydrogen cyanide (HSDB, 2009b). Nitrocellulose is resistant to biological degradation and is persistent in the environment. Alkaline hydrolysis appears to yield products that can be decomposed by microbial activity (Sullivan et al., 1978).

(a) Acute Oral. The acute oral LD_{50} in rats is reported to be >5000 mg/kg, making PNC essentially non-toxic (ICI, 2002).

(b) Subacute Oral. No adverse effects that could be related to nitrocellulose were identified in 13-week studies of dogs, rats, and mice (Ellis et al., 1976; Ellis et al., 1978). A 96-hour toxicity test using fathead minnow resulted in an LC_{50} >10,000 mg/L (ICI, 2002).

(c) Subchronic Oral. No data found.

(d) Chronic Oral. Long-term (2-year) studies conducted in dogs, rats, and mice indicated a dose-related increase in total feed consumption and decreases in weight gain in animals receiving 10 percent nitrocellulose in feed (Ellis et al., 1980). At 10 percent content by weight, the effect of bulk fiber mass becomes more important than the chemical nature of the compound. Necropsy of animals being fed at this level often reveals the presence of masses of cotton fibers that block the digestive tract interfering with normal digestive processes, resulting in malnutrition and increased feeding to overcome hunger. Rats receiving cotton fiber at the 10 percent level will fill their enclosures with fiber taken from the food ration, making it impossible to compute dose rates.

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal. No data found.

(j) Reproduction and Development. No data found.

(k) Mutagenicity.

i. Hartley et al. (1992) describe mutagenicity experiments conducted by Ellis et al. (1976). *Salmonella typhimurium* test strains TA1535, TA1537, TA1538, TA98, and TA100 were exposed to nitrocellulose at levels of 100, 1000, and 5000 microgram (μg)/plate for 48 hours. Results were all negative, either with or without S9 microsomal activation.

ii. Cytogenetic effects were examined in rats fed nitrocellulose at a level of 10 percent of feed mass. There were no changes in chromosome frequency distribution, tetraploidy, frequency of chromosome breaks, gaps, or translocations in either blood lymphocytes or kidney cells examined (Ellis et al., 1976).

(l) Carcinogenicity. Long term (2-year) studies in dogs, rats, and mice failed to find an increased incidence of tumors compared to control animals (Ellis et al., 1980).

(m) Ecotoxicology.

i. No acutely toxic effects of nitrocellulose have been observed among fish, invertebrate species, or algal species except the green algae *Selenastrum capricornutum.* Sediments containing nitrocellulose indicated no adverse effects among *Chironomid* populations exposed to 540 mg/kg of sediment over two generations (Bentley et al., 1976).

ii. Four species of invertebrates and four species of fish were unaffected by nitrocellulose concentrations as high as 1000 mg/L. Four species of algae were exposed to concentrations up to 1000 mg/L. Three were unaffected, but *Selenastrum capricornutum* showed a 96-hour exposure concentration (EC_{50}) of 731 mg/L (Sullivan et al., 1978).

(3) Diethyleneglycol dinitrate (DEGDN).

(a) Acute Oral. Krasovsky, et al. (1973) reported an oral LD_{50} of 1250 mg/kg in mice; dosage at this level was accompanied by cyanosis and changes in motor activity. In other mammals, the LD_{50} for oral exposure is reported to be 753-1180 mg/kg in rats, 1060 mg/kg in rabbits, and 650 mg/kg in guinea pigs. Effects on the central nervous system, to include behavior changes, muscle spasticity, and susceptibility to seizures were noted in all of these experimental species (Krasovsky et al., 1973; USEPA, 1992; CIDPL, 2009a).

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. Krasovsky et al. (1973) dosed rats by oral gavage at rates of 0.05, 0.5, and 5 mg/kg-day DEGDN in vegetable oil six times per week for 6 months and found the LOAEL to be 0.5 mg/kg-day. Responses at this exposure level included changes in conditioned

reflex activity, central nervous system (CNS) activity, and immunologic condition. Decreased blood pressure and changes in bone marrow mitotic activity were observed in the 5 mg/kg-day exposed rats towards the end of the study (fifth and sixth months) (original article in German; summarized in USEPA, 1992).

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal. Dermal exposure of rabbits resulted in a determination that the lethal dose was >2000 mg/kg (CIDPL, 2009a).

(j) Reproduction and Development. No data found.

(k) Mutagenicity. From the IRIS database, DEGDN was reported as not mutagenic in strains TA97, TA98, TA100, and TA102 either with or without S9 activation using a 1000-fold concentration range (IRIS, 2009). DEGDN was reported as having weak mutagenic activity in a mouse lymphoma cell line (IRIS, 2009).

(l) Carcinogenicity. The USEPA assessment that took oral and inhalation exposures into account categorized DEGDN as Class D: not classifiable as to human carcinogenicity (IRIS, 2009).

(m) Ecotoxicology.

i. Spanggord et al. (1985) found uptake of DEGDN to be negligible in the blue-green algae *Selenastrum capricornutum* and *Anabaena flosaquae* following a 4-day incubation period (USEPA, 1992).

ii. Fisher et al. (1989) exposed an array of freshwater species to DEGDN. The species employed in the tests were the fathead minnow (*Pimephales promelas*), channel catfish (*Ictalurus punctatus*), bluegill (*Lepomis macrochirus*), rainbow trout (*Salmo gairdneri*), water flea (*Daphnia magna*), midge larva (*Paratanytarsus parthenogeneticus*), mayfly larva (*Hexagenia bilinata*), amphipods (*Gammarus pseudolimnaeus*), and the algae *Selenastrum capricornutum*. DEGDN proved to be relatively nontoxic to all of these organisms. The invertebrate 48-hour LC_{50}s ranged from 90.1 to 355.3 mg/L, with the water flea being the most sensitive. All of the fish species had similar sensitivities (mean 96-hour LC_{50} of 273.5 mg/L) except for the fathead minnow, which was somewhat more tolerant, with a 96-hour LC_{50} of 491.4 mg/L.

iii. DEGDN degrades in the environment, but the rate of degradation depends upon the conditions. In dry soil under aerobic conditions, degradation is slow, with an observed reduction of 16-24 percent after a period of 5 weeks. However, in river and pond sediments, samples were completely degraded in 21 days, irrespective of the oxygen conditions or the sterility of the sample. Kinetics of degradation are dependent upon conditions. First-order kinetics are observed under non-sterile, aerobic conditions; non-first order (order not specified) under sterile, aerobic conditions. This suggests there are at least two mechanisms for DEGDN degradation in the environment (Spanggord et al., 1985).

iv. DEGDN will not be distributed as a vapor, but migrates rapidly through soils and can persist for months in ground or surface waters (USEPA, 1992). DEGDN would be of potential concern if it were present in larger quantities but in the quantities present in this formulation is judged to present little hazard.

