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 Security Technology Certification Program (ESTCP), Program Manager for Weapon Systems and Platforms (Mr. Bruce Sartwell), US Department of Defense, 901 North Stuart Street, Suite 303, Arlington, VA 22203.

SUBJECT: Environmental Health Assessment Lead-Free Extruded Propellant Environmental Science and Technology Certification Program (ESTCP) Toxicology Report No. 87-XE-074Z-09D

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. Larry Williams, Directorate of Toxicology, Health Effects Research Program. He may be contacted at DSN (312) 584-7159 or commercial (410) 436-7159.

FOR THE COMMANDER:

Encl

GLENN J. LEACH
Acting Director, Toxicology

U.S. Army Public Health Command
(Provisional)

USAPHC

ENVIRONMENTAL HEALTH ASSESSMENT
TOXICOLOGY STUDY NO. 87-XE-074Z-09D
LEAD-FREE EXTRUDED PROPELLANT
ENVIRONMENTAL SCIENCE AND TECHNOLOGY
CERTIFICATION PROGRAM (ESTCP)
DECEMBER 2009

Approved for public release; Distribution unlimited.

Toxicity Tests: 40-5k1

PHC FORM 433-E (MCHB-CS-IP), NOV 09

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14. ABSTRACT

The ESTCP 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 is to eliminate lead (Pb) from rocket and missile propellant formulations. After extensive testing, a formulation has been derived that replaces Pb with bismuth β-resorcylate, formulation RPD-540. 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. However, due to a near complete lack of experimental data for bismuth β-resorcylate, toxicity data need to be acquired prior to proceeding with finalization of this formulation. In addition, 2-nitrodiphenylamine (2-NDPA) presents a potential risk to aquatic species, and an additional Microtox® screen is recommended as a surrogate for aquatic toxicity tests.

15. SUBJECT TERMS

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Toxicology Report No. 87-XE-074Z-09D
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Environmental Science and Technology Certification Program (ESTCP)
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Performing Laboratory

U.S. Army Public Health Command (Provisional)
Directorate of Toxicology
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Toxicology Report No. 87-XE-074Z-09D, Dec. 09

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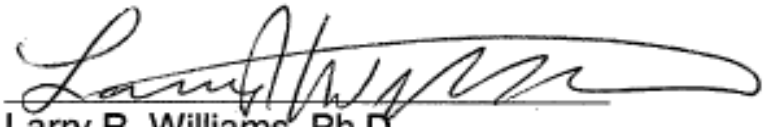

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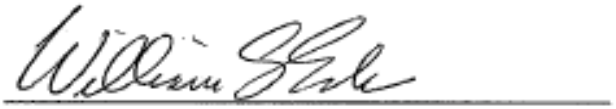

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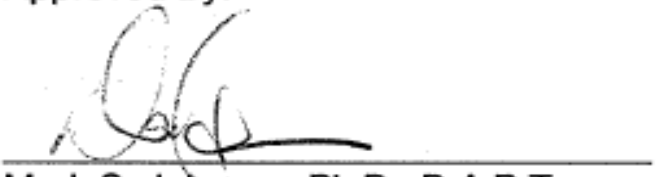

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DEPARTMENT OF THE ARMY
US ARMY PUBLIC HEALTH COMMAND (PROVISIONAL)
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MCHB-TS-THE

EXECUTIVE SUMMARY
ENVIRONMENTAL HEALTH ASSESSMENT
TOXICOLOGY STUDY NO. 87-XE-074Z-09D
LEAD-FREE EXTRUDED PROPELLANT
ENVIRONMENTAL SCIENCE AND TECHNOLOGY CERTIFICATION PROGRAM
DECEMBER 2009

1. PURPOSE. To provide environmental and occupational health information on new or replacement energetic compounds for Department of Defense use in the research, development, testing, and evaluation (RDT&E) of alternatives under the Environmental Security Technology Certification Program (ESTCP) and the 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. Department of Defense and the Army. Continuous assessment of the potential alternatives, begun early in the RDT&E process, can save significant time, effort, and cost during RDT&E, as well as over the life cycle of the items developed. Moreover, to safeguard the health of Soldiers, civilians, and the environment an assessment of alternatives before they are fielded is prudent.

b. The ESTCP 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 is to eliminate lead (Pb) from rocket and missile propellant formulations.

2. CONCLUSIONS. Based upon known or estimated properties of substances or structurally-similar surrogates, conditions, and amounts for projected use, this formulation is not expected to pose significant human health or environmental concerns. Toxicological as well as chemical-physical properties were obtained and reviewed for the individual chemicals used in this formulation to assess whether there were concerns relative 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. However, there are 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. Toxicity data gaps exist for bismuth β-resorcylate and di-n-propyl adipate; however, since these compounds are used in very limited quantities the risks from exposures are suspected to be minimal. It is recommended that this program progress to further stages. Still, due to a near complete lack of experimental data for bismuth β-resorcylate, toxicity data need to be acquired prior to proceeding with finalization of this formulation. In addition, 2-nitrodiphenylamine (2-NDPA) presents a potential risk to aquatic species, and an additional Microtox® screen is recommended as a surrogate for aquatic toxicity tests in fathead minnow; (Microtox® is a registered trademark of Strategic Diagnostics, Inc., Newark, DE).

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TOXICOLOGY REPORT NO. 87-XE-074Z-09D
LEAD-FREE EXTRUDED PROPELLANT
ENVIRONMENTAL SCIENCE AND TECHNOLOGY CERTIFICATION PROGRAM (ESTCP)
DECEMBER 2009

1. REFERENCES. See Appendix A for a listing of references used in this report.

2. PURPOSE. To provide environmental and occupational health information on new or replacement compounds and mixtures for the Army's use in explosives, propellants, and pyrotechnics. This information is necessary for work unit evaluation.

3. AUTHORITY. This Environmental Health Assessment addresses, in part, the environmental safety and occupational health (ESOH) requirements outlined in Army Regulations (AR) 200-1 (2007), AR 40-5 (2007), and AR 70-1 (2003); Department of Defense Instruction (DODI) 4715.4 (2008); and Army Environmental Research and Technology Assessment (AERTA, 2007) requirement A (3.3.c), *Compliant Ordnance Lifecycle for Readiness of the Transformation and Objective Forces*. This study was completed on behalf of the Naval Surface Warfare Center, Indian Head, Maryland, and the Environmental Security and Technology Certification Program (ESTCP).