(4) Desmodur-Hexamethylene diisocyanate (N3200). Desmodur N3200 is a "solvent-free" aliphatic polyisocyanate resin polymerized from the monomer 1,6-hexamethylene diisocyanate (HDI; CASRN 822-06-0) or prepolymers containing HDI. HDI is a component of automobile paint coatings (polyurethanes) and is also used in paint thickeners. Its primary purpose in the present formulation is to act as a binder. The monomer, HDI, would be the source of toxicity associated with this substance. Some monomer will inevitably be present in this formulation; however, any residual monomeric hexamethylene diisocyanate (CASRN: 822-06-0) remaining in the finished product will likely be combusted during ignition. The greater concern with this component lies with the manufacturing phase, as diisocyanates are sensitizers and can cause asthma (ERPG, 2002; ACGIH, 2005). As such, even small amounts may cause respiratory problems to asthmatics in workplace scenarios. Given that Desmodur N3200 makes up only 1.5 percent of the mass of the formulation and Desmordur 3200 contains only 0.7 percent HDI it is not likely to present a significant environmental risk. The toxicological information provided below is characteristic of the monomer, HDI, for which a comprehensive ATSDR study exists (ATSDR, 1998). Information provided below should be considered representative of the rather large amount of data available on HDI.

(a) Acute Oral. Based on the information available, large, single doses of HDI (>940 mg/kg) administered to rats orally were associated with increased mortality, while lower single doses (<620 mg/kg) or lower multiple doses were associated with little or no mortality in rats (ATSDR, 1998).

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. No data found.

(e) Acute Inhalation.

i. There are several reports of death after inhalation exposure of laboratory animals. In one study, male and female Wistar rats were exposed to doses ranging from 105 to 719 milligrams (mg) HDI/cubic meter (m^3) in inhalation chambers for 4 hours and observed for 4 weeks after exposure. Deaths approximately followed a dose-response pattern in both sexes. Deaths began to occur among the test animals at 259 mg/m^3, and the death rate increased with dose above that point. Deaths occurred between 1 and 20 days after exposure; the LC_{50} was determined to be 310 mg/m^3 (Kimmerle, 1976).

ii. Groups of 4 male albino ChR-CD rats were exposed to various concentrations of HDI for 4 or 8 hours. When rats were exposed to 370 parts per million (ppm), they died after 2-3 hours of exposure. Prior to death, rats showed signs of irritation, gasping, and convulsions. Tracheitis, pleural effusion, and small areas of pulmonary hemorrhage were observed at necropsy but were not considered extensive enough to cause death. Rats survived exposures to 5-72 ppm HDI (Haskell Laboratory, 1961).

iii. Groups of 4 male albino ChR-CD rats were exposed to 30 ppm HDI for 4 hours daily for 10 days over a 2-week period. Two of 4 animals (50 percent) of the HDI-exposed rats died (one during the 8th exposure and the other 6 days after the last exposure). Bronchitis with purulent obstruction of some bronchial branches was observed in the rat that died during exposure. Bronchopneumonia was observed in the rat that died after exposure (Haskell Laboratory, 1961).

iv. A significant immune component is present in HDI-induced respiratory toxicity, resulting in asthma-like symptoms (Belin et al., 1981; Grammar et al., 1988; Patterson et al., 1990).

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. Fischer 344 rats of both sexes were exposed to HDI (whole-body exposure) over a period of 90 days. Rats were exposed to 0, 0.011, 0.041, or 0.143 ppm HDI in air for 6 hours per day for 66-69 days over a period of approximately 13 weeks. No deaths occurred in any of the treatment groups during or after exposures (Mobay Corporation, 1988).

(h) Chronic Inhalation. In a chronic inhalation study, groups of 60 each male and female Fischer 344 rats were exposed (whole body) to 0.005, 0.025, or 0.175 ppm HDI for 2 years. None of the three inhaled concentrations of HDI was shown to have an effect on mortality compared to control animals (Mobay Corporation, 1989).

(i) Dermal. No data found.

(j) Reproduction and Development. No data found.

(k) Mutagenicity. No evidence of mutagenicity of HDI has been detected using the Ames *Salmonella typhimurium* test system, with or without S9 activation of the test substance. Strains employed in testing include TA98, TA100, TA102, TA1535, and TA1537. Results were also negative using Chinese Hamster Ovary (CHO) cells and *Escherichia coli* strains WP2UVRA and WP2UVRA/PKM101 (CCRIS, 2009).

(l) Carcinogenicity. No studies were located regarding cancer in humans after inhalation exposure to HDI. Only one study was identified that described the potential carcinogenic activity in laboratory animals. In that study, groups of 60 male and 60 female Fischer 344 rats were exposed 6 hour a day, 5 day a week for 2 years to 0, 0.005, 0.025, or 0.175 ppm HDI via inhalation. Control rats were sham-exposed (conditioned air exposure). At the end of the 2-year study period, none of the three inhaled concentrations of HDI was shown to have an effect on the incidence of cancer in treated rats when compared to control animal populations (Mobay Corporation, 1989).

(m) Ecotoxicology. No data found.

(5) Bismuth subsalicylate. Bismuth subsalicylate is largely not absorbed through the gastrointestinal epithelium (>99 percent found in feces) and is therefore considered non-toxic for potential environmental exposures. Adverse reactions that do occur are mild, transient, and infrequent (Tillman et al., 1996). Bismuth subsalicylate is employed medically in the treatment of diarrhea (Pepto-Bismol®), and bismuth salts have been used historically for other diseases, including syphilis and malaria. Patients exhibiting bismuth toxicity have a median blood level of >3 μg/dL (Goyer, 1995). Bismuth is a known neurotoxicant capable of causing emotional disturbances, encephalopathies, and myoclonus (Anthony et al., 1995). Encephalopathy is rare and is associated with extensive oral consumption of bismuth salicylate or other bismuth salts. Hasking and Duggan (1982) reported a case of encephalopathy in a 60-year-old man who had taken bismuth subsalicylate for many years as treatment for diarrhea. This patient was found to have a blood bismuth level of 7.2 micrograms per deciliter (μg/dL), which fell to 1.0 μg/dL during the first two weeks of convalescence. Because of the small quantities of bismuth subsalicylate used in this formulation, the risk to Soldiers from either bismuth or salicylate toxicity is judged to be low; risks might be slightly higher in a manufacturing environment. As bismuth subsalicylate will be involved in a combustion process, the oxidation product of bismuth—bismuth trioxide, Bi_2O_3—has also been researched, especially for inhalation exposure. (Pepto-Bismol® is a registered trademark of the Proctor & Gamble.)

(a) Acute Oral. Mice were given a single, intragastric dose of bismuth subsalicylate at 40 to 1200 mg/kg body weight (Pamphlett et al., 2000). After 1 week, animals were euthanized, and sections of nervous tissue were obtained; autometallography was used to detect bismuth grains. Bismuth was found in neurons with processes outside of the CNS, neurons outside of the CNS (i.e., posterior root ganglion cells), and in neurons in the CNS served by blood vessels lacking blood-brain barrier properties. The lowest bismuth dose resulting in bismuth deposition in motor neurons was 57 mg/kg. No bismuth deposition was seen in mice receiving an alternate

low-selenium diet.

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. No data found.

(e) Acute Inhalation. When burned in air, bismuth forms yellow bismuth trioxide Bi_2O_3 (CRC, 1978). Bismuth trioxide is not thought to be a health hazard (Mallinkrodt Baker, 2006); however, there is no open-source experimental data at present to support this conclusion.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal. Bismuth can cause hyperpigmentation of skin (Rice and Cohen, 1995).

(j) Reproduction and Development. No data found.

(k) Mutagenicity.

i. Bismuth subsalicylate has proven negative in Ames *Salmonella typhimurium* testing. Strains employed included TA 98, TA100, TA1535, and TA1537, with or without S9 activation (CCRIS, 2009).

ii. Bismuth trioxide when given orally to mice at levels of 400, 667, and 1000 mg/kg body weight for up to 21 days showed the compound to be moderately clastogenic (causing breaks in chromosomes). Chromosomal aberrations and mitotic indices were studied in bone marrow cells. A dose-related increase in the number of chromosomal aberrations and chromosomal breaks was observed with increasing Bi_2O_3 concentration (Gurnani et al., 1993).

(l) Carcinogenicity. No data found.

(m) Ecotoxicology. No data found.

(6) 2-Nitrodiphenylamine (2-NDPA). Very little toxicological information for 2-NDPA could be located; however, a toxicological profile for Otto Fuel II, a torpedo fuel for which 2-NDPA is a minor component, exists (ATSDR, 1995). A primary source of information on 2-NDPA is a 1979 literature review carried out for the Army by Atlantic Research Corporation (Army, 1979).

(a) Acute Oral.

i. A USACHPPM study performed by Crouse and coworkers evaluated acute oral toxicity using a sequential stage-wise probit methodology and found the LD_{50} in rats to be >2000 mg/kg (USACHPPM, 2008).

ii. A rat oral LD_{50} for 2-NDPA was reported as 6150 mg/kg (Army, 1979). A Navy study released in 1982 reported an LD_{50} for Otto Fuel II, of which 2-NDPA is a component, of 2000 mg/kg in rats; few experimental details were provided (ATSDR, 1995).

iii. The Army review concluded that 2-NDPA had a low acute toxicity to mammals, and that metabolism to the 4-hydroxy- and 4, 4'-dihydroxy-metabolites with rapid elimination from the body was likely (Army, 1979). N-hydroxyl-2-nitrodiphenylamine was also postulated as a metabolite based upon the appearance of methemoglobin in the blood. Exposing rats to an oral dose of 3070 mg/kg for an unspecified time resulted in elevation of methemoglobin levels to 9.45 percent.

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. No data found.

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal.

i. American Cyanamid reported in their Material Safety Data Sheet (MSDS)0 on 2-NDPA that there was neither skin irritation nor ocular effects when unspecified amounts of 2-NDPA were applied to rabbits' skin or eyes, respectively (ATSDR, 1995). Additionally, the acute dermal toxicity of 2-NDPA applied to the skin of rabbits was reported to be greater than 10 g/kg.

ii. A more recent MSDS from Acros Organic indicates 2-NDPA is irritating to eyes, respiratory system, and skin, that it may be harmful if absorbed through the skin or inhaled, and may cause irritation of the digestive tract (Acros Organics, 2009). This MSDS further notes that 2-NDPA is not listed as a carcinogen by ACGIH®, International Agency for Research on Cancer

(IARC), National Toxicology Program (NTP), or California Proposition 65, that its toxicological properties have not been fully investigated, and that it should not be disposed of by discharging into drains. (ACGIH® is a registered trademark of the American Conference of Governmental Industrial Hygienists.)

(j) Reproduction and Development. No data found.

(k) Mutagenicity. Results from Ames tests with *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535 were negative for mutagenicity, with or without microsomal S9 fraction activation (CCRIS, 2009).

(l) Carcinogenicity. No data found.

(m) Ecotoxicology.

i. The Army study concluded that 2-NDPA was probably toxic to fish and invertebrates in the low ppm range (Army, 1979). This conclusion was based upon aquatic toxicity data for compounds similar to 2-NDPA, as no toxicologic data were available for 2-NDPA. .

ii. Decomposition of 2-NDPA was observed when an aqueous solution containing both 2-NDPA and propylene glycol dinitrate (another component of Otto Fuel II) was exposed to ultraviolet light under either air or nitrogen (Wyman et al., 1984). Under both sets of conditions, 2-NDPA was removed from the solution based upon disappearance of its characteristic peak at 442 nanometers (nm); no data on its decomposition were presented. This does not necessarily indicate that 2-NDPA will be destroyed by exposure to sunlight, as UV wavelengths less than 290 nm, which are not present in sunlight due to atmospheric absorption, were not filtered out (ATSDR, 1995).

iii. 2-NDPA has reportedly been degraded by mixed cultures of microorganisms in soil or sediment, when it is available as the sole carbon source (Kessick et al., 1978). However, when presented to a culture of mixed microorganisms designed to degrade recalcitrant substances in waste water from treatment plants, there was no evidence of biodegradation of 2-NDPA based upon failure to detect any metabolites (Wyman et al., 1984). Microbial degradation does not appear to be of significant importance in the environmental fate of 2-NDPA (ATSDR, 1995).

iv. The Army study calculated a bioconcentration factor (BCF) of 127, based upon an estimated log K_{OW} value of 3.07 (Army, 1979). Using the same method of calculation, but with the experimentally determined log K_{OW} of 3.66 (CIDPL, 2009b), the BCF is estimated to be 356, indicating 2-NDPA will bioaccumulate in aquatic organisms, and may be concentrated in the food chain.

(7) N-Methyl-p-nitroaniline (MNA). No experimental toxicity data could be located. The QSAR estimates of cancer risk were equivocal.

(a) Acute Oral. No experimental data found. Rat LD_{50} was estimated by QSAR (TOPKAT system) to be 546 mg/kg.

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. No experimental data found. Rat chronic LOAEL was estimated by QSAR (TOPKAT system) to be 4.8 mg/kg/day.

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal. No data found.

(j) Reproduction and Development. No data found.

(k) Mutagenicity. No data found.

(l) Carcinogenicity. No data found.

(m) Ecotoxicology. No data found.

(8) Polycaprolactone polymer (CAPA). Polycaprolactone polymers are readily biodegradable polyesters formed from polymerization of the caprolactone monomer (CASRN: 502-44-3). A number of different polymerized products are commercially available for a variety of applications. A subset of these polymers is approved by the FDA for use in implanted biomedical devices, so they have essentially no human health or environmental impact. The mill specifications for the product in this formulation are consistent with CAPA 6806®. According to the MSDS and product data sheet, CAPA 6806 is a powder with 98 percent of the particles being smaller than 600 μm in diameter. The MSDS claims the only hazard associated with this product is mechanical irritation should it come in contact with the eyes, or burns when coming into contact with the product at high temperature (Solvay Interox Ltd., 2000). (CAPA 6806® is a registered trademark of Solvay Corporation, UK.)

(a) Acute Oral. No data found.

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. No data found.

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal. No data found.

(j) Reproduction and Development. No data found.

(k) Mutagenicity. No data found.

(l) Carcinogenicity. No data found.

(m) Ecotoxicology. No data found.

(9) Polyethylene glycol (PEG). The physical and chemical properties of PEG depend on its molecular weight. It is available in a variety of molecular weights, from 200 to tens of thousands with the numerical designation generally being indicative of the molecular weight. For example, PEG-200, has an average molecular weight of about 200 g/mol. It is a flexible, water-soluble polymer at any molecular weight (60 percent at 20 degrees Celsius (^{o}C) for PEG-2000). The extent of PEG absorption by living systems appears to be dependent on the molecular weight of the specific polymer, - more complete absorption has been reported for the lower weight polyethylene glycols, while absorption is much more limited in the case of the higher molecular weight polyethylene glycols.

(a) Acute Oral. Rat oral LD_{50}s for PEGs 200-9000 have been reported to range from >5 to >50 grams per kilogram (g/kg) body weight. Similarly, the LD_{50} values for the same molecular weight range of PEG in mice were reviewed by the European Food Safety Authority (EFSA) and were reported to be >30 g/kg in the EFSA opinion document (EFSA, 2006).