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 research, development, testing, and evaluation (RDT&E) process in order to avoid unnecessary costs, conserve physical resources, and sustain the health of those potentially exposed.

b. In an effort to support this preventive approach, the U.S. Army Public Health Command (Provisional) (USAPHC (Prov) (formerly known as U.S. Army Center for Health Promotion and Preventive Medicine) has been tasked with developing a phased process to reduce adverse ESOH effects impacting readiness, training, and development costs. This is an on-going effort, and this study represents the status of information available as of the date of publication.

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 to 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 (CAS RN) (see Table 1). While all compounds do not necessarily have a single CAS RN, the CAS RN is an unambiguous way of accessing information for chemical substances. The CAS RN 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. The molecular structures for some of the chemicals are provided in Figure 1.

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

Chemical Substance	**CAS Number**	**Percentage Formulation for one unit**[†]	**Function**
Pelletized nitrocellulose (12.2% N)	9004-70-0	50	binder/fuel/oxidizer
Nitroglycerin	55-63-0	38	oxidizer plasticizer
Triacetin	102-76-1	3	Fuel/plasticizer
2-nitro-diphenyl amine (2-NDPA)	119-75-5	2	stabilizer
Dipropyl adipate (DnPA)	106-19-4	2	Fuel/plasticizer
Candelilla wax	8006-44-8	0.1	Fuel/processing aid
Carbon	7440-44-0	0.7	ballistic modifier
Bismuth β-resorcylate Bismuth (~55% wt/wt) β-resorcylic acid (~40% wt/wt)	 7440-69-9 89-86-1	3	ballistic modifier

b. This report addresses compounds investigated as part of this work unit through the end of fiscal year (FY) 2008. 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. 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.

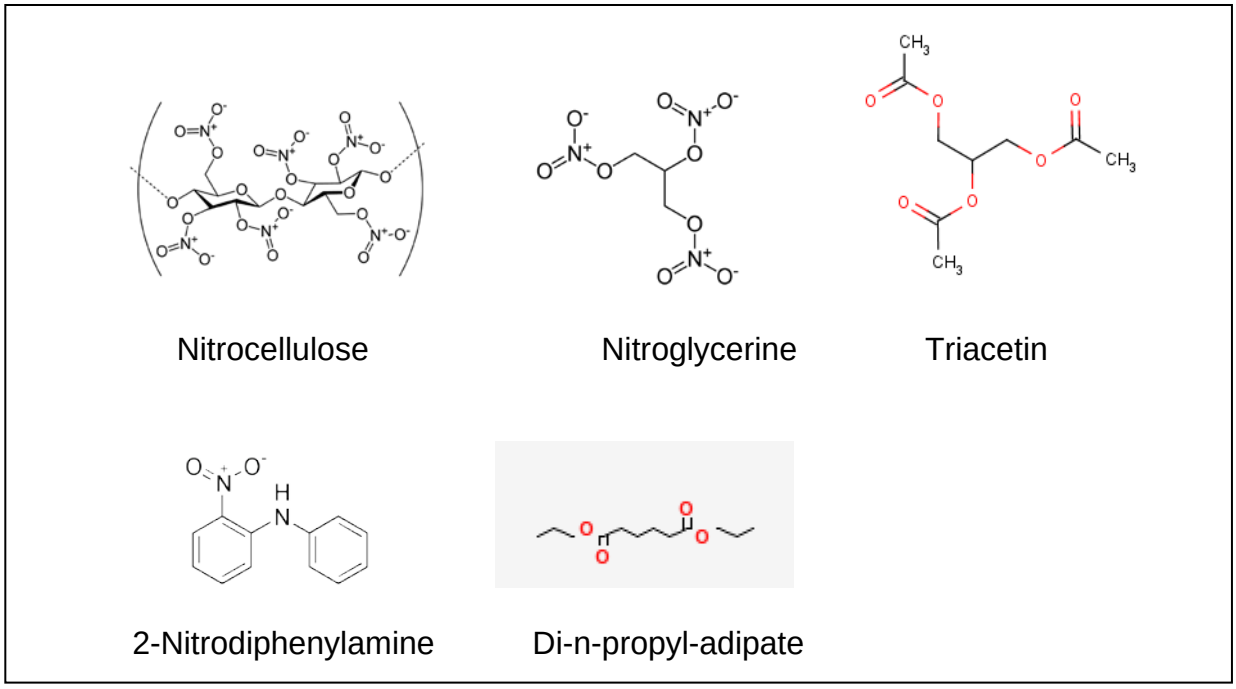

Figure 1. Chemical Structures of Components/Surrogates

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* (Roberts and Hartley, 1992), were also consulted. Commercial suppliers are sometimes contacted for results of in-house research that may not appear in the open literature.

e. Online sources include the U.S. National Library of Medicine's Toxicology Data Network (TOXNET®) that provides access to information from the National Institutes of Health and the USEPA. The TOXNET is a suite of individual databases including ChemIDplusLite® and ChemIDplus® Advanced (i.e., chemical and registration numbers, and chemical identification and structure, 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 (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). 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 U.S. National Library of Medicine; HSBD® is a registered trademark of the 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 and coworkers (2006). Table 2 describes the criteria used in the categorization, though the relative proportions of each substance were also factored into the final assessment.

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-d	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

Legend:
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-d = milligram per kilogram per day; µg/L = microgram per liter

7. RESULTS.

a. Physical and Chemical Properties. Physical and chemical properties are summarized in Table 4. When no data were found, “nd” (no data) was inserted. In some cases, the property named is not applicable (“n/a”) to the substance being described. For example, if the compound is a nonvolatile solid or an inorganic salt, vapor pressure, K_{OW}, K_{OC}, and the Henry’s Law constant (K_H) are typically negligible.

b. Summaries. Quantitative toxicological data are presented in Table 5. Assessments 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 the available data, the amount of each compound present in the formulation, and the nature of potential exposure associated with use of the end item.

c. Compound Characterizations.

(1) 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 nitrocellulose in solution finds use with ethyl alcohol and diethyl ether as a topical adhesive and protectant for cuts and small burns (O'Neil, 2006). The U.S. Food and Drug Administration (USFDA) 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, 2009c). 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 milligrams per kilogram (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 (Ellis et al., 1980) 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. 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 this level (10 percent) 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) Reproduction and Development. No data found.

(i) Mutagenicity.

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

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).

(j) 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).

(k) Ecotoxicology.

i. No acutely toxic effects of nitrocellulose were 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 EC_{50} of 731 mg/L (Sullivan et al., 1978).

(2) Nitroglycerin (NG). Also known as trinitroglycerin, trinitroglycerine, 1,2,3-trinitroxypropane, 1,2,3-propanetriol trinitrate and glyceryl trinitrate, is a heavy, colorless, oily, explosive liquid obtained by nitrating glycerol. Since the 1860s, it has been used as an active ingredient in the manufacture of explosives, specifically dynamite, and as such is employed in the construction and demolition industries. Similarly since the 1880s, it has been used by the military as an active ingredient and a gellatinizer for nitrocellulose, in some solid propellants, such as Cordite and Ballistite. In its pure form, it is a primary contact explosive (physical shock can cause it to explode) and degrades over time to even more unstable forms. This makes it highly dangerous to transport or use. In this undiluted form, it is one of the more powerful explosives. Nitroglycerin is also used medically as a vasodilator to treat heart conditions, such as angina and chronic heart failure. Nitroglycerin has profound effects on systemic as well as cardiac microcirculation. Its actions are mediated by stimulation of soluble guanylate cyclase in vascular smooth muscle cells. Long-term industrial exposure to NG has been associated with withdrawal symptoms and sudden death from cardiovascular accidents (Klaassen, 1996).

(a) Acute Oral. The oral LD_{50} was reported to be approximately 500-900 mg/kg in rats and 500-1200 mg/kg in mice (Lee et al., 1975; Oketani et al., 1982).

(b) Subacute Oral.

i. No adverse effects were seen in dogs given up to 1 mg/kg-day of NG for 4 weeks, then 5 mg/kg-day for 9 more weeks. Dogs given 25 to 200 mg/kg-day for 5 days had transient and dose-related severe methemoglobinemia, while 200 mg/kg-day produced depression; dogs given 1, 5, or 25 mg/kg-day for 12 months had transient and dose-related mild methemoglobinemia (Lee et al., 1977; Ellis et al., 1984).

ii. Rats fed 0.1 percent NG for 5 weeks, then 0.5 percent (230-234 mg/kg/day) for 8 more weeks had decreases in feed consumption and weight gain after the increase in dosage; rats fed 2.5 percent NG (1406 or 1416 mg/kg/day for males and females, respectively) for 13 weeks suffered adverse effects, including weight loss, compensated anemia, and testicular degeneration, but they resumed gaining weight as feeding continued (Ellis et al., 1984).

iii. No adverse effects were seen in mice fed up to 0.1 percent NG for 3 weeks, then 0.5 percent for 10 more weeks (Ellis et al., 1984).

(c) Chronic Oral.

i. Rats fed 1 percent NG (363 or 434 mg/kg-day for males and females, respectively) for 2 years had decreased weight gain, decreased grooming, methemoglobinemia and its sequelae, cholangiofibrosis , hepatocellular carcinoma, and interstitial cell tumors of the testis. A decrease in the naturally occurring pituitary chromophobe adenoma and mammary tumors increased the life span of the females. Some rats fed 0.1 percent TNG (31.5 or 38.1 mg/kg/day for males and females, respectively) had mild hepatic lesions similar to those seen in rats fed the larger doses (Ellis et al., 1984).

ii. No adverse effects were seen in mice fed up to 0.1 percent NG for 3 weeks, then 0.5 percent for 10 more weeks. Mice fed 1 percent NG (1022 or 1058 mg/kg/day for males and females, respectively) for 2 years had decreased weight gain, decreased grooming, and methemoglobinemia and its sequelae, but no obvious cellular changes as found in the rats (Ellis et al., 1984).

iii. Decreased food intake and decreased weight gain with methemoglobinemia was observed in mice after 2 years exposure to NG in the diet. The no-observed adverse effect level (NOAEL) for males was 114.6 mg /kg-day and 96.4 mg /kg-day for females.

(d) Acute Inhalation. No data found.

(e) Subchronic Inhalation. No data found.

(f) Chronic Inhalation. No data found.

(g) Dermal. Nitroglycerin is absorbed through intact skin in amounts sufficient to cause vasodilation. In humans, the most prominent manifestations of NG toxicity are severe headaches and adverse cardiovascular effects, including organic nitrate dependence in the case of chronic exposure (Gilman et al., 1990). In animals, the adverse effect most often observed after administration of NG at high-dosage levels is decreased weight gain (related to decreased food consumption); effects were also seen in the liver (lesions), blood (methemoglobinemia), and testes (lesions and aspermatogenesis) (USEPA, 1992).

(h) Reproduction and Development. Reproduction and developmental studies in animals have failed to demonstrate that NG is a teratogen. However, exposure to high concentrations of NG can result in testicular lesions and male infertility, and delayed development of offspring (Smith, 1986).

(i) Mutagenicity.

i. NG was active in TA1537 and TA1535 strains of *S. typhimurium* at concentrations ≥ 0.5 mg/plate (Ellis et al., 1978; Maragos et al., 1993).

ii. NG had no mutagenic effect after exposure of CHO-K1 cells Chinese hamster (K-1) cells and was negative in male and female rat chromosome aberration assays after sub chronic and chronic exposure (Ellis et al., 1976; Ellis et al., 1978).

(j) Carcinogenicity. No data found.

(k) Ecotoxicology.

i. In rainbow trout after 96-hour exposure, the LC_{50} was 1.90 mg/L, and in fathead minnow after 96-hour exposure LC_{50} was 3.58 mg/L (Burton et al., 1993).

ii. In quail (*C. virginianus)* in an 8-day feeding study, the LD_{50} was >5620 parts per million (ppm) with a LOAEL = 5620 ppm and a NOAEL = 3160 ppm (Fink et al., 1980).

iii. The 96-hour EC_{50} for alga *S.capricornutum* is 1.15 mg/L (Burton et al., 1993).

iv. The 48-hour LC_{50} for Daphnia *C. dubia* is 17.83 mg/L (Burton et al., 1993).