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No adverse effects levels of 1.1 and 2.8 g/kg PEG-400, in male and female rats, respectively, were determined following a 13-week exposure to up to 5.6 g/kg (animals were gavaged 5 days/week; (Hermansky et al., 1995)). The NOAELs were based on the following urinary parameters: increased urinary osmolality, specific gravity, and protein concentrations and decreases in urinary pH in both sexes. Males additionally showed increases in N-acetyl-β-D-glucosamidase (NAG) activity, urinary bilirubin, and erythrocyte and leukocyte numbers. No histopathological lesions were observed in renal organs of either sex.

(d) Chronic Oral.

i. Polyethylene glycols 200 to 4000 have been administered at rates of up to 1 g/kg-day for durations up to 2 years to Wistar rats, at up to 4 g/kg-day to Sherman rats, and at up to 2 g/kg-day to rats; no neoplasms, incidences of histopathological lesions in the renal organs, or any other adverse observations were noted (EFSA, 2006).

ii. Pups from pregnant CD-1 mice dosed with 0.7 milliliters per day (mL/day) PEG-200 on gestation days 6-17 were born with malformations of the skull, paws, and thoracic skeleton (Vannier et al., 1989). In Sprague-Dawley rats, no malformations were observed in pups born from females dosed with up to 5 mL/d PEG-200 on gestation days 6-14 or 11-16 (Vannier et al., 1989). Absences of teratogenic effects observed in additional studies performed with rats and rabbits exposed to polyethylene glycols 200 or 400 at dose levels from 1 to 10 g/kg-day suggest that the effects in mice are species-specific (EFSA, 2006).

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal. No data found.

(j) Reproduction and Development. No data found.

(k) Mutagenicity. No data found.

(l) Carcinogenicity. Results from a mouse lymphoma L5178Y thymidine kinase locus assay were positive for potential mutagenicity; however, it is believed that any indication of mutagenicity in mice is species-specific since no mutagenic effects have been observed in studies done with rats and rabbits (Wangenheim and Bolcsflodi, 1988; EFSA, 2006). Exposure to a maximum of 2 percent PEG-6000 in female rats for 104 week resulted in no incidences of tumors. The Scientific Panel on Food Additives, Flavorings, Processing Aids and Materials in

Contact with Food concluded that the available data from *in vitro* and *in vivo* mutagenicity and genotoxicity studies do not give rise to safety concerns with regard to the genotoxicity of PEG and noted that although PEG-6000 and 8000 were not included in any carcinogenicity tests, the low levels of absorption stemming from their higher molecular weights made them of no concern (EFSA, 2006). As evidence of their low toxicity and low adsorption, PEG 3350 is the active ingredient in Miralax®, a prescription laxative. (Miralax® is a registered trademark of Schering Plough Corporation).

(m) Ecotoxicology. The LC_{50} values for PEG-400 in goldfish (*Carassius auratus*), carp (*Carassius carassius*), and rainbow trout (*Oncorhynchus mykiss*) have been determined to be 5000 mg/kg, 20,000 mg/kg, and 20,000 mg/kg, respectively (Bathe et al., 1975; Bridie et al., 1979).

(10) Carbon. Most toxicological information available for carbon reflects the concern with the potential of carcinogenicity associated with respiration of inhalable carbon particles. However, a limited amount of non-inhalational data are available for various forms of carbon.

(a) Acute Oral. The LD_{50} for rats orally exposed to carbon black has been determined to be >15,400 mg/kg and >3000 mg/kg in rabbits (RTECS, 2006).

(b) Subacute Oral. No data found.

(c) Subchronic Oral. Female Sprague-Dawley rats and female CF1 mice treated with 1,2-dimethylhydrazine to induce adenocarcinomas of the colon were fed carbon black at 2.05 grams per kilogram (g/kg) for 52 weeks (Pence and Buddingh, 1985). No differences in tumor incidences were seen in rats or mice. Although exact amounts were not reported, no effects of a diet of 10 percent carbon black in mice for 72 weeks were observed (Nau et al., 1976).

(d) Chronic Oral. No differences in tumor incidences were observed in a two-year feeding study with 2.05 g/kg carbon black in female Sprague-Dawley rats and female CF1 mice (Pence and Buddingh, 1985).

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. Rhesus monkeys that were exposed at 1.5 milligrams per cubic feet (mg/ft^3) for 160 days did not have any impairment in pulmonary function (Nau et al., 1976). However, these monkeys did have accumulations of carbon black particles in the lymphatics surrounding the bronchiolar areas and were observed to have experienced destruction of the alveolar walls in the bronchioles and parenchyma surrounding the pulmonary veins.

(h) Chronic Inhalation.

i. Hamsters exposed to 3 mg/ft^3 black carbon for 172 days did not have any observable differences in pathological changes to the larynx, trachea, hypopharynx, or cervical esophagus compared to controls (Nau et al., 1976). Exposure to 1.5 mg/ft^3 did, however, result in edema in the subepithelial area of the thyroaryntenoid fold and retention of amorphous eosinophilic material in the subglotic glands. In the same study, Rhesus monkeys that were exposed to 1.5 mg/ft^3 for 160 days did not have any impairment in pulmonary function but did have accumulations of carbon black particles in the lymphatics surrounding the bronchiolar areas and were observed to have experienced destruction of the alveolar walls in the bronchioles and parenchyma surrounding the pulmonary veins (Nau et al., 1976).

ii. Carbon black is considered to be a non-specific irritant with toxic effects similar to other insoluble particulates (USEPA, 2005). Due to the concern over the potential for cancer from longer term exposures, few toxicity data exist for acute inhalational exposure to carbon black (Heinrich et al., 1994; Driscoll et al., 1996). A description of the current views on the mechanism of inhalational carcinogenicity is discussed in the carcinogenesis section.

(i) Dermal. No data found.

(j) Reproduction and Development. No data found.

(k) Mutagenicity. No data found.

(l) Carcinogenicity. A recent review by Valberg et al. (2006) reassesses the IARC's 1996 reclassification of carbon black from group 3 to group 2B (Valberg et al., 2006). The elucidated mechanism for carcinogenicity reveals that the particulate exposures result in macrophage activation of various signaling pathways that amplify inflammation (IARC, 1996). Mutations and fibrosis result from the chronic state of inflammation that help to cause metaplastic changes and lung tumors (Knappen et al., 2004). The carcinogenic properties are, therefore, similar to any poorly soluble particle (i.e., toxicity results from particle overload more than the molecules' chemistries). In light of the new mechanistic data for carbon black's potential carcinogenicity, it has been determined that there is inadequate evidence of cancer risk in humans and limited evidence in experimental animals (Valberg et al., 2006).

(m) Ecotoxicology. Ecotoxicity data were available for the common carp (*Cyprinus carpio*) using activated charcoal. Activated charcoal is used in many aquatic filtering systems; however, effects to the fry in a slurry had not yet been tested. No adverse effects were found (Kaviraj and Das, 1995). An inhalation study conducted with carbon fibers (graphite) using brown-headed cowbirds and red-winged blackbirds was found to result in no adverse effects except at high concentrations which the authors attributed to particle overload in the lungs (Driver et al., 2005). The ECOSAR-predicted endpoints from the USEPA's assessment for carbon black are presented in Table 3 (USEPA, 2005).