(3) Triacetin. Triacetin is the triacetate ester of glycerol. It finds application as a solvent in manufacture of celluloid photographic films, as a fixative in perfumery, and as a solvent in various types of dying and tanning. It also has medical applications as a topical antifungal (O'Neil et al., 2006)**.**

(a) Acute oral.

i. Triacetin is Generally Recognized As Safe (GRAS) as a human food ingredient by the USFDA. Triacetin was not toxic to animals in acute oral exposures (Fiume, 2003).

ii. Oral LD_{50} in mice is reported to be 1100 mg/kg, and 3000 mg/kg in rats (CIDPL, 2009d).

iii. Triacetin has been extensively studied for its role in parenteral nutrition (Bailey et al., 1991; Karlstad et al., 1992; Bleiberg et al., 1993).

(b) Subchronic Oral. Triacetin was not toxic to animals in subchronic feeding studies (Fiume, 2003).

(c) Chronic Oral. No data found.

(d) Acute Inhalation. Triacetin was not toxic to animals in acute inhalation studies (Fiume, 2003).

(e) Subchronic Inhalation. No data found.

(f) Chronic Inhalation. No data found.

(g) Dermal. Triacetin was not toxic to animals in dermal studies, except in one study where it was reported to cause erythema, slight edema, alopecia, and desquamation, and some slight irritation in rabbit eyes. It was not sensitizing in guinea pigs, and only slightly irritating to guinea pig skin. A Duhring-chamber test was conducted on 20 healthy volunteers. Triacetin was applied in 50 percent dilution for 24 hours. Only very mild skin irritation was observed. In humans, triacetin reportedly has caused ocular irritation but no injury (Fiume, 2003).

(h) Reproduction and Development. Triacetin is quickly metabolized to glycerol and acetic acid, neither of which are developmental toxins (Fiume, 2003).

(i) Mutagenicity.

i. Triacetin is not mutagenic, being quickly metabolized to acetic acid and glycerol. In adult *Drosophila*, a dose of 0.2-0.3 mg had a spontaneous mutation rate of approximately one per 750 chromosomes (Fiume, 2003).

ii. Triacetin was negative in the four primary Ames *Salmonella* strains, with or without metabolic activation, at concentrations up to 5000 µg/plate (ECB, 2000).

(j) Carcinogenicity. No data found.

(k) Ecotoxicology.

i. Triacetin is reported to have an oral LD_{LO} of 150 mg/kg in frogs (CIDPL, 2009d).

ii. Common carp (*Ciprinus carpio*) were exposed to triacetin by force-feeding. The fish received an oral dose comparable to 122-184 mg/L and survived 2.75 days (Loeb and Kelly, 1963)

(4) 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 study carried out for the Army by Atlantic Research Corporation (Army, 1979).

(a) Acute Oral.

i. Acute oral toxicity was evaluated using a sequential stage-wise probit methodology, and found the LD_{50} in rats to be >2000 mg/kg (Crouse et al., 2008).

ii. A rat oral LD_{50} for 2-NDPA was reported as 6150 mg/kg (American Cyanamide, 1976). 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. An Army study (Army, 1979) 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. 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) on 2-NDPA that there were 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 the American Conference of Governmental Industrial Hygienists (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).

(k) Carcinogenicity. The 1995 ATSDR study reported no information could be located regarding carcinogenicity of 2-NDPA via any route of exposure, and nothing has been found in the intervening years.

(l) Ecotoxicology.

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

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 ultraviolet (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 the experimentally-determined log K_{OW} of 3.66 (CIDPL, 2009c), the bioconcentration factor (BCF) is estimated to be 356, indicating 2-NDPA will bioaccumulate in aquatic organisms and may be concentrated in the food chain.

v. EPI Suite™ (ECOSAR) modeling of the aquatic toxicity of 2-NDPA predicts the acute toxicity to fish, Daphnid and green algae is <10 mg/L with chronic exposure values < 1 mg/L (USEPA, 2008).

(m) Miscellaneous.

i. American Cyanamid reported in their MSDS 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). The acute dermal toxicity of 2-NDPA applied to the skin of rabbits was reported to be greater than 10 g/kg (American Cyanamide, 1976).

ii. A more recent MSDS (Acros Organics, 2009) 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. 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.

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

(5) Di-n-propyl adipate (DnPA). Di-n-propyl adipate is also known as dipropyl adipate or adipic acid, dipropyl ester. DnPA is used in the production of cosmetics as an odorant and is a bitter flavor additive for baked goods and nonalcoholic beverages (Luebke, 2009). DnPA is considered generally recognized as safe (GRAS) at a maximum concentration of 500 ppm in food (Smith et al., 2009). There is little toxicity data for DnPA; however, there are data for related diester adipic acid chemicals. Where available and pertinent, toxicity data for diethyl adipate (DEA), dibutyl adipate (DBA), di-n-octyl adipate (DnOA) and bis(2-ethylhexyl) adipate (BEHA) are provided.

(a) Acute Oral. No data found for DnPA. DnOA LD_{50} for rat and mouse are 9110 and 15,000 mg/kg, respectively (HSDB, 2009b). The LD_{50} for DEA in rat is 1600 mg/kg (HSDB, 2009b). The LD_{50} for DBA is 12900 mg/kg (rat) and 16890 mg/kg (mouse) (CIDPL, 2009b). TOPKAT model analysis predicts a rat LD_{50} of 6600 mg/kg for DnPA.

(b) Subacute Oral. No data found.

(c) Subchronic Oral. No data found.

(d) Chronic Oral. No data found.

(e) Acute Inhalation. No data found were found for DnPA. The rat acute 4-hr LC_{50} for DBA is 17 mg/m^3 and the mouse 2-hr acute LC_{50} was reported as >17 mg/m^3 (CIDPL, 2009b).

(f) Subacute Inhalation. No data found.

(g) Subchronic Inhalation. No data found.

(h) Chronic Inhalation. No data found.

(i) Dermal. No data found for DnPA. The structurally related DBA is used on dogs and clothing as a repellent against chiggers and ticks (Gosselin et al., 1984).

(j) Reproduction and Development. No data found.

(k) Mutagenicity. The related chemical, DEA was reported as positive in a dominant lethal test in male rodents (GENETOX, 2009).

(l) Carcinogenicity. No data found.

(m) Ecotoxicology. No data were found for dipropyl adipate; however, data were found for DEA and DBA.

i. For DEA, the 24- and 48-hr acute LC_{50} for fathead minnow (*Pimephales promelas*) was reported as 22,500 and 17,300 µg/L respectively (USEPA, 2007).

ii. For DBA, the 96 hr LC_{50} for fathead minnow was reported to be 3640 µg/L (USEPA, 2007).

iii. Adipate esters contain a functional group that can absorb light at >290 nm and ,therefore, may undergo direct photolysis in the environment (HSDB, 2009b).

iv. Using EPI Suite, the log BCF for the series DEA, DnPA, and DBA are estimated to be 1.23, 1.88 and 1.15 respectively, which suggests these adipate esters will not bioaccumulate.

(6) Candelilla Wax. Candelilla wax is obtained from candelilla plants *(Euphorbia antisiphilitica, Euphorbia cerifers, Pedilanthus pavonis)* through extraction by immersion in a tank containing boiling water acidified with sulfuric acid. Candelilla wax is a hard and brittle wax. It is composed of about 20-29 percent wax esters, 12-14 percent alcohols and sterols,49-50 percent hydrocarbons, 7-9 percent free acids, 2-3 percent moisture, and 1 percent mineral matter. The chemical and physical properties of the wax vary with the age of the plant and the year in which it is collected. The wax is insoluble in water but soluble in acetone, chloroform, benzene, and other organic solvents (ACT, 1984; IPCS, 2009).

(a) Acute Oral. Candelilla wax is reported to have an LD_{50} in the rat greater than 5000 mg/kg (ACT, 1984; IPCS, 2009).

(b) Subchronic Oral. Candelilla wax is reported to have an LD_{50} in the rat greater than 5000 mg/kg (ACT, 1984; IPCS, 2009).

(c) Chronic Oral. Candelilla wax is reported to have an LD_{50} in the rat greater than 5000 mg/kg (ACT, 1984; IPCS, 2009).

(d) Acute Inhalation. No data found.

(e) Subchronic Inhalation. No data found.

(f) Chronic Inhalation. No data found.

(g) Dermal. No data found.

(h) Reproduction and Development. No data found.

(i) Mutagenicity. Four different tests showed that candelilla wax was not mutagenic, either with or without S9 activation (IPCS, 2009).

(j) Carcinogenicity. Black agouti (C57) mice were fed a gum base diet containing 25 percent candelilla wax for 12 to 13 months. At doses as high as 7500 mg/kg-day, the candelilla wax mixture was not carcinogenic. Sprague-Dawley rats fed up to 7500 mg/kg-day of a gum base containing 25 percent candelilla wax showed no signs of carcinogenicity different from controls (IPCS, 2009).

(k) Ecotoxicology. No data found.

(7) 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 is 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) 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 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).

(c) Chronic Oral. No differences in tumor incidences were observed in a 2-year feeding study with 2.05 g/kg carbon black in female Sprague-Dawley rats and female CF1 mice (Pence and Buddingh, 1985).

(d) Acute Inhalation. Carbon black is considered to be a non-specific irritant with toxic effects similar to other insoluble particulates (USEPA, 2005). Few toxicity data

exist for acute inhalational exposure to carbon black due to the concern over the potential for cancer from longer term exposures (Heinrich et al., 1994; Driscoll et al., 1996).

(e) Subacute Inhalation. No data found.

(f) Subchronic Inhalation. No data found.

(g) Chronic Inhalation. Hamsters exposed to 3 milliagrams per cubic feet (mg/ft^3) black carbon for 172 days did not have any observable differences in any 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 thyroarytenoid 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.

. (h) Reproduction and Development. No data found.

(i) Mutagenicity. No data found.

(j) Carcinogenicity. A recent review 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 and precede metaplastic changes and lung tumors. The carcinogenic properties are therefore similar to any poorly soluble particle: 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).

(k) 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 have not been reported. No adverse effects were found (Kaviraj and Das, 1995). An inhalation study conducted with carbon fibers using northern bobwhite (*Colinus virginianus*) was found not to result in adverse effects except at high concentrations (C. Driver, personal communication). ECOSAR-predicted data from the USEPA's assessment for carbon black (USEPA, 2005) are presented below (Table 3).

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)
Chv = "Chronic value," point estimate of a safe concentration; the geometric mean of the NOEC (No-observed effect concentration) and the LOEC (Lowest-observed effect concentration).			

(8) Bismuth β-resorcylate. Bismuth β-resorcylate is a salt of bismuth (III) and β-resorcylic acid (2,4-dihydroxybenzoic acid, 2,4-DHBA; discussed separately below) used in propellant formulations as a burn-rate modifier in double base propellants (U.S. Patent 5,652,409, 29 Jul 1997). Burn rate modifiers alter the dependence of the burning rate of the propellant on combustion chamber temperature and pressure. Mixtures of copper or bismuth salts of hydroxy-substituted benzoic acids have been found effective at flattening the burn rate as a function of pressure, and producing so-called "mesa" burning ("mesa" referring to a flat-topped physical terrain feature). It is critical that mixture of both the bismuth acid salt and the copper acid salt be used together. The bismuth acid salt used alone slows down the burn rate slightly, but it does not produce a plateau or mesa effect. Similarly, monobasic copper salicylate used alone slows down the burn rate but does not produce a plateau or mesa effect. A more extensive discussion of the phenomenon can be found in the narrative portion of the patent. The toxicity profile for Bismuth β-resorcylate is divided into its components bismuth and β-resorcylate.

(9) Bismuth. Bismuth is grayish-white, with a reddish tinge and bright metallic luster. It is superficially oxidized by air, frequently becoming iridescent. It is a poor conductor of electricity, and the volume decreases on melting. Bismuth is attacked chemically by dilute nitric acid, hot sulfuric acid, and concentrated hydrochloric acid. Cold solutions of bismuth give a white precipitate with sodium hydroxide (O'Neil et al., 2006). Bismuth has been used as a substitute for lead in many applications, including brass plumbing fixtures, ceramic glazes, crystalware, fishing sinkers, lubricating greases, pigments and solders (USGS, 2001). The ionic form of bismuth is a trivalent cation Bi^{+3}. Bismuth is poorly absorbed, distributes throughout the soft tissues and bone and the highest concentrations are found in the liver and kidney (HSDB, 2009b). The total daily intake via food is about 5-20 µg (HSDB, 2009b).

(a) Acute Oral. An acute LD_{LO} in man is reported to be 221 mg/kg, and 535 mg/kg in rabbits. The LD_{50} values for mice and rats are 10,000 mg/kg and 5000 mg/kg, respectively (CIDPL, 2009a).

(b) Subchronic Oral. No data found.

(c) Chronic Oral. No data found.

(d) Acute Inhalation. No data found.