Table 3. ECOSAR-Predicted Endpoints for Carbon Black

Organism	Duration	End Pt.	Predicted mg/L
Fish	14-day	LC_{50}	249
Fish	96-hour	LC_{50}	167
Daphnid	48-hour	LC_{50}	164
Green Algae	96-hour	EC_{50}	96
Fish	30-day	ChV*	17.6
Daphnid	16-day	EC_{50}	4.9
Green Algae	96-hour	ChV	4.7
Fish	96-hour	LC_{50}	21.7
Mysid Shrimp	96-hour	LC_{50}	115
Earthworm	14-day	LC_{50}	235 (dry wt soil)

Legend:
LC_{50} – lethal concentration (50%)
EC – exposure concentration (50%)
ChV = chronic value

(11) Aluminum. While a considerable body of knowledge exists about aluminum and its salts, the two most important forms under consideration with respect to this project are elemental aluminum (CASRN: 7429-90-5), and its combustion product, aluminum oxide, also known as alumina (CASRN: 11092-32-3; 1344-28-1). According to ATSDR (1999), with the exception of aluminum phosphide, the anionic component does not appear to influence toxicity, although it does appear to influence bioavailability.

(a) Acute Oral.

i. No oral LD_{50} value for elemental aluminum or aluminum oxide has been established for humans. Aluminum-containing food additives are Generally Recognized as Safe (GRAS) by the FDA (ATSDR, 1999). Users of aluminum-containing medications that have normal kidney function can ingest much larger amounts of aluminum than normally found in the diet, possibly as much as 12-71 milligrams of aluminum per kilograms per day (mg Al/kg-day) from antacid/antiulcer products and 2-10 mg Al/kg-d from buffered analgesics when taken at recommended dosages (Lione, 1985).

ii. Aluminum causes death in laboratory animals only at doses that are high compared to normal human exposure. Because animals can be exposed to large amounts of aluminum through their diets, dose rates must be computed carefully and are often underestimated (ATSDR, 1999). The LD_{50} values of 261 and 286 mg Al/kg-d (as the nitrate salt) have been reported for Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al., 1987). For aluminum chloride, LD_{50} values of 370, 222, and 770 mg Al/kg-d have been reported for Sprague-Dawley rats, Swiss Webster mice, and male Dobra Voda mice, respectively (Ondreicka et al., 1966; Llobet et al., 1987). Ondrieicka et al (1966) also found the LD_{50} for aluminum sulfate to be 980 mg Al/kg.

(b) Subacute Oral. No data found.

(c) Subchronic Oral. Mortality occurred in female Swiss Webster mice exposed to aluminum lactate for 42 days throughout gestation and lactation at doses of 184 or 280 mg Al/kg-d (Golub et al., 1987), but not in a different study by the same group of investigators at 330 mg Al/kg-day (Donald et al., 1989). This apparent contradiction was attributed to shortcomings in the animals' diet in the first study. When several essential nutrients, particularly calcium, magnesium, and phosphate, were restored to the diet, survivability of the test animals improved. Only one of nine pregnant Swiss Webster mice receiving 250 mg Al/kg-day as aluminum lactate failed to survive (ATSDR, 1999). No mortality was observed in male Sprague-Dawley rats receiving 70 mg Al/kg-day as aluminum chloride in water for 30, 60, or 90 days (Dixon et al., 1979), or up to 158 mg Al/kg-d as aluminum hydroxide in feed for 16 days (Greger and Donnaubauer, 1986). These doses do not reflect aluminum consumed as part of the base diet (ATSDR, 1999).

(d) Chronic Oral. In chronic-duration studies, exposure to aluminum at 100 mg Al/kg-day, as aluminum lactate in the diet or 103 mg Al/kg-day, as aluminum nitrate with added citric acid in drinking water did not result in significant alterations in mortality (Golub et al., 2000; Roig et al., 2006).

(e) Acute Inhalation.

i. No LC_{50} value for metallic aluminum in humans has been established.

ii. Of the experiments performed in animals, none has shown death from inhalation exposure to aluminum or its compounds. For example, no deaths were reported following an acute 4-hour exposure to up to 1000 mg/m^3 as aluminum oxide in groups of 12–18 male Fischer 344 rats (Thomson et al., 1986).

iii. At about 30 mg/m^3, alveolar wall thickening and increased number of macrophages were consistent observations in the Golden Syrian hamster (33 mg/m^3 aluminum chlorhydrate 3 hours/day for 3 days) and the New Zealand rabbit (43 mg/m^3 aluminum chlorhydrate 4 hours/day for 5 days) (Drew et al., 1974).

iv. Respiratory effects typically associated with inhalation of particulates and lung overload have been observed in animals. The pulmonary toxicity of alchlor, a propylene glycol complex of aluminum chlorhydrate and a common component of antiperspirants, was examined in hamsters in a series of studies (Drew et al., 1974). Three-day inhalation exposure to 31 or 33 mg Al/m^3 resulted in moderate-to-marked thickening of the alveolar walls due to neutrophil and macrophage infiltration and small granulomatous foci at the bronchioloalveolar junction. A decrease in the severity of the pulmonary effects was observed in animals killed 3, 6, 10, or 27 days after exposure termination.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation.

i. Drew et al. (1974) also observed pulmonary effects in hamsters exposed to 10 mg Al/m^3 as alchlor for 6 hours/day, 5 days/week, for 2, 4, or 6 weeks. The severity of effect was directly related to exposure duration.

ii. Steinhagen et al. (1978) exposed groups of rats and guinea pigs to 0.25, 2.5, or 25 mg/m^3 of aluminum chlorhydrate for 6 months via inhalation. Decreases in body weight were seen in rats exposed at the 25 mg/m^3 level. Marked increases in lung weights and lung-to-body weight ratios were seen in both rats and guinea pigs at the 25 mg/m^3 level. The lungs of all rats and guinea pigs showed significant dose-related increases in aluminum accumulation at all exposure levels. Lungs of both rats and guinea pigs at the two higher dose levels contained granulomatous reactions characterized by giant, vacuoled macrophages containing basophilic material in association with eosinophilic cellular debris.

(h) Chronic Inhalation.

i. While there are no systematic studies in humans, several deaths have been reported after occupational exposure to a finely powdered metallic aluminum used in paints, explosives, and fireworks (Mitchell et al., 1961). A 19-year old male working in an atmosphere heavily contaminated with aluminum (615-685 mg Al/m^3; respirable dust 51 mg Al/m^3) developed dyspnea (difficulty breathing) after 2.5 years. His symptoms grew worse, and he had to stop working after an additional 3 months; he died 8 months later. Of 27 workers at this plant, 2 died and 4 had radiological changes on X-rays.

ii. McLaughlin et al. (1962) described the death of a male exposed to aluminum flake powder. Prior to death, the man exhibited memory loss, convulsions, weakness, electroencephalogram (EEG) abnormalities, dysarthria (speech difficulties), hemiparesis (paralysis on one side of the body), and slowed reactions. However, neurological symptoms were not found in 53 other workers at the factory, and contemporaneous renal problems may have contributed to the fatality in this case.

iii. No death occurred following chronic exposure to 2.18 or 2.45 mg Al/m^3 as refractory alumina fiber for 86 weeks in groups of 50 male and female Wistar rats (Pigott et al., 1981). At 5.1 milligrams aluminum chlorhydrate per cubic meter (mg aluminum chlorhydrate/m^3) x 6 hours/day x 5 days/week for 24 months in Fischer 344 rats, a 108-274 percent increase in the lung-to-body weight ratio was observed, due mostly to the 16-26 percent decrease in body weight (Stone et al., 1979). Following the same dosing regimen, a 21 percent increase in lung-to-body weight ratio was observed at in guinea pigs (Stone et al., 1979).