(e) Subchronic Inhalation. No data found

(f) Chronic Inhalation. No data found.

(g) Dermal. Bismuth compounds (containing Bi^{+3}) are used in cosmetics and in veterinary dusting powder preparations (O'Neil, 2006).

(h) Reproduction and Development. No data found.

(i) Mutagenicity. No data found.

(j) Carcinogenicity. No data found.

(k) Ecotoxicology. In aerated water, bismuth oxidizes to yellow Bi_2O_3 by way of $Bi(OH)_3$. In the presence of atmospheric CO_2, white $Bi_2(CO_3)_3$ forms (HSDB, 2009a).

(10) β-Rescorcylic acid. 2,4-Dihydroxy benzoic acid, (2,4-DHBA), or beta-resorcylic acid is a phenolic acid similar to salicylic acid, and is used as an intermediate in dye and drug manufacturing (O'Neil, 2006). Resorcylic acid is a metabolic degradation product of aspirin (acetylsalicylic acid), and most of the available literature addresses the compound in this context. The available data is most often the result of application of 2,4-DHBA to the test system as part of a mixture containing other metabolites, making it impossible to separate out the effects attributable to 2,4-DHBA alone. However, the experimental outcomes typically indicate that 2,4-DHBA has less of an impact on the test system than acetylsalicylic acid. The 2,3- and 2,5- DHBA isomers are minor metabolic degradation products of salicylate or aspirin (acetylsalicylic acid), and most of the available literature addresses 2,4-DHBA in this context (HSDB, 2009b). The 2,3- and 2,5- DHBA isomers are nephrotoxic metabolites of salicylate (HSDB, 2009b).

(a) Acute Oral. The experiementally derived mouse oral LD_{50} for 2,5-DHBA is 4500 mg/kg (CIDPL, 2009b).

(b) Subchronic Oral. No data found.

(c) Chronic Oral. No experimental data were found. TOPKAT model analysis predicts a rat LOAEL of 662.1 mg/kg.

(d) Acute Inhalation. No data found.

(e) Subchronic Inhalation. No data found

(f) Chronic Inhalation. No data found.

(g) Dermal. No data found.

(h) Reproduction and Development. Yokoyama, Akita, and coworkers treated 11.5-day post-conception rat embryos in culture with either 200 µg/mL of salicylate or a mixture containing 70 percent salicylate, 10 percent 2,4-DHBA, and 20 percent 2,5-dihydroxybenzoic acid (Akita et al., 1991; Yokoyama et al., 2000). After 48-hour of culture, blood circulation of the embryos treated with the mixture of three compounds was reduced when compared to controls but less than those treated with salicylate alone. The treatment also delayed growth of the whole body and forehead. The incidence of malformation in the embryos was higher in embryos treated with salicylate alone than those treated with the mixture. It appears likely that the effects observed from treatment with the mixture were caused by the presence of salicylate, but because of the nature of the mixture, this is impossible to determine.

(i) Mutagenicity. No data found.

(j) Carcinogenicity. No data found.

(k) Ecotoxicology. Limited data are available on the impact of 2,4-DHBA on wild animals and plants.

i. In *Daphnia magna*, 2,4-dihydroxybenzoic acid had an EC_{50} of 188 mg/L for a 1-day exposure and 120 mg/L for a 2-day exposure (Kamaya et al., 2005).

ii. Various aromatic compounds were examined for effects on germination of lettuce when plants were exposed for a period of 72 hours. 2,4-DHBA had an EC_{50} for germination inhibition of 1.23 mM (18.9 µg/L) (Reynolds, 1978).

(l) Other. The effect of 2,4-DHBA on ethanol-induced gastric injury was examined in the rat. 2,4-DHBA was found to be gastroprotective, and inhibited *ex vivo*

leukotriene C4 formation by ethanol-stimulated gastric mucosa. However, the gastroprotective effect was not correlated with specific effects on mucosal cylclooxygenases, 5-lipoxygenase, or 15-lipoxygenase activity (Trautmann et al., 1991).

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Table 4. List of Physical and Chemical Properties

Compound (CASRN)	MW	mp (°C)	bp (°C)	Aqueous solubility (mg/L)	log Kow†	log Koc†	Henry's Law Constant (25 °C) †	vp (mmHg) @ 25 °C †
Pelletized nitrocellulose (PNC) (9004-70-0)	Varies, ~298-446 kDa; NC monomer f.w. 297.14 [a]	Flash point ~4 ^{O}C [a]	n/a	Insoluble [b]	n/a	n/a	n/a	n/a
Nitroglycerin (55-63-0)	227.09	13.5[c]	250 [c]	1380 [c]	1.62 [c]	1.41 (est.) [d]	9.87E-08 [c]	4.0E-04 [d]
Triacetin (102-76-1)	218.2	78	258-260 [c]	5.08E+04 [c]	0.25 [c]	0.93 [d]	1.23E-08 (est)[c]	0.00248 (est) [c]
Di-n-propyl adipate (106-19-4)	230.31[c]	-15.7[c]	273 [c]	230 [d]	3.350 (est) [c]	2.64 (est)[d]	3.03E-06 (est)[c]	
2-Nitrodiphenyl amine (2-NDPA) (119-75-5)	214.22 [e]	75 [c]	346 [f]	27.7 [c]	3.66 [c]	3.12 (est)[d]	9.07E-08 (est) [c]	1E-05 [f]
Candelilla wax (8006-44-8)	Hydrocarbon polymer-monomer f.w. ~437 [d]	67-79 [b]	>240 [b]	Insoluble [b]	n/a	n/a	n/a	n/a
Carbon	12.01 [g]	3550 [g]	4827 [g]	Insoluble [g]	n/a	n/a	n/a	n/a
Bismuth β-resorcylate (178558-50-4)								
Bismuth (7440-69-9)	208.98 [b]	271 [b]	1560 [b]	Insoluble	n/a	n/a	n/a	n/a
β-resorcylate (resorcylic acid) (89-86-1)	154.12 [b]	226 [c]	414.8 [b]	5780 [c]	1.63 [c]	1.39 (est) [d]	1.48E-12 (est) [c]	2.1E-6 (est) [c]

(dec) = decomposes; (est) = estimated; f.w.= formula weight; kDa=kiloDaltons; n/a = not applicable; nd = no data; †=derived from experimental data unless otherwise stated.