(i) Dermal. No data found.

(j) Reproduction and Development. Groups of male rats were dosed with 0, 5, 50, or 500 mg/L Aluminum (anticipated adsorbed dose: 0, 0.005, 0.005, or 0.05 mg/kg) for 30, 60, or 90 days (Dixon et al., 1979). Animals were euthanized at days 30, 60, or 90 and assessed for abnormalities in reproductive capacity. No histopathology or changes in plasma gonadotropin compared to controls were observed. Subsets of the 90-day treatments were allowed to mate as part of a dominant lethal study. Treated groups were not significantly different from controls in number of implantation sites or litter size.

(k) Mutagenicity. Aluminum lactate was negative in the standard Ames assay; activation assay not performed; aluminum sulfate was positive in an in vitro micronucleus assay (CCRIS, 2009).

(l) Carcinogenicity. Significantly increased incidences of gross tumors were reported for Long Evans rats (males) and Swiss mice (females) given 0.6 or 1.2 mg/kg-day aluminum potassium sulfate in drinking water, for 2-2.5 years (Schroeder, 1975; Schroeder and Mitchener, 1975). The incidence of "lymphoma leukemia" was significantly increased (10/41 versus 3/47 in controls) in the female mice. A dose-response relationship could not be determined for either species because only one aluminum dose was used and the types of tumors and organs in which they were found were not specified. Another study in Wistar rats found no increase in the incidence of neoplasms in male and female rats fed diets containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg, 1972). The incidence of spontaneous hepatocellular carcinoma in B6C3F1 mice that ingested ≤979 mg/kg-d aluminum potassium sulfate for 20 months was significantly decreased in the high-dose males: 5.5 percent compared to 20.5 percent in controls; (Oneda et al., 1994). In summary, mammalian studies performed to date have not reported any conclusive evidence for carcinogenicity of aluminum. Also, the Department of Health and Human Services and the USEPA have not yet evaluated the human carcinogenic potential of aluminum.

(m) Ecotoxicology.

i. Available data suggest that aluminum is low in toxicity. Many aquatic species have been used in toxicity assays, as were many forms of aluminum, including oxides (USEPA, 2007). Terrestrial plants and animals have also shown relatively low toxicity associated with aluminum, but a significant reduction in pH may cause an increase in bioavailability and toxicity as a consequence.

ii. Khangarot (1991) exposed tubifex worms (*Tubifex tubifex [Muller]*) to aluminum ammonium bis(sulfate) dodecahydrate in water. The EC_{50} values and 95 percent confidence intervals were 69.82 mg/L (61.82-80.54) for 24 hours, 55.85 mg/L (48.45-66.89) for 48 hours, and 50.23 mg/L (40.96-64.32) for 96 hours.

(12) Dibutyltin dilaurate (DBTDL). Dibutyltin dilaurate is used industrially as a catalyst for polyurethane polymers. It also finds application in veterinary medicine as an antihelmintic

and a coccidiostat (HSDB, 2009a). In aqueous environments, the lauric acid moieties of this salt will dissociate from the cation, leaving the dibutyltin cation as the active species. Therefore, data on any dibutyltin salt is relevant to the evaluation of this compound.

(a) Acute Oral. LD_{50} in male rats is reported to be 175 mg/kg in oil solution (HSDB, 2009a). Alam et al. (1993) (1993) exposed groups of weanling, juvenile, and adult rats of both sexes to oral doses of 20 or 40 mg/kg in oil over a period of 3 days. All animals receiving the treatment were observed to be lethargic, dull, and weak when compared to controls. Swelling around the mouth area was accompanied by brown pigmentation on the central body. Animals exposed to 40 mg/kg also showed hind limb weakness. All groups showed a loss in body weight, but this was most pronounced in the juveniles.

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. Ema et al. (2007) administered dibutyltin dichloride (DBTDC) to mated, female ICR mice at rates of 0, 7.6, 15.2, or 30.4 mg/kg by gastric intubation on days 0-3 or 4-7 of pregnancy. All animals were sacrificed on day 18. For females given DBTDC on days 0-3, the rate of non-pregnant females and incidence of preimplantation embryonic loss were significantly increased at 30.4 mg/kg-d. Incidences of post-implantation embryonic loss were higher for females given 15.2 mg/kg on days 0-3, and 7.6 mg/kg on days 4-7. No increase in fetal malformation was observed. Blood chemistry indicated progesterone levels were decreased in animals receiving 30.4 mg/kg-d, indicating a possible mechanism for fetal loss.

(e) Acute Inhalation. No data found.

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. The ACGIH has established a time-weighted average (TWA) threshold limit value (TLV) of 0.1 mg/m^3; the 15 minute Short Term Exposure Limit is 0.2 mg/m^3 (HSDB, 2009a). (TLV® is a registered trademark of the American Conference of Governmental Industrial Hygenists.)

(i) Dermal. No data found.

(j) Reproduction and Development. No data found.

(k) Mutagenicity.

i. DBTDL was tested in the Ames *Salmonella typhimurium* system at doses of 0, 1, 3,

10, 33, 100 and 166 µg/plate in strains TA98, TA100, TA1535, and TA1537 both with and without activation by Aroclor-induced rat or hamster liver S9 fractions. Results were negative in all cases (HSDB, 2009a).

ii. Boyer (1989) reported that the acetate analog of DBTDL did not appear to be mutagenic in a large battery of mutagenicity assays but produced base-pair substitutions in one of the bacterial strains tested.

iii. Dibutyltin compounds have been shown to cause malformations in rats during gestation. On day 8 of gestation, pregnant rats were treated with 80 micromol per kilogram (µmol/kg) (50 mg/kg) and the fetuses removed on day 20 by Cesarean section. Malformations observed included cleft mandible, ankyloglossia, and fused ribs (Noda et al., 1993).

(l) Carcinogenicity. DBTDL is not classified as a human carcinogen by the ACGIH (2005).

(m) Ecotoxicology.

i. Attribution of ecological impact of DBTDL is complicated by the fact that dibutyl salts are degradation products of tributyltin, widely used as an antifouling coating in marine applications. Dibutyltin species are readily detected in the environment (Viglino et al., 2004). The DBTDL bioconcentration factor in carp ranges from 31 (muscle) to 813 (liver) (HSDB, 2009a) and has been observed to bioaccumulate in marine mammals, especially cetaceans, with transplacental transfer (Yang. and Miyazaki, 2006).

ii. Accidental agricultural misuse of DBTDL has also caused problems for domestic and wild animals. Addition of DBTDL to calf concentrates at levels of up to 25,000 ppm on 18 farms caused poisoning in 1000 cattle, of which 171 died and 287 were slaughtered. High concentrations of tin were found in the cattle tissue, precluding consumption of the meat by humans. Wild palm doves that consumed the feed were also killed; about 150 dead and dying doves were found within days of the feeding event. Two doves were experimentally fed 2500 ppm tin in a laboratory environment. Eight days after feeding, one of these birds had died and the other moribund. High concentrations of tin (27-141 ppm) were found in their livers. Both wild and laboratory birds exhibited severe depression and yellow diarrhea. Mink inadvertently receiving oral doses of about 1700 ppm in a vitamin-mineral supplement were also poisoned and appeared to be the most susceptible of the species evaluated (Shlosberg et al., 1978; Shlosberg and Egyed, 1979).