[a] O'Neil, 2006
[b] MSDS
[c] CIDPL, 2009b
[d] USEPA, 2008
[e] National Institute of Standards and Technology (NIST, 2006
[f] CPIA, 1985
[g] HSDB, 2009b

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
Pelletized nitrocellulose (PNC)	>5000 (rat) [a]	n/a [±]	4866 (LOAEL, rat) [b]	n/a [±]	Negative [c]	Negative [c]
Nitroglycerin	500-900 rat [d] 500-1200 mouse [d]	nd	5 (NOAEL, dog) [d] 25 (NOAEL, rat) [d]	3 (NOAEL, rat)[d] 32 (LOAEL, rat) [d]	Positive [e]	nd
Triacetin	3000 (rat) [f] 1100 (mouse) [f]	nd	1000 (NOAEL, rat) [g]	nd	Negative (tumor promotion) [f]	Negative Ames [f]
Di-n-propyl adipate	nd	nd	nd	nd	nd	nd
2-nitro-diphenyl amine (2-NDPA)	2000 (rat) [h]	nd	nd	nd	nd	Negative [i]
Candelilla wax	>5000 (rat) [j]	n/a [±]	>5000 (rat) [j]	>5000 (rat) [j]	Negative [j]	Negative [j]
Carbon	>15,400 (rat) [f] >3000 (rabbit) [f]	n/a [±]	n/a [±]	n/a [±]	Negative [f]	nd
Bismuth β-resorcylate						
Bismuth	10,000 (mouse)[a] 5000 (rat) [a]	n/a [±]	n/a [±]	n/a [±]	nd	nd
β-resorcylate	6600 mg/kg (rat)*	n/a [±]	n/a [±]	nd	nd	nd

*= based on QSAR predictions; ± = limit dose exceeded; n/a = not applicable; nd = no data

[a] CIDPL, 2009b
[b] Ellis, et al., 1980
[c] Hartley, et al., 1992
[d] Lee, et al., 1975, Oketani, et al., 1982, Ellis, et al., 1984, Ellis, et al., 1978
[e] Ellis, et al., 1978, Maragos, et al., 1993
[f] HSDB, 2009b
[g] IPCS-ICSC, 2009
[h] U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM, 2008)
[i] Noda, et al., 1993
[j] INCHEM, 2009, IPCS, 2009

Table 6. Human Health Impact Assessment

Compound	Acute Oral	Subchronic oral	Acute inhalation	Sub-chronic inhalation	Cancer probability	Comments
Pelletized nitrocellulose (PNC)	Low	Low	n/a	n/a	Low	Non-volatile; not absorbed by any route and insoluble in water. Large doses cause gastro-intestinal blockage.
Nitroglycerin	Low	Moderate	n/a	n/a	nd	
Triacetin	Low	Low	Low	Low	Low	Rapidly metabolized to glycerol and acetic acid.
2-nitro-diphenyl amine (2-NDPA)	Low	Low	n/a	n/a	Low	ACGIH TWA TLV® for related compound diphenylamine of 10 mg/m^3.
Di-n-propyl-adipate	Low (modeled)*	Low (modeled)*	unknown	unknown	unknown	
Candelilla wax	Low	Low	n/a	n/a	Low	GRAS; non-volatile; not absorbed by any route and insoluble in water.
Carbon	Low	Low	Low	Low	Low	Non-volatile; ACGIH TWA TLV = 3.5 mg/m^3 for respirable particulates causing lung irritation.
Bismuth β resorcylate	Low	Low	Low	Low	Low	
Bismuth	Low	Low (expected)**	Low (expected)**	Low (expected)**	Low (expected)**	
beta resorcylate	Low	Low (expected)**	Low (expected)**	Low (expected)**	Low (expected)**	

n/a = not applicable; nd = no data; GRAS = Generally Recognized As Safe by USFDA; TWA=time-weighted average; TLV=threshold limit value; PEL= permissible exposure limit; STEL= short term exposure limit;
* = based on Quantitative structure-activity relationship (QSAR) predictions;
**= based on weight of evidence and physical/chemical properties.
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Table 7. Ecotoxicology Impact Assessment

Compound	Aquatic	Invertebrates	Plants	Mammals	Birds	Comments
Pelletized nitrocellulose (PNC)	Low (algae, fish)	Low (expected)**	Low (algae)	Low (rat)	Low (expected)**	Non-volatile; not absorbed by any route and insoluble in water. Large doses cause gastro-intestinal blockage.
Nitroglycerin	Low (algae, fish)	Low (Daphnia, Aquatic sowbug)	Low (algae)	Moderate (rat	Low (quail)	
Triacetin	Low (carp, frogs)	Low (expected)**	Low (expected)**	Low	Low (expected)**	
Di-n-propyl-adipate	Low (expected)**	Moderate (expected)**	Low (expected)**	Low (modeled*/ expected**)	Low (expected)**	Closely related compound used as insecticide.
2-nitro-diphenyl amine (2-NDPA)	unknown	unknown	unknown	Low (rat)	unknown	
Candelilla wax	Low	Low (expected)**	Low (expected)**	Low	Low (expected)**	Non-volatile and insoluble in water. GRAS.
Carbon	Low (carp)	Low (modeled)*	Low (expected)**	Low (rats, mice)	Low (bobwhite, inhal.)	Non reactive in many biological systems.
Bismuth β resorcylate	Low (expected)**	Low (expected)**	Low (expected)**	Low (expected)**	Low (expected)**	Toxicity expected to be low based on low toxicity of constituents.
Bismuth	Low (algae)	Low (expected)**	Low (algae)	Low (expected)**	Low (expected)**	
β resorcylate	Low (expected)**	Low (expected)**	Low (expected)**	Low	Low (expected)**	
* = based on QSAR predictions; **= professional judgment based on weight of evidence and physical/chemical properties;						

8. DISCUSSION.

a. Environment. Most of the components are water insoluble, suggesting a low potential to enter the environment. With scarce data on bioaccumulation and affinity to organic carbon; however, it is not possible to give this estimated potential a high confidence rating

b. Current Formulation. Available information suggests the proposed 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**.** However, bismuth β resorcylate is a novel compound for which there is little specific information.

c. Regulatory Considerations. The National Institute for Occupational Safety and Health/Occupational Safety and Health Administration) NIOSH/OSHA) and HSDB websites were searched for regulatory information on the compounds in this formulation. Individual compounds that have NIOSH-recommended exposure limits (REL), short-term exposure limits (ST), OSHA permissible exposure limits (PEL), ceiling concentrations (C), 8-hr time TWA exposure limits or are GRAS are described below.