Table 4. Physical and Chemical Properties

Compound	MW	mp (°C)	bp (°C)	Aq. sol. (mg/L)	log Kow†	log Koc†	Henry's Law Constant (25 °C) †	vp (mmHg) @ 25 °C †
Butanetriol trinitrate (BTTN)	241.11 [a]	11 [b]	230 [c]	800 @20 °C [c]	2.0 [d] (est)	2.3 [d] (est)	3.37E-09 [d] (est)	1.1E-03 @ 20 °C [e]
Pelletized nitrocellulose (PNC)	Varies, ~298-446 kDa; NC monomer formula wt 297.14 [f]	Flash point = 4.4 (40°F) [f]	n/a	insoluble [c]	n/a	n/a	n/a	n/a
Diethyleneglycol dinitrate (DEGDN)	196.1 [a]	11.3 [g]	139 [h]	3900 mg/L @ 25°C [g]	0.98 [g]	1.37 [d] (est)	3.90E-07 [g] (est)	5.9E-03 [g]
Desmodur® hexamethylene diisocyanate (N3200) [i]	168.2 [c]	Flash point = 196 (385°F) [j]	>127 [k]	Reacts with water to form hexamethylene diamine, rapidly biodegrades [c]	3.20 [g] (est)	1.06 [d] (est)	4.8E-05 [g]	7 [c]
Bismuth subsalicylate	362.11 [m]	100 (dec) [g]	n/a	insoluble in cold water [c]	2.46 [g] (est)	2.5 [d] (est)	n/a	6.07E-06 [g]
2-Nitro-diphenyl amine (2-NDPA)	214.22 [a]	75 [g]	346 [e]	27.7 [g]	3.66 [g]	3.12 [d] (est)	9.07E-08 [g] (est)	1E-05 [e]
N-Methyl-p-nitroaniline (MNA)	152.15 [a]	152.2 [c]	nd	<1 [c]	2.04 [g]	2.2 [d] (est)	1.65E-08 [g] (est)	7.64E-3 [g] (est)
Polycaprolactone polymer (CAPA)	80,000 [c]	~35 [j]	58-60 [j]	insoluble [c]	n/a	n/a	n/a	negligible
Polyethylene glycol (PEG)	varies	varies w/MW	n/a	varies with molecular weight, but very soluble	varies	varies	n/a	n/a
Carbon	12.01 [m]	3550 [m]	4827 [m]	insoluble [m]	n/a	n/a	n/a	n/a
Aluminum	26.98 [m]	660 [g]	2327 [m]	insoluble [m]	n/a	n/a	n/a	1 @ 1284°C [m]
Dibutyltin dilaurate (DBTDL)	631.57 [m]	23 [g]	205 [m]	insoluble [m]	3.12 [g]	3.07 [d] (est)	n/a	4.5E-09 [m] (est)

a = (NIST, 2006); b = (Paulet, 1984); c =MSDS; d = (USEPA, 2007); e = (CPIA, 1985); f= (O'Neil, 2006); g = (CIDPL, 2009a); h = (IPCS-ICSC, 2009); i = Data for 1,6-hexamethylene diisocyanate; j = manufacturer data sheet; k = (USEPA, 1992); m = (HSDB, 2009a); (dec) = decomposes; (est) = estimated; kDa=kiloDaltons; n/a = not applicable; nd = no data; †=derived from experimental data unless otherwise stated

Table 5. Toxicity Data

Compound	Acute LD_{50} (mg/kg)	Sub-acute (mg/kg-day)	Sub-chronic (mg/kg-day)	Chronic (mg/kg-day)	Carcinogenicity	Mutagenicity
Butanetriol trinitrate (BTTN)	>2000 (rat) [e]	250 (rat; NOAEL)[e] 500 (rat;LOAEL)[e]	nd	n/a [±]	Negative (modeled)	Negative (modeled)
Pelletized nitrocellulose (PNC)	>5000 (rat) [a]	96 hr LC50 >10,000 mg/L (fathead minnow)[i]	4866 (LOAEL, rat) [b]	n/a [±]	Negative [h]	Negative [h]
Diethyleneglycol dinitrate (DEGDN)	753 (rat) [a] 1250 (mouse) [a] 1060 (rabbit) [a] 650 (guinea pig) [a]	nd	nd	0.5 (LOAEL, rat)[j]	class D[d]	Negative Ames [d] Weak mouse lymphoma [d]
Desmodur hexamethylene diisocyanate (N3200)	940 (rat; ALD[†]) [c] 45 ppm (rat; inhal.) [c]	300 (rat; NOAEL)[c]	0.01ppm (rat; NOAEL) [c]	0.005 ppm (rat; NOAEL) [c]	nd	negative[d]
Bismuth subsalicylate	nd	nd	nd	nd	nd	negative[d]
2-nitro-diphenyl amine (2-NDPA)	2000 (rat) [e]	nd	nd	nd	nd	negative[g]
N-Methyl-p-nitroaniline (MNA)	nd	nd	nd	nd	nd	nd
Polycaprolactone polymer (CAPA)	nd	nd	nd	nd	nd	nd
Polyethylene glycol (PEG)	> 5000 (rat) [f]	nd	1100 (rat; NOAEL)[f]	1000 (rat; NOAEL)[f]	not suspected [f]	nd
Carbon	>15,400 (rat) [d] >3000 (rabbit) [d]	n/a [±]	n/a [±]	n/a [±]	negative	nd
Aluminum	261 (rat) [d] 286 (mouse) [d]	nd	nd	nd	equivical	nd
Dibutyltin dilaurate (DBTDL)	175 (rat) [d]	nd	nd	nd	class A4[d]	Negative Ames test, but teratogenic [d,g]

a =(CIDPL, 2009a); b = (Ellis et al., 1980), in smaller species, mortality due to intestinal blockage; c = (ATSDR, 1998); d = (HSDB, 2009a); e = (USACHPPM, 2008); f =(EFSA, 2006); g= (Noda et al., 1993); h = (Hartley et al., 1992); i = (ICI, 2002); j = (Krasovsky et al., 1973) *= based on QSAR predictions; [†] ALD= approximate lethal dose;± = limit dose exceeded; n/a = not applicable; nd = no data

Table 6: Human Health Impact Assessment

Compound	Acute oral	Subchronic oral	Acute inhalation	Subchronic inhalation	Cancer probability	Comments
Butanetriol trinitrate (BTTN)	Mod	Mod	Low (modeled)*	Low (modeled)*	Low (modeled)*	Possible mutagen/teratogen. Oral lethal dose >1200 mg/kg; no apparent inhalation or dermal toxicity; little experimental data.
Pelletized nitrocellulose (PNC)	Low	Low	Low **	Low **	Low	Non-volatile; large doses cause gastro-intestinal blockage.
Diethyleneglycol dinitrate (DEGDN)	Low	Low	Low **	Low **	Low	Non-volatile; neurological effects.
Desmodur® hexamethylene diisocyanate (N3200)*	Low	Unknown	Mod	Mod	Unknown	USEPA NOAEL = 0.005 ppm (0.035 mg/m^3); National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL)=0.035 mg/m^3; HDI is an occupational sensitizer.0.0.
Bismuth subsalicylate	Low	Low	Low **	Low **	Low	Non-volatile; not significantly absorbed from the gastro-intestinal tract.
2-nitro-diphenyl amine (2-NDPA)	Low	Low (modeled)*	Low (modeled)*	Low (modeled)*	Low	ACGIH TWA TLV for related compound diphenylamine of 10 mg/m^3.
N-Methyl-p-nitroaniline (MNA)	Unknown	Unknown	Low **	Low **	Unknown	Non-volatile solid. ACGIH TWA TLV for related compound aniline of 2 ppm.
Polycaprolactone polymer (CAPA)	Low	Low	Low	Low	Low	Used in biomedical implants; ACGIH TWA TLV = 5 mg/m^3; lung irritation
Polyethylene glycol (PEG)	Low	Low	Low **	Low **	Low	Non-volatile; properties vary with average molecular weight of polymer.
Carbon	Low	Low	Low	Low	Low	Non-volatile; ACGIH TWA TLV = 3.5 mg/m^3 for respirable particulates causing lung irritation.
Aluminum	Low	Low	Low **	Low **	Low	GRAS orally; ACGIH & OSHA TWA TLV/ PEL = 5 mg/m^3 for pyro powders; NIOSH TWA REL = 10 mg/m^3; nano-Al may have additional issues.
Dibutyltin dilaurate (DBTDL)	Mod	Mod	Low **	Low **	Low	ACGIH = 0.2 mg/m^3, TWA TLV = 0.1 mg/m^3; toxic to aquatic species; very small quantities in formulation.

* = based on QSAR predictions; **=**= professional judgement based on weight of evidence and physical/chemical properties; GRAS = Generally Recognized as Safe b FDA; * =Data for hexamethylene diisocyanate (HDI); TWA=time-weighted average TLV=threshold limit value; PEL= permissible exposure limit; STEL= short term exposure limit; ACGIH= American Conference of Gov. Industrial Hygienists

Table 7. Ecotoxicology Assessment

Compound	Aquatic	Invertebrate	Plants	Mammalian	Avian	Comments
Butanetriol trinitrate (BTTN)	Unknown	Unknown	Unknown	Low-moderate (rat)	Unknown	
Pelletized nitrocellulose (PNC)	Low (algae, fish)	Low **	Low (algae)	Low (rat)	Low **	
Diethyleneglycol dinitrate (DEGDN)	Moderate (algae, fish)	Unknown	Moderate (algae)	Moderate (rat, mouse, guinea pig)	Unknown	
Desmodur hexamethylene diisocyanate (N3200)	Unknown	Unknown	Unknown	Low (rat)	Unknown	Rapidly hydrolyzes in water
Bismuth subsalicylate	Low **	Low **	Low **	Low **	Low **	Generally recognized as safe (GRAS) item.
2-nitro-diphenyl amine (2-NDPA)	Unknown	Unknown	Unknown	Low (rat)	Unknown	
N-Methyl-p-Nitroaniline (MNA)	Unknown	Unknown	Unknown	Unknown	Unknown	Non-volatile solid; low water solubility
Polycaprolactone polymer (CAPA)	Unknown	Unknown	Unknown	Unknown	Unknown	Non-volatile solid; insoluble in water
Carbon	Low (carp)	Low (modeled)*	Low **	Low (rats, mice)	Low (bobwhite, inhal.)	Non reactive in many biological systems.
Aluminum	Low (fish, frog)	Low (copepods, midge, bivalves, crayfish)	Low-moderate (algae, ryegrass, *Gleditsia, Acer, Picea,* spp.)	Low (rats, mice)	Low **	Toxicity contingent on bioavailability (soil pH)[a].
Dibutyltin dilaurate (DBTDL)	Moderate-high (*Daphnia*, fish)	Moderate-high (*Daphnia*, mosquito)	Unknown	Moderate (rat)	Unknown	

a= (ATSDR, 1999) ; ALD= approximate lethal dose;.* = based on QSAR predictions; **= professional judgment based on weight of evidence and physical/chemical properties;

8. DISCUSSION.

a. Current Formulation. The current formulation contains lead which has been identified as an environmental and human health hazard. Available information suggests the proposed replacement formulation is a relatively benign lead-free alternative propellant formula. Based upon known, or estimated, properties of substances or structurally-similar surrogates, conditions and amounts of projected use, none of the RM 05-04 work group compounds are thought to be of immediate environmental or human health concern in this application. The DBTDL would be of potential concern if it were present in larger quantities, but in the quantities present in this formulation it is judged to present little hazard.

b. Regulatory Considerations.

(1) The USEPA has established an inhalation reference concentration (RfC) for HDI, with the NOAEL set at 0.005 ppm (0.035 mg/m^3) and LOAEL at 0.025 ppm (0.175 mg/m^3) (IRIS, 2009). The NIOSH recommends use of a supplied-air respirator when working with HDI and has established an REL TWA dose of 0.005 ppm (0.035 mg/m^3) (NIOSH, 2005b).

(2) Florida and Minnesota regulate tin levels in drinking water at 4200 and 4000 µg/L, respectively (HSDB, 2009c).

(3) According to the FDA, polyethylene glycol is GRAS.

(4) The NIOSH has established a TWA REL of 10 mg/m^3 for total aluminum particulates, and 5 mg/m^3 for respirable particles. The OSHA PEL is 15 mg/m^3 with 5 mg/m^3 for respirable particles (NIOSH, 2005a).

(5) There is no USEPA reference dose or reference concentration for Otto Fuel II or any of its components (ATSDR, 1995).

9. RECOMMENDATIONS. Given the available data, the new formulation appears to be relatively environmentally benign, and has a low potential to adversely affect human health and the environment. The use of diisocynates has the potential to cause sensitization in occupational settings; however, it biodegrades rapidly in the environment. Toxicity data are needed for N-methyl-p-nitroaniline (MNA) and polycaprolactone polymer (CAPA). However, since these are used in very limited quantities, risks from exposures are suspected to be minimal. It is recommended that this program progress to further stages. Additional research is needed to fill the data gaps for several of these compounds.

a. BTTN-Recommend an Ames test be conducted on this compound. BTTN may be expected to reach ground water, as a somewhat water-soluble substance, although it will not

partition to the atmosphere from water on the basis of its Henry's Law constant. Based upon its structural similarity to trinitrotoluene, it is recommended that BTTN be screened with the acute aquatic toxicity bioluminescent assay.

b. DEGDN-An *in vitro* mutagenicity battery, to include Ames test and bioluminescent bacteria screen are recommended.

c. 2-NDPA. Due to potential risk to aquatic species, a luminescent bacteria screen is recommended.

d. MNA. MNA is of low solubility but physical properties suggest it can enter the vapor phase. Rat LD_{50} and rat chronic LOAEL were estimated by QSAR to be 546 mg/kg and 4.8 mg/kg-day, respectively. Information concerning cancer risk was not found, and QSAR estimates were equivocal. Although it is present in low amounts in this formulation, experimental work on this compound is desirable. A preliminary *in vitro* toxicologic screen to include genotoxicity assays is recommended. Depending upon the outcome of the *in vitro* testing, a 2-week rat study might also be indicated.

APPENDIX A

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