(1) Nitrocellulose. (As hydrocellulose CAS # 9004-34-6) NIOSH/OSHA REL: TWA 10 mg/m3 (total) TWA 5 mg/m^3 (respirable).

(2) Nitroglycerin. NIOSH REL: ST 0.1 mg/m^3 (skin) OSHA PEL C 2 mg/m^3 (skin).

(3) Triacetin. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) exempt; GRAS (FDA) (HSDB, 2009b).

(4) Candelilla wax. GRAS food additive (JECFA, 2005).

(5) Carbon. OSHA PEL TWA 15 mg/m^3 (total) TWA 5 mg/m^3 (respirable).

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.

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

b. Bismuth β-resorcylate. The bismuth β-resorcylate is a novel compound and toxicity data for it could not be located. Although bismuth is considered non-toxic, β-resorcylate toxicity has not been evaluated. The resorcylate molecule is in the same

chemical family as salicylate which has been reported to be a dermal irritant under chronic exposure conditions. At a minimum, each should be evaluated in an acute oral dosing study and a battery of *in vitro* assays in order to obtain basic information on their toxicity and potential environmental impacts. 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.

c. Di-n-propyl adipate. DnPA is an adipic acid ester. Related adipic acid esters are used as plasticizers. Although toxicity data are available for other adipic acid esters there is little information on DnPA. At a minimum, it is recommended that an *in vitro* assay battery be performed to assess mutagenicity (Ames), aquatic toxicity (luminescent bacteria screen), and cytotoxicity (neutral red uptake).

d. Summary. The three aforementioned compounds constitute less than 3 percent of the formulation. Additional research is needed to fill the data gaps for several of these compounds. The following tests are recommended before finalization of the formulation:

(1) Acute oral toxicity evaluation.

(2) Inhalation and dermal toxicity tests.

(3) *In vitro* battery including Ames test (mutagenicity), Microtox assays (aquatic toxicity), and micronucleus assays (chromosome damage).

APPENDIX A

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APPENDIX B

THE TOPKAT SYSTEM

The TOPKAT consists of a basic program that controls data entry, toxicity estimate calculations and search functions for its model databases. An individual model is provided for each toxicologic endpoint, e.g. LD_{50}, LOAEL, mutagenicity, carcinogenicity (male rat), carcinogenicity (female rat), and so forth.

A module may contain more than one database, each comprised of compounds in a certain structural class (e.g., multiple benzenes, alicyclics, and so forth). All predictive equations and validation procedures applied to a given query compound are based on the database for the structural class to which the query belongs. Thus, from each database a separate model is developed for making estimates of the relevant endpoint for chemicals in that structural class.

Each database contains a substantial number of compounds, often between 100 and 300, and an indication for reach compound of the actual toxicity, carcinogenicity, and so forth, from laboratory data, and whether it was used in generating the model. If it was used in model generation, the toxicity prediction for the compound, generated by the model, is also given. Generally, a small number of compounds are omitted from model generation as outliers or as wielding an undue influence on the model. Typically, the models yield an accuracy of about 95 percent for compounds in the model's database and compounds falling within the model's "optimum prediction space" (OPS).

The TOPKAT predicts the toxicity of a chemical structure based on statistically derived structure-activity relationships (SAR). The models are discrete molecular descriptors that identify functional groups present on a molecule and other parameters that can be used to quantify attributes of a particular structure. Standard databases were evaluated to obtain experimental values as input to the SAR equations.

For toxicity endpoints displaying continuous values, such as rat oral acute LD_{50} and rat chronic LOAEL, the system uses linear multiple regression equations, and the predictions represent estimates in dose units (mg/kg). For dichotomous endpoints, such as carcinogenicity and Ames mutagenicity, the models use two-group linear discriminant functions, and the output represents a probability, from 0 to 1, of a positive outcome for that endpoint. TOPKAT considers probability estimates from 0.3 to 0.7 to be indeterminate.

Carciniogenicity endpoints were estimated for four animal models (male rat, female rat, male mouse, and female mouse). Each TOPKAT-predictive model is developed from its own separate database and is limited to one of the foregoing animal models. Each covers

a wide range of organic compounds, both aliphatic and aromatic. Results for a given compound sometimes vary from one animal model to another, even when confidence in the estimate is high or moderate.

Probable responses in rabbit eye and skin irritation tests (Draize) estimate probability of a severe response and also probability of a negative response. These two probabilities are then combined into an overall estimate (e.g., mild/moderate, severe, less than severe, or 'not negative').

TOPKAT software includes an extensive procedure for internal validation of the estimate. The system checks to see if all substructures that comprise the query compound are represented among the compounds included in the database. The query compound is characterized by many descriptors, and the resulting multivariate description, or position in a multidimensional space, is automatically checked against the multidimensional OPS of the model. Generally, the SAR predictions generated by TOPKAT show a high probability of being accurate when all substructures are covered and the compound falls within the calculated OPS.

In all cases where actual data are not available, the user attempts to determine what level of confidence should be placed in the estimate. For estimates generated by the more recent versions of the software, the determinations provided by the built-in validation procedures are of first importance. Other factors used in developing suggestions of high medium or low confidence include, without being limited to the following:

- Whether all major structural features of the query compound are well represented in the model's database. At a certain level this results in an automatic warning from the software.

- Whether there are in the database a number of compounds that are judged by the software to be electrotopologically close to the query compound.

- Whether these near-by compounds are estimated accurately by the model and tend to present toxicity levels similar to that estimated for the query compound.

- Whether the model's database is reasonably large.

- Whether the compounds in the model's database are in general estimated with high accuracy.

For many estimates, meaningful results are not obtained. This usually results from the location of the query compound outside of the model's OPS, and not within an acceptable distance from the OPS, o, alternatively, the presence in the query compound of a molecular

fragment not adequately represented in the model's database.
For QSAR results, such as those discussed here, varying degrees of uncertainty always exist. It is common for about 80-90 percent of compounds not present in the pertinent database (but within the OPS of the model) to be predicted within a factor of five of the experimental value. Quantitative predictions, including mouse LC_{50}, rat LD_{50}, and rat chronic LOAEL, are accompanied by a 95 percent confidence range; these typically encompass values within a factor of four or five in either direction